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What Will Be the Role of Pharmacogenetics in Evaluating Drug Safety and Minimising Adverse Effects?

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Abstract

In the US, adverse drug reactions (ADRs) rank between the fourth to sixth leading cause of death, ahead of pneumonia and diabetes mellitus. An important reason for the high incidence of serious and fatal ADRs is that the existing drug development paradigms do not generate adequate information on the mechanistic sources of marked variability in pharmacokinetics and pharmacodynamics of new therapeutic candidates, precluding treatments from being tailored for individual patients.

Pharmacogenetics is the study of the hereditary basis of person-to-person variations in drug response. The focus of pharmacogenetic investigations has traditionally been unusual and extreme drug responses resulting from a single gene effect. The Human Genome Project and recent advancements in molecular genetics now present an unprecedented opportunity to study all genes in the human genome, including genes for drug metabolism, drug targets and postreceptor second messenger machinery, in relation to variability in drug safety and efficacy. In addition to sequence variations in the genome, high throughput and genome-wide transcript profiling for differentially regulated mRNA species before and during drug treatment will serve as important tools to uncover novel mechanisms of drug action. Pharmacogenetic-guided drug discovery and development represent a departure from the conventional approach which markets drugs for broad patient populations, rather than smaller groups of patients in whom drugs may work more optimally.

Pharmacogenetics provides a rational framework to minimise the uncertainty in outcome of drug therapy and clinical trials and thereby should significantly reduce the risk of drug toxicity.

A recent meta-analysis of prospective studies in hospitalised patients between 1966 to 1996 found that the incidence of serious and fatal adverse drug reactions (ADR) in the US was 6.7 and 0.32%, respectively.[1] Thus, adverse drug reactions ranked between the fourth to sixth leading cause of death, ahead of pneumonia and diabetes mellitus.[1] Importantly, these ADRs occurred during treatment with usual doses of drugs that already met the regulatory requirements for clinical use, and excluded cases related to intentional or accidental overdose, errors in drug administration or noncompliance.[1] On the other hand, it takes 8 to 12 years to introduce a new drug from discovery to clinical practice, with costs approaching up to US$300 million. It is also estimated that approximately 90% of new drug candidates under development fail to meet regulatory approval requirements for clinical use.[2,3] Evidently, the existing pharmacotherapy guidelines and drug development paradigms are not optimal and do not efficiently predict variability in drug safety and clinical trial outcomes.

An important reason for the apparently high incidence of ADRs is that the marked person-to-person differences in pharmacokinetics and pharmacodynamics are overlooked during routine pharmacotherapy. The choice of drugs and dose titration regimens is often based on the average drug response in the population as specified on drug labels, rather than pharmacokinetic and pharmacodynamic attributes of each patient. Similarly, the dose ranges tested in phase 3 clinical trials rely on the limited safety and efficacy information obtained during phase 1 and phase 2 trials with relatively small sample sizes.

Are there alternative approaches to drug development that may permit a safer and personalised drug therapy? The medical subspecialty of pharmacogenetics aims to determine the role of heredity on variations in drug response among individuals and populations. Pharmacogenetic inquiries in the past 40 years have firmly established that genetics importantly contributes to dose-concentration-response relationship of numerous drugs.[4-7] More recently, the Human Genome Project initiative and the numerous spin off high-throughput genomic techniques now make it possible to unlock novel drug targets and identify genetically determined discrete patient subpopulations that differ in drug efficacy and safety.[8-10] Pharmacogenetic-guided drug discovery and development represents a departure from the conventional approach which markets drugs for broad patient populations, rather than smaller groups of patients in whom drugs may work more optimally.

The aim of this commentary is to provide an overview of recent breakthroughs in pharmacogenetics and their relevance for drug safety evaluations and personalised medicine.

1. Genetic Contribution to Drug Safety

1.1 Pharmacokinetic Considerations

Drug metabolism is one of the pivotal factors contributing to variability in pharmacokinetics and drug safety. The foundations of contemporary pharmacogenetics were established in the early 1950s by reports of unusual drug toxicity secondary to defects in drug metabolising enzymes (DMEs).[6,7,11-13] Examples include primaquine-induced haemolysis observed among African-American soldiers in the US army during World War II and peripheral neuropathy in slow-acetylators of isoniazid.[11,12] Some argue that the field of pharmacogenetic inquiry dates as early as 510 B.C., when Pythagoras in Croton, southern Italy, warned about the '. . . dangers of some, but not other, individuals who eat the fava bean'.[11] The molecular basis of this historical observation and of primaquine haemolysis was later found to be haemolytic anaemia attributable to glucose-6-phosphate dehydrogenase deficiency.[11,12]

Today, many genetic polymorphisms are documented in cytochrome P450 (CYP) enzymes which play a central role in the oxidative and reductive metabolism of a large variety of medications and other xenobiotics.[14-17] For instance, all 12 human CYP enzymes investigated have shown interindividual genetic variability; in 8 of these interethnic differences in variant frequencies have been established.[14-17] Thus, it appears that an occurence of a

marked person-to person variation is often or usually associated with ethnic variability. For example, gene deletion of *CYP2A6* had an allele frequency of about 1% in Caucasians and 15% in Asians.[14] The inactive *CYP2C19*2* occurs with an allele frequency of 13 to 14% in Caucasians and Africans and at double this frequency in Asians.[14] Besides differences in variant frequency, specific kinds of mutations may occur only in some, but not all, populations.[14-17] For instance, the inactive *CYP2D6*4* characterises the 7% of homozygous poor metabolisers of debrisoquine in Europe, but this variant is rare or practically absent elsewhere.[17] By contrast, the unstable *CYP2D6*10* displays an allele frequency of 51% in Asian populations but is infrequent (1 to 2%) in Caucasians.[14-17]

CYP2D6 (debrisoquine/sparteine) genetic polymorphism is one of the most intensively studied monogenic defects in drug metabolism.[18-20] More than 40 commonly used drugs including antidepressants, antipsychotics, codeine and some drugs of abuse are dependent on CYP2D6 for their clearance.[21-23] In general, poor metabolisers attain high drug concentrations at conventional doses and are at risk for drug toxicity.[23-27] For prodrugs that need to be activated by oxidative metabolism (e.g. codeine), poor metaboliser phenotype causes lack of efficacy.[26]

At present, drug candidates are characterised early on during the discovery phase with respect to their disposition by CYP2D6 and other genetically polymorphic DMEs.[28,29] The knowledge of major CYP isoforms which play a role for clearance of a lead compound is useful to forecast its pharmacokinetic variability in the general population, since the distribution of catalytic activity of most CYPs is established in different populations. Further, this information may contribute to design of phase 1 and 2 clinical trials in patients selected according to their CYP genotype, and to decisions concerning the dose ranges that can be tested in larger phase 3 trials with optimum safety.[30] Also, as a result of the global harmonisation attempts to standardise drug development and approval process, the settings of future clinical trials will be expanded well beyond North America and Western Europe. Thus, sample size calculations and drug safety evaluations in different populations may benefit from incorporation of the existing data on genetically determined inter-ethnic variations in DMEs. For example, 29% of the population in Ethiopia carry alleles with duplicated and multiduplicated *CYP2D6* genes associated with ultrarapid metabolism of substrates.[31] Overlooking such genetic differences may lead to failure of clinical trials because of subtherapeutic drug concentrations or toxicity from altered metabolite profiles of CYP2D6 substrates.

So far, many pharmaceutical companies appear to limit the development of compounds whose disposition is influenced by genetic polymorphisms in drug metabolism.[14] An important shortcoming of this approach is that it may prevent the clinical availability of drugs which may otherwise have efficacy.[14] Such compounds can in fact be used safely, provided adequate dose adjustments are made before drug administration. Moreover, the implicit assertion that selective substrates of nonpolymorphic DMEs are associated with reduced pharmacokinetic variability carries a false premise. For example, CYP3A4 is the most abundant CYP isoform in the adult human liver with large inter-individual variability in its expression.[32,33] *In vivo*, CYP3A4 activity displays at least 20-fold difference in the population.[32] Yet, the distribution of CYP3A4 catalytic activity is unimodal and nonpolymorphic in many populations.[32] In short, variability in drug disposition is the rule, rather than the exception.[34]

Ideally, the dosage of drugs should be individualised based on both disposition characteristics of medications as well as genetic make up of patients. Despite the established clinical importance of pharmacogenetics for many decades, there are few examples where drug therapy is guided by genetic tests. For example, thiopurine methyltransferase (TPMT) activity or genotype is routinely evaluated prior to 6-mercaptopurine treatment in several major institutions in the US (Mayo Clinic, Rochester, MN; St Jude's Children Research Hospital, Memphis, TN).[12] Patients who carry nonfunctional TPMT alleles experience serious adverse effects,[12,35-37] but

they can be safely treated with 6-mercaptopurine at doses 10 to 15 times lower than conventional doses.[12] Recent pharmacoeconomic analyses indicate that the annual cost of treating patients at extremes for CYP2D6 activity (poor metabolisers and ultrarapid metabolisers with gene duplication) is on average $US4 000 to $US6 000 greater than the rest of the population.[38] However, a fundamental change in the folklore of medical therapeutics is necessary before genotyping for pharmacogenetic variations becomes the standard practice, including amendments to the medical curriculum to improve the limited training offered in genetics.

Historically, there has been a tendency to compartmentalise the overall variance in drug safety and efficacy into discrete 'genetic' and 'environmental' components. Although this paradigm provided some conceptual framework for pharmacogenetic studies in the past, it overlooks the gene-environment interactions.[39,40] For example, smoking has been known for a long time as a potent inducer of CYP1A2 activity. However, there is considerable person-to-person variation in the extent of CYP1A2 induction among smokers.[41] A recent study in a sample of Caucasian volunteers identified a single nucleotide polymorphism (C→A) in intron 1 of the *CYP1A2* gene at position 734 downstream from the transcription initiation site (allelic variants C and A).[42] In smokers, those with A/A genotype had approximately 60 to 70% higher CYP1A2 activity than individuals with A/C or C/C genotypes.[42] Smoking is often included as an important co-variate that may explain variability in pharmacokinetics of new drug candidates. Clearly, consideration of genetic factors which modify the influence of smoking or other environmental factors on the organism should help to refine safety evaluations during drug development.

A common misconception about DMEs is that they solely interact with drugs. There is an increasing trend towards the use of herbs and other 'natural' products as part of the regular diet or to supplement conventional drug therapy. It is becoming clear that these supplements, although naturally occurring, may cause unexpected toxicity through interactions with DMEs. A case in point is St John's Wort (*Hypericum perforatum*).[43-45] Over-the-counter availability and claims for efficacy against a broad range of symptoms including mood stabilisation, premenstrual dysphoria and antiviral effects resulted in wide spread use of St John's Wort.[44,45] Recently, controlled clinical studies indicate that St John's Wort may induce CYP3A4, the most abundant CYP isoform in the human liver, as well as the P-glycoprotein during long term use.[43-45] This may potentially lead to subtherapeutic concentrations and treatment-resistance to drugs eliminated by CYP3A4 and P-glycoprotein during concurrent administration, and drug toxicity upon withdrawal of St John's Wort. Similarly, the studies in the past decade have shown that grapefruit juice may cause drug interactions by inhibition of intestinal CYP3A4 activity.[46] Therefore, it would be advisable to develop regulatory guidelines for formal assessment of herb-drug interactions and the influence of DME genetic polymorphisms on efficacy and safety of herbal products.

Traditionally, genetic contribution to pharmacokinetic variability was studied mainly in the context of drug metabolism.[47] However, other pharmacokinetic variables such as drug absorption, distribution and transport are also likely subject to genetic control.[48-51] For example, P-glycoprotein encoded by the *MDR1* gene affects transmembrane efflux and intracellular or tissue availability of numerous drugs.[48,50] The antidepressant amitriptyline can penetrate the brain more readily in knockout mice that do not express P-glycoprotein.[52] Hence, *MDR1* genetic polymorphisms may be useful to explain tissue specific toxicity and variability in concentration-response relationships during pharmacokinetic-pharmacodynamic modelling.[48]

1.2 Pharmacodynamic Considerations

The final pharmacological effects of medications are determined by an interplay of numerous genes and environmental factors. In the past decade, the increasing application of mathematical models for 'concentration-effect' relationships have documented large person-to-person differences in phar-

macodynamics across a broad range of drugs from opiate analgesics to benzodiazepines.[53] More recent breakthroughs in molecular biology are beginning to put on record examples of genetic variations in receptors and other drug targets of relevance for drug safety.[54-57] For example, tardive dyskinesia is a disabling and potentially irreversible movement disorder predominantly in the orofacial region and develops in approximately 20% of patients during long term treatment with typical antipsychotics. Dopamine D3 receptor gene (*DRD3*) is expressed in the basal ganglia and is thought to play a role in locomotion. Three independent studies found that patients with the Ser9Gly polymorphism in the N terminal extracellular domain of the DRD3 (homozygosity for the glycine variant) is associated with an increased propensity to develop tardive dyskinesia in patients treated with typical antipsychotics.[58-60] This finding may be clinically useful to minimise the risk for ADRs caused by antipsychotics agents.

The search for genetic variability in pharmacodynamics should not be viewed only in the context of receptors. Other drug targets, including second messenger systems are also under genetic control.[54,55,57] Further, the clinical impact of genetic variability in drug receptors may be modified by drug transport to the site of action and the amount of endogenous ligands available for competition at the drug-receptor interface. Thus, future pharmacogenetic studies should incorporate the influence of genetics on receptors and other drug targets as well as on physiologically relevant ligands for these targets.

An important corollary of correlation between genetic variability in drug targets and adverse effects is that it can lead to population stratification and selection bias in molecular genetic studies of complex diseases. For example, patients homozygous for the Ser9Gly variant of DRD3 may use healthcare services more frequently because of an increased risk of tardive dyskinesia and thereby may have an increased chance of being included in genetic studies of schizophrenia.[60] Indeed, several studies found an over-representation of the Ser9Gly polymorphism of the *DRD3* gene among patients with schizophrenia but this observation could not be replicated uniformly in subsequent studies (see discussion by Steen et al.[60]). Hence, relationships between receptor genetic polymorphisms and drug toxicity may also contribute to design of future genetic association studies focusing on disease pathophysiology.

From the point of therapeutics and drug development, the implication of genetic changes in drug targets can be dramatic; it may mean that the choice of drugs – not only the dosage – may have to be guided by the genetic make up of individuals. Pharmacogenetics may therefore decrease the segment of the population for which drugs can be marketed. On the other hand, prior knowledge of genetic determinants of efficacy and safety may allow targeting of discrete subpopulations in clinical trials and demonstration of 'proof of concept' in a smaller number of patients. In theory, this should significantly reduce the research and development costs and expedite the regulatory approval of new therapeutic candidates. Moreover, in an era of limited funds for health services and managed care, drugs with genetic predictors of drug safety and efficacy may gain a competitive marketing advantage.

The study of genetic contribution to pharmacodynamics and its relevance for drug response is a relatively new but rapidly expanding research field. In the near future, joined genetic investigations of both pharmacokinetics and pharmacodynamics should improve our ability to explain and predict a greater percentage of variability in drug safety.[61,62] Further examples of genetic variability in pharmacodynamics are reviewed elsewhere.[55,57]

2. Genomics and Impact on Drug Safety Evaluations

The focus of pharmacogenetic investigations has traditionally been unusual and extreme drug responses resulting from a single gene effect. Pharmacogenomics is a recently introduced concept that attempts to explain the hereditary basis of more subtle and continuous variations in drug response.[8] Similar to pharmacogenetics, the objective of phar-

macogenomics is to determine the precise molecular genetic basis of variability in drug efficacy and safety. However, pharmacogenomics broadens the scope of inquiry in pharmacogenetics from a 'one gene at a time' approach, to encompass all genes in the human genome, including genes for DMEs, drug targets and postreceptor second messenger machinery.

There are 2 experimental approaches commonly used in pharmacogenomics. First is the 'candidate gene' strategy where frequency of polymorphisms in a target gene is compared between responders and nonresponders to a given medication. A hallmark, as well as a limitation, of this approach is that the candidate genes are chosen depending on a given drug's presumed mechanism of action and/or the pathophysiology of the disease for which the study drug is targeted. Therefore, the success of the candidate gene technique rests on the validity of such assumptions and hence, is unlikely to identify the novel genes that may not be predicted by our current knowledge about disease biology or drug action. The second approach involves genome wide association studies between genetic markers and drug response phenotypes. Single nucleotide polymorphisms (SNPs) are the most commonly used genetic markers in genomic association studies. SNPs are biallelic single nucleotide polymorphisms in genomic DNA where the abundance of the least frequent allele is 1% or greater. In practice, alleles with lower frequency (i.e. <1%) are sometimes incorrectly labelled as SNPs but the correct terminology for such infrequent variants should be 'rare mutations'. It is thought that the complete human sequence will contain approximately 1 million SNPs including the coding regions, introns and promoters.[63] Therefore, SNPs can serve as dense and informative markers that can be used to 'cover' the whole genome in association studies dealing with polygenic pharmacological traits.[64] In addition, because of their biallelic nature, SNPs are amenable to high throughput genotyping.[3] An important advantage of the genome wide association studies is that they do not carry assumptions on mechanism of drug action and thus, may help to discover unprecedented novel genes relevant for drug response.

A genomic association study may require 100 000 SNP markers per individual.[3] In a clinical sample of 1000 patients, this will amount to 100 million genotypes.[3] A few years ago, this would have been a daunting task to accomplish. The new genomic technologies such as DNA microarrays – sometimes referred to as 'DNA chips' – allow scoring of 10 000 or more genes simultaneously. In principle, DNA microarray is an extension of the southern blot procedure and is comprised of different cDNAs or oligonucleotides etched systematically on a solid surface such as silica or glass plate.[65] Each DNA species on the array represents a specific gene or expressed sequence tag which is used to identify SNPs or transcripts by hybridisation and fluorescence detection.

An interesting application of microarrays is temporal monitoring of changes in gene expression during disease progression and drug treatment or in patients versus healthy individuals. The premise in this 'hit-and-observe' approach is that changes in patterns of gene expression in response to physiological or environmental stimuli (e.g. drugs) may serve as indirect clues about disease causing genes or drug targets. Moreover, the effects of drugs with established efficacy on global gene expression patterns may provide a guidepost, or a 'genetic signature', against which the new drug candidates can be validated.[66] Microarrays are only one of the many emerging genomic techniques. Other methods for DNA sequencing, novel SNP detection and genotyping such as denaturing high performance liquid chromatography, multiplexed capillary electrophoresis and mass spectrometry are being developed at a very rapid pace.

How will the advancements in molecular genetics affect drug development and safety? The drug discovery has long depended on serendipity or synthesis of ligands by combinatorial chemistry against receptors or other targets that have questionable pathophysiological significance. Genomic sciences are likely to identify the molecular genetic basis of most complex diseases such as hypertension, dia-

betes and schizophrenia.[3,67] As a result, it will be possible to design drugs targeted at precise disease mechanisms, rather than their symptoms and other downstream effects. These precision drugs will minimise the risk for adverse effects by avoiding biological targets that are not crucial for efficacy. With the advent of high throughput genomic tools, it will also be possible to identify the genetic basis of variability in drug safety during the development phase in large samples of patients.

3. Standardisation of the Definition of Drug Response Phenotype in Safety Evaluations

While there is much emphasis placed on technological proficiency in pharmacogenetics, relatively little attention is being paid to accurate assessment and definition of the 'pharmacological response phenotype'.[13] In classical populational genetics, the term 'phenotype' is used to define disease entities, including presentation and severity of symptoms, age of onset, familial versus sporadic forms of the disease.[13,64] In the context of pharmacology, several obvious factors including dose, route of drug administration and duration of treatment can all influence the final pharmacological effects or the 'drug response phenotype'. In the absence of any standardisation, genetic contribution to drug response phenotypes under such nonuniform conditions will also vary. Therefore, it is crucial to introduce some convention and structure to measurement and definition of drug response to allow comparisons of data from independent laboratories and prevent false-positive findings. The definitions of response may, of course, differ based on the study drug and the target disease, but an attempt should be made to control for, at the very least, dose and time dependencies. These issues are in fact well known to population geneticists but they are relatively less appreciated in the field of pharmaceutical research.

A solution to this problem would be to use pharmacologically relevant parameters such as ED_{50} [the dose of drug producing 50% of E_{max} (the maximum effect a drug produces)] and EC_{50} (the concentration of the drug producing 50% of E_{max}) as measures of drug response phenotype and test the influence of various genotypes on these parameters. The use of parameters as dependent variables in pharmacogenetic inquiries should provide a more complete characterisation of dose-concentration-effect relationships (as opposed to assessments at a single dose or time point) and prevent bias due to dose and time dependencies. In 1927, Trevan introduced the concept of LD_{50}, the dose that causes death in 50% of a population.[68] Prior to Trevan, the measurement of toxicity was unstructured and it was difficult to communicate and establish a consensus on drug toxicity and its determinants.[69]

Pharmacological parameters and their variability can be calculated by standard 2-stage methods in rich data sets with intensive pharmacokinetic and pharmacodynamic sampling or alternatively, by a population approach and mixed effect modelling in experiments with sparse data sets or missing data points.[70,71] A point to keep in mind is that parameters should be derived with use of pharmacologically and biologically plausible models.[72,73]

4. Evaluation of the Overall Genetic Control in Drug Safety: a Repeated Drug Administration Method

An evaluation of the overall genetic control of pharmacokinetic and pharmacodynamic characteristics of a new drug candidate is necessary before further molecular genetic studies can be planned and justified. Traditionally, twin studies have been used to estimate the heritability of pharmacological traits.[47] However, the feasibility of twin studies is limited by their high cost and problems associated with the recruitment of twins, to mention a few.

Recently, we have shown that the repeat investigations in a panel of volunteers or patients can be a useful alternative to twin studies to estimate the genetic component of drug disposition.[74] We termed this new approach the method of repeated drug administration (RDA). The RDA studies are possible in pharmacology because most pharmacological responses disappear over time after the administra-

tion of the drug and, thus, can be repeatedly reproduced, unlike the permanent characteristics of an individual (e.g. stature).[74] We therefore posed the following question: 'Instead of administering a drug once to each member of a pair of monozygotic and dizygotic twins, is it possible to give a drug twice or more to the same individual and obtain similar information on heritability of pharmacological traits?' The proposed equation for the RDA studies is

$$r_{GC} = genetic\ component = \frac{(SD_b{}^2 - SD_w{}^2)}{SD_b{}^2}$$

where SD_b and SD_w are standard deviations for between- and within-individual variations, respectively (an equivalent equation is used to estimate heritability in twin studies). The r_{GC} values approaching to 1.0 point to overwhelming genetic control, whereas those close to zero suggest that environmental factors dominate.

The RDA studies may provide rapid and cost effective early lead information during large scale screening and identification of new compounds that are most amenable to further pharmacogenetic-guided drug development. In a broader biological context, any dynamic biological phenomenon exhibiting 'time-dependent decay' and 'negligible carry-over effects between repeat observations' should be amenable to RDA studies to dissect the genetic contribution to inter-individual variability in the corresponding biological phenotype.[75]

5. Conclusions and Future Directions

Pharmacogenetics is not a new concept. However, as once claimed by Victor Hugo, nothing can be as powerful as an idea whose time has come.[76] Recent progress in molecular genetics and at least one-order of magnitude increase in throughput, coupled with decreasing costs for identification of human genetic variation, now make it entirely feasible to use genetic differences among patients and populations for prediction of drug safety and clinical trial outcomes.[12] In keeping with the Human Genome Project initiative, the traditional gene by gene study design used in earlier pharmacogenetic studies is rapidly evolving into a polygenic approach to explain the multifactorial basis of drug response. Soon, genome-wide association studies between highly informative SNP markers and drug effects may unlock unprecedented novel mechanisms for therapeutic and adverse effects of medications. We may be surprised that the mechanism of action of some drugs rests on targets entirely different than what the conventional pharmacological wisdom suggests.

The genomic approach to drug development is not simply a scale up application of the former molecular genetic techniques but also changes the type of questions that are posed during drug discovery and development. For example, a new challenge is to establish the significance of differences in global gene expression patterns in relation to drug effects and targets. High throughput and genome-wide transcript profiling for differentially regulated mRNA species in disease, normal physiology and after drug treatment will offer an additional dynamic perspective for drug discovery. In the near future, temporal monitoring of gene expression may prove to be a useful co-variate that may someday substitute the current reliance on pharmacokinetics and other surrogate markers of efficacy and safety during drug development.

With the Human Genome Project close to its completion, virtually every gene in the genome can be studied as a potential drug target. The challenge in the postgenomic era is to discern the function of each gene in relation to disease pathophysiology and drug response.[77] The bottleneck in pharmacogenetics is no longer data acquisition but interpretation of the enormous volumes of genomic data. This presents a challenge for the emerging field of bioinformatics. Regardless of the statistical significance, as a general rule, biological plausibility and adequate *in vitro* mechanistic rationale should always be sought in studies dealing with clinical associations between candidate genes and variability in drug response.

It is not clear how and when genetic testing will be implemented best at various phases of drug development and medical practice as well as its re-

Table I. Educational sources on pharmacogenetics and drug development available on the worldwide web

Source	Focus	Web address
Affymetrix	DNA microarray technology	www.affymetrix.com
Celera Genomics	Human genome sequencing and variation	www.celera.com
Center for Drug Development Science	Drug development	www.dml.georgetown.edu/depts/pharmacology/cdds/index.html
Center for Ecogenetics and Environmental Health	Gene-environment interactions	depts.washington.edu/ceeh
Cold Spring Harbor Laboratory	Genetics education	www.cshl.org
Food and Drug Administration	Drug development and regulation	www.fda.gov
Genaissance Pharmaceuticals	Human genetic variation	www.genaissance.com
Genset Corporation	Genomics and drug development	www.genxy.com/index.html
Human Genic Bi-allelic Sequences Database	SNPs	http://hgbase.cgr.ki.se
Human Genome Project	Human genetic variation	www.ornl.gov/TechResources/Human_Genome/home.html
Karolinska Institute	Genetics of drug metabolism	www.imm.ki.se/CYPalleles
National Institute of Health	Glossary of genetic terms	www.nhgri.nih.gov/DIR/VIP/Glossary
Nature Genetics	Genomics	http://www.nature.com/genomics
Orchid Biocomputer	SNPs	www.snps.com
Pharsight Corporation	Drug development	www.pharsight.com
SNP Consortium	Human genetic variation	Snp.cshl.org
Stanford University	Genome resources	www-genome.stanford.edu/index.html
Whitehead Institute	Genome resources	www-genome.wi.mit.edu

SNPs = single nucleotide polymorphisms.

percussions for health policy and managed care organisations.[78,79] Confidentiality of the genetic test results is critical since it has important bearings on finding employment and obtaining life, health or disability insurance. Very soon, physicians may be legally liable if they prescribe drugs that are unsafe in certain patients who can be readily identified by genetic testing. There is an urgent need to amend the existing medical curriculum to educate the future clinical personnel for genetic counselling and fundamentals of molecular medicine.[80] About 5% of the budget for the Human Genome Project is reserved to address these social, ethical and legal issues. Several useful information sources on genetics and drug development are available on the world wide web (table I).

The overall potential of pharmacogenetics in medicine and drug development still has to be realised. Nonetheless, it is clear that pharmacogenetics has raised the standards for drug safety evaluations and personalised medicine. Pharmacogenetics provides the necessary conceptual framework for understanding variability in drug response. The new genomic techniques will apply these principles to various facets of medicine and biology and should lead to a more predictable and efficient drug development and significantly reduce the risk of drug toxicity.[9,81-83]

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