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Personalized medicine: is it a pharmacogenetic mirage?

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The notion of personalized medicine has developed from the application of the discipline of pharmacogenetics to clinical medicine. Although the clinical relevance of genetically-determined inter-individual differences in pharmacokinetics is poorly understood, and the genotype-phenotype association data on clinical outcomes often inconsistent, officially approved drug labels frequently include pharmacogenetic information concerning the safety and/or efficacy of a number of drugs and refer to the availability of the pharmacogenetic test concerned. Regulatory authorities differ in their approach to these issues. Evidence emerging subsequently has generally revealed the pharmacogenetic information included in the label to be premature. Revised drugs labels, together with a flurry of other collateral activities, have raised public expectations of personalized medicine, promoted as 'the right drug at the right dose the first time.' These expectations place the prescribing physician in a dilemma and at risk of litigation, especially when evidence-based information on genotype-related dosing schedules is to all intent and purposes non-existent and guidelines, intended to improve the clinical utility of available pharmacogenetic information or tests, distance themselves from any responsibility. Lack of efficacy or an adverse drug reaction is frequently related to non-genetic factors. Phenoconversion, arising from drug interactions, poses another often neglected challenge to any potential success of personalized medicine by mimicking genetically-determined enzyme deficiency. A more realistic promotion of personalized medicine should acknowledge current limitations and emphasize that pharmacogenetic testing can only improve the likelihood of diminishing a specific toxic effect or increasing the likelihood of a beneficial effect and that application of pharmacogenetics to clinical medicine cannot adequately predict drug response in individual patients.

Introduction

Pharmacogenetics is a well-established discipline of pharmacology and its principles have been applied to clinical medicine to develop the notion of personalized medicine. The principle underpinning personalized medicine is sound, promising to make medicines safer and more effective by genotype-based individualized therapy rather than prescribing by the traditional 'one-size-fits-all' approach. This principle assumes that drug response is intricately linked to changes in pharmacokinetics or pharmacodynamics of the drug as a result of the patient's genotype. In essence, therefore, personalized medicine represents the application of pharmacogenetics to therapeutics. With every newly discovered disease-susceptibility gene receiving the media publicity, the public and even many professionals now believe that with the description of the human genome, all the mysteries of therapeutics have also been unlocked. Therefore, public expectations are now higher than ever that soon, patients will carry cards with microchips encrypted with their personal genetic information that will enable delivery of highly individualized prescriptions. As a result, these patients may expect to receive the right drug at the right dose the first time they consult their physicians such that efficacy is assured without any risk of undesirable effects [1]. In this review, we explore whether personalized medicine is now a clinical reality or just a mirage from presumptuous application of the principles of pharmacogenetics to clinical medicine.

It is important to appreciate the distinction between the use of genetic traits to predict (i) genetic susceptibility to a disease on one hand and (ii) drug response on the

other. Genetic markers have had their greatest success in predicting the likelihood of monogeneic diseases but their role in predicting drug response is far from clear. In this review, we consider the application of pharmacogenetics only in the context of predicting drug response and thus, personalizing medicine in the clinic. It is acknowledged, however, that genetic predisposition to a disease may lead to a disease phenotype such that it subsequently alters drug response, for example, mutations of cardiac potassium channels give rise to congenital long QT syndromes. Individuals with this syndrome, even when not clinically or electrocardiographically manifest, display extraordinary susceptibility to drug-induced torsades de pointes [2, 3]. Neither do we review genetic biomarkers of tumours as these are not traits inherited through germ cells. The clinical relevance of tumour biomarkers is further complicated by a recent report that there is great intra-tumour heterogeneity of gene expressions that can lead to underestimation of the tumour genomics if gene expression is determined by single samples of tumour biopsy [4].

Expectations of personalized medicine have been further fuelled by a flurry of other collateral activities that, collectively, serve to perpetuate the impression that personalized medicine 'has already arrived'. Quite rightly, regulatory authorities have engaged in a constructive dialogue with sponsors of new drugs and issued guidelines designed to promote investigation of pharmacogenetic factors that determine drug response. These authorities have also begun to include pharmacogenetic information in the prescribing information (known variously as the label, the summary of product characteristics or the package insert) of a whole range of medicinal products, and to approve various pharmacogenetic test kits. The year 2004 witnessed the emergence of the first journal ('*Personalized Medicine*') devoted exclusively to this subject. Recently, a new open-access journal ('*Journal of Personalized Medicine*'), launched in 2011, is set to provide a platform for research on optimal individual healthcare. A number of pharmacogenetic networks, coalitions and consortia dedicated to personalizing medicine have been established. Personalized medicine also continues to be the theme of numerous symposia and meetings.

Expectations that personalized medicine has come of age have been further galvanized by a subtle change in terminology from *'pharmacogenetics'* to *'pharmacogenomics'*, although there seems to be no consensus on the difference between the two. In this review, we use the term 'pharmacogenetics' as originally defined, namely the study of pharmacologic responses and their modification by hereditary influences [5, 6]. The term 'pharmacogenomics' is a recent invention dating from 1997 following the success of the human genome project and is often used interchangeably [7]. According to Goldstein *et al*. the terms pharmacogenetics and pharmacogenomics have different connotations with a range of alternative definitions [8]. Some have suggested that the difference is just in scale and that pharmacogenetics implies the study of a single gene whereas pharmacogenomics implies the study of many genes or entire genomes. Others have suggested that pharmacogenomics covers levels above that of DNA, such as mRNA or proteins, or that it relates more to drug development than does the term pharmacogenetics [8]. In practice, the fields of pharmacogenetics and pharmacogenomics often overlap and cover the genetic basis for variable therapeutic response and adverse reactions to drugs, drug discovery and development, more effective design of clinical trials, and most recently, the genetic basis for variable response of pathogens to therapeutic agents [7, 9]. Yet another journal entitled '*Pharmacogenomics and Personalized Medicine*' has linked by implication personalized medicine to genetic variables. The term 'personalized medicine' also lacks precise definition but we believe that it is intended to denote the application of pharmacogenetics to individualize drug therapy with a view to improving risk/benefit at an individual level.

In reality, however, physicians have long been practising 'personalized medicine', taking account of many patient specific variables that determine drug response, such as age and gender, family history, renal and/or hepatic function, co-medications and social habits, such as smoking. Renal and/or hepatic dysfunction and co-medications with drug interaction potential are particularly noteworthy. Like genetic deficiency of a drug metabolizing enzyme, they too influence the elimination and/or accumulation profiles of a drug and therefore, dictate the need for an individualized selection of drug and/or its dose. For some drugs that are primarily eliminated unchanged (e.g. atenolol, sotalol or metformin), renal clearance is a very significant variable when it comes to personalized medicine. Titrating or adjusting the dose of a drug to an individual patient's response, often coupled with therapeutic monitoring of the drug concentrations or laboratory parameters, has been the cornerstone of personalized medicine in most therapeutic areas. For some reason, however, the genetic variable has captivated the imagination of the public and many professionals alike. A crucial question then presents itself – what is the added value of this genetic variable or pre-treatment genotyping?

Elevating this genetic variable to the status of a biomarker has further created a situation of potentially self-fulfilling prophecy with pre-judgement on its clinical or therapeutic utility. It is therefore timely to reflect on the value of some of these genetic variables as biomarkers of efficacy or safety, and as a corollary, whether the available data support revisions to the drug labels and promises of personalized medicine. Although the inclusion of pharmacogenetic information in the label may be guided by precautionary principle and/or a desire to inform the physician, it is also worth considering its medico-legal implications as well as its pharmacoeconomic viability.

Personalized medicine through prescribing information

The contents of the prescribing information (referred to as label from here on) are the important interface between a prescribing physician and his patient and have to be approved by regulatory authorities. Therefore, it seems logical and practical to begin an appraisal of the potential for personalized medicine by reviewing pharmacogenetic information included in the labels of some widely used drugs. This is especially so because revisions to drug labels by the regulatory authorities are widely cited as evidence of personalized medicine coming of age. The Food and Drug Administration (FDA) in the United States (US), the European Medicines Agency (EMA) in the European Union (EU) and the Pharmaceutical Medicines and Devices Agency (PMDA) in Japan have been at the forefront of integrating pharmacogenetics in drug development and revising drug labels to include pharmacogenetic information.

Of the 1200 US drug labels for the years 1945–2005, 121 contained pharmacogenomic information [10]. Of these, 69 labels referred to human genomic biomarkers, of which 43 (62%) referred to metabolism by polymorphic cytochrome P450 (CYP) enzymes, with CYP2D6 being the most common. In the EU, the labels of approximately 20% of the 584 products reviewed by EMA as of 2011 contained 'genomics' information to 'personalize' their use [11]. Mandatory testing prior to treatment was required for 13 of these medicines. In Japan, labels of about 14% of the just over 220 products reviewed by PMDA during 2002–2007 included pharmacogenetic information, with about a third referring to drug metabolizing enzymes [12].

The approach of these three major authorities frequently varies. They differ not only in terms of the details or the emphasis to be included for some drugs but also whether to include any pharmacogenetic information at all with regard to others [13, 14]. Whereas these differences may be partly related to inter-ethnic differences in relevance of the available pharmacogenetic data, they also indicate differences in the assessment of the quality of these association data. Pharmacogenetic information can appear in different sections of the label (e.g. indications and usage, contraindications, dosage and administration, interactions, adverse events, pharmacology and/or a boxed warning, etc) and broadly falls into one of the three categories: (i) pharmacogenetic test required, (ii) pharmacogenetic test recommended and (iii) information only [15]. The EMA is currently consulting on a proposed guideline [16] which, among other aspects, is intending to cover labelling issues such as (i) what pharmacogenomic information to include in the product information and in which sections, (ii) assessing the impact of information in the product information on the use of the medicinal products and (iii) consideration of monitoring the effectiveness of genomic biomarker use in a clinical setting if there are requirements or recommendations in the product information on the use of genomic biomarkers.

For convenience and because of their ready accessibility, this review refers mainly to pharmacogenetic information contained in the US labels and where appropriate, attention is drawn to differences from others when this information is available. Although there are now over 100 drug labels that include pharmacogenomic information, some of these drugs have attracted more attention than others from the prescribing community and payers because of their significance and the number of patients prescribed these medicines.

The drugs we have selected for discussion fall into two classes. One class includes thioridazine, warfarin, clopidogrel, tamoxifen and irinotecan as examples of premature labelling changes and the other class includes perhexiline, abacavir and thiopurines to illustrate how personalized medicine can be possible. Thioridazine was among the first drugs to attract references to its polymorphic metabolism by CYP2D6 and the consequences thereof, while warfarin, clopidogrel and abacavir are selected because of their significant indications and extensive use clinically. Our choice of tamoxifen, irinotecan and thiopurines is particularly pertinent since personalized medicine is now frequently believed to be a reality in oncology, no doubt because of some tumour-expressed protein markers, rather than germ cell derived genetic markers, and the disproportionate publicity given to trastuzumab (Herceptin®). This drug is frequently cited as a typical example of what is possible. Our choice of drugs, apart from thioridazine and perhexiline (both now withdrawn from the market), is consistent with the ranking of perceived importance of the data linking the drug to the gene variation [17]. There are no doubt many other drugs worthy of detailed discussion but for brevity, we use only these to review critically the promise of personalized medicine, its real potential and the challenging pitfalls in translating pharmacogenetics into, or applying pharmacogenetic principles to, personalized medicine. Perhexiline illustrates drugs withdrawn from the market which can be resurrected since personalized medicine is a realistic prospect for its use.

We discuss these drugs below with reference to an overview of pharmacogenetic data that impact on personalized therapy with these agents. Since a detailed review of all the clinical studies on these drugs is not practical and beyond the scope of this review, we will only review or summarize a selective but representative sample of the available evidence-based data.

Thioridazine

Thioridazine is an old antipsychotic agent that is associated with prolongation of the QT interval of the surface electrocardiogram (ECG). When excessively prolonged, this can degenerate into a potentially fatal ventricular arrhythmia known as torsades de pointes. Although it was withdrawn from the market worldwide in 2005 as it was perceived to have a negative risk : benefit ratio, it does

provide a framework for the need for careful scrutiny of the evidence before a label is significantly changed. Initial pharmacogenetic information included in the product literature was contradicted by the evidence that emerged subsequently.

Earlier studies had indicated that thioridazine is principally metabolized by CYP2D6 and that it induces dose-related prolongation of QT interval [18]. Another study later reported that *CYP2D6* status (evaluated by debrisoquine metabolic ratio and not by genotyping) might be an important determinant of the risk for thioridazine-induced QT interval prolongation and associated arrhythmias [19]. In a subsequent study, the ratio of plasma concentrations of thioridazine to its metabolite, mesoridazine, was shown to correlate significantly with CYP2D6-mediated drug metabolizing activity [20].

The US label of this drug was revised by the FDA in July 2003 to include the statement '*thioridazine is contraindicated . . . . in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and PRECAUTIONS)*'.

Unfortunately, further studies reported that *CYP2D6* genotype does not substantially affect the risk of thioridazine-induced QT interval prolongation. Plasma concentrations of thioridazine are influenced not only by *CYP2D6* genotype but also by age and smoking, and that *CYP2D6* genotype did not appear to influence on-treatment QT interval [21]. This discrepancy with earlier data is a matter of concern for personalizing therapy with thioridazine by contraindicating it in poor metabolizers (PM), thus denying them the benefit of the drug, and may not altogether be too surprising since the metabolite contributes significantly (but variably between individuals) to thioridazine-induced QT interval prolongation. The median dose-corrected, steady-state plasma concentrations of thioridazine had already been shown to be significantly lower in smokers than in non-smokers [20]. Thioridazine itself has been reported to inhibit CYP2D6 in a genotype-dependent manner [22, 23]. Therefore, thioridazine : mesoridazine ratio following chronic therapy may not correlate well with the actual *CYP2D6* genotype, a phenomenon of phenoconversion discussed later. Additionally, subsequent *in vitro* studies have indicated a major contribution of CYP1A2 and CYP3A4 to the metabolism of thioridazine [24].

Warfarin

Warfarin is an oral anticoagulant, indicated for the treatment and prophylaxis of thrombo-embolism in a variety of conditions. In view of its extensive clinical use, lack of alternatives available until recently, wide inter-individual variation in daily maintenance dose, narrow therapeutic index, need for regular laboratory monitoring of response and risks of over or under anticoagulation, application of its pharmacogenetics to clinical practice has attracted probably the greatest interest with regard to personalized medicine. Warfarin is a racemic drug and the pharmacologically active S-enantiomer is metabolized predominantly by CYP2C9. The metabolites are all pharmacologically inactive. By inhibiting vitamin K epoxide reductase complex 1 (VKORC1), S-warfarin prevents regeneration of vitamin K hydroquinone for activation of vitamin K-dependent clotting factors.

The FDA-approved label of warfarin was revised in August 2007 to include information on the effect of mutant alleles of *CYP2C9* on its clearance, together with data from a meta-analysis that examined risk of bleeding and/or daily dose requirements associated with *CYP2C9* gene variants. This is followed by information on polymorphism of vitamin K epoxide reductase and a note that about 55% of the variability in warfarin dose could be explained by a combination of *VKORC1* and *CYP2C9* genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy. There was no specific guidance on dose by genotype combinations, and healthcare professionals are not required to conduct *CYP2C9* and *VKORC1* testing before initiating warfarin therapy. The label in fact emphasizes that genetic testing should not delay the start of warfarin therapy. However, in a later updated revision in 2010, dosing schedules by genotypes were added, thus making pre-treatment genotyping of patients de facto mandatory.

A number of retrospective studies have certainly reported a strong association between the presence of *CYP2C9* and *VKORC1* variants and a low warfarin dose requirement. Polymorphism of *VKORC1* has been shown to be of greater importance than *CYP2C9* polymorphism. Whereas *CYP2C9* genotype accounts for 12–18%, *VKORC1* polymorphism accounts for about 25–30% of the inter-individual variation in warfarin dose [25–27]. However, prospective evidence for any clinically relevant benefit of *CYP2C9* and/or *VKORC1* genotype-based dosing is still very limited. What evidence is available at present suggests that the effect size (difference between clinically- and genetically-guided therapy) is relatively small and the benefit is only limited and transient and of uncertain clinical relevance [28–33].

Estimates vary substantially between studies [34] but known genetic and non-genetic factors account for only just over 50% of the variability in warfarin dose requirement [35] and factors that contribute to 43% of the variability are unknown [36]. Under the circumstances, genotype-based personalized therapy, with the promise of right drug at the right dose the first time, is an exaggeration of what is possible and much less appealing if genotyping for two apparently major markers referred to in drug labels (CYP2C9 and VKORC1) can account for only 37–58% of the dose variability. The emphasis placed hitherto on *CYP2C9* and *VKORC1* polymorphisms is also questioned by recent studies implicating a novel polymorphism in the *CYP4F2* gene, particularly its variant V433M allele that also influences variability in warfarin dose requirement. Some studies suggest that *CYP4F2* accounts for only 1 to 4% of variability in warfarin dose [37, 38]

whereas others have reported larger contribution, somewhat comparable with that of *CYP2C9* [39].

The frequency of the *CYP4F2* variant allele also varies between different ethnic groups [40]. V433M variant of *CYP4F2* explained approximately 7% and 11% of the dose variation in Italians and Asians, respectively [41, 42] but its contribution to warfarin maintenance dose in the Japanese and Egyptians was relatively small when compared with the effects of *CYP2C9* and *VKOR* polymorphisms [43, 44]. Because of the differences in allele frequencies and differences in contributions from minor polymorphisms, benefit of genotype-based therapy based on one or two specific polymorphisms requires further evaluation in different populations. Inter-ethnic differences that impact on genotype-guided warfarin therapy have been documented [34, 45]. A single *VKORC1* allele is predictive of warfarin dose across all the three racial groups but overall, *VKORC1* polymorphism explains greater variability in Whites than in Blacks and Asians. This apparent paradox is explained by population differences in minor allele frequency that also impact on warfarin dose [46]. *CYP2C9* and *VKORC1* polymorphisms account for a lower fraction of the variation in African Americans (10%) than they do in European Americans (30%), suggesting the role of other genetic factors. Perera *et al*. have identified novel single nucleotide polymorphisms (SNPs) in *VKORC1* and *CYP2C9* genes that significantly influence warfarin dose in African Americans [47].

Given the diverse range of genetic and non-genetic factors that determine warfarin dose requirements, it seems that personalized warfarin therapy is a difficult goal to achieve, although it is an ideal drug that lends itself well for this purpose. Available data from one retrospective study show that the predictive value of even the most sophisticated pharmacogenetics-based algorithm (based on *VKORC1, CYP2C9* and *CYP4F2* polymorphisms, body surface area and age) designed to guide warfarin therapy was less than satisfactory with only 51.8% of the patients overall having predicted mean weekly warfarin dose within 20% of the actual maintenance dose [48].

The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial is aimed at assessing the safety and clinical utility of genotype-guided dosing with warfarin, phenprocoumon and acenocoumarol in daily practice [49]. Recently published results from EU-PACT reveal that patients with variants of *CYP2C9* and *VKORC1* had a higher risk of over anticoagulation (up to 74%) and a lower risk of under anticoagulation (down to 45%) in the first month of treatment with acenocoumarol, but this effect diminished after 1–6 months [33]. Full results concerning the predictive value of genotype-guided warfarin therapy are awaited with interest from EU-PACT and two other ongoing large randomized clinical trials [Clarification of Optimal Anticoagulation through Genetics (COAG) and Genetics Informatics Trial (GIFT)] [50, 51].

With the new anticoagulant agents (such as dabigatran, apixaban and rivaroxaban) which do not require monitoring and dose adjustment now appearing on the market, it is not inconceivable that when satisfactory pharmacogenetic-based algorithms for warfarin dosing have ultimately been worked out, the role of warfarin in clinical therapeutics may well have eclipsed. In a 'Position Paper' on these new oral anticoagulants, a group of experts from the European Society of Cardiology Working Group on Thrombosis are enthusiastic about the new agents in atrial fibrillation and welcome all three new drugs as attractive alternatives to warfarin [52]. Others have questioned whether warfarin is still the best choice for some subpopulations and suggested that as the experience with these novel anticoagulants accumulates and competition possibly brings the drug acquisition cost down, a broader transition from warfarin can be anticipated and will be justified [53]. Clearly, if genotype-guided therapy with warfarin is to compete effectively with these newer agents, it is imperative that algorithms are relatively simple and the cost-effectiveness and the clinical utility of genotype-based strategy are established as a matter of urgency.

Clopidogrel

Clopidogrel, a $P2Y_{12}$ receptor antagonist, has been demonstrated to reduce platelet aggregation and the risk of cardiovascular events in patients with prior vascular diseases. It is widely used for secondary prevention in patients with coronary artery disease. Clopidogrel is pharmacologically inactive and requires activation to its pharmacologically active thiol metabolite that binds irreversibly to the $P2Y_{12}$ receptors on platelets. The first step involves oxidation mediated mainly by two CYP isoforms (CYP2C19 and CYP3A4) leading to an intermediate metabolite, which is then further metabolized either to (i) an inactive 2-oxo-clopidogrel carboxylic acid by serum paraoxonase/arylesterase-1 (PON-1) or (ii) the pharmacologically active thiol metabolite. Clinically, clopidogrel exerts little or no anti-platelet effect in 4–30% of patients, who are therefore at an elevated risk of cardiovascular events despite clopidogrel therapy, a phenomenon known as 'clopidogrel resistance'.

A marked decrease in platelet responsiveness to clopidogrel in volunteers with *CYP2C19*2* loss-of-function allele first led to the suggestion that this polymorphism may be an important genetic contributor to clopidogrel resistance [54]. However, the issue of *CYP2C19* genotype with regard to the safety and/or efficacy of clopidogrel did not at first receive serious attention until further studies suggested that clopidogrel might be less effective in patients receiving proton pump inhibitors [55], a group of drugs widely used concurrently with clopidogrel to minimize the risk of gastro-intestinal bleeding but some of which may also inhibit CYP2C19.

Simon *et al*. studied the correlation between the allelic variants of *ABCB1, CYP3A5, CYP2C19, P2RY12* and *ITGB3* with the risk of adverse cardiovascular outcomes during a 1 year follow-up [56]. Patients with two variant alleles of *ABCB1* (T3435T) or those carrying any two *CYP2C19* loss-of-

function alleles had a higher rate of cardiovascular events compared with those carrying none. Among patients who underwent percutaneous coronary intervention, the rate of cardiovascular events among patients with two *CYP2C19* loss-of-function alleles was 3.58 times the rate among those with none. Later, in a clopidogrel genome-wide association study (GWAS), the correlation between *CYP2C19*2* genotype and platelet aggregation was replicated in clopidogrel-treated patients undergoing coronary intervention. Furthermore, patients with the *CYP2C19*2* variant were twice as likely to have a cardiovascular ischaemic event or death [57].

The FDA revised the label for clopidogrel in June 2009 to include information on factors affecting patients' response to the drug. This included a section on pharmacogenetic aspects which explained that several CYP enzymes converted clopidogrel to its active metabolite, and the patient's genotype for one of these enzymes (CYP2C19) could affect its anti-platelet activity. It stated:

'T*he CYP2C19*1 allele corresponds to fully functional metabolism, while the CYP2C19*2 and CYP2C19*3 alleles correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced-function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population'.* The above information was followed by a commentary on various outcome studies and concluded with the statement *'Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity. There may be genetic variants of other CYP450 enzymes with effects on the ability to form clopidogrel's active metabolite*.'

Over the period, a number of association studies across a range of clinical indications for clopidogrel confirmed a particularly strong association of *CYP2C19*2* allele with the risk of stent thrombosis [58, 59]. Patients who had at least one reduced function allele of *CYP2C19* were about three or four times more likely to experience a stent thrombosis than non-carriers. The *CYP2C19*17* allele encodes for a variant enzyme with higher metabolic activity and its carriers are equivalent to ultra-rapid metabolizers. As expected, the presence of the *CYP2C19*17* allele was shown to be significantly associated with an enhanced response to clopidogrel and increased risk of bleeding [60, 61].

The US label was revised further in March 2010 to include a boxed warning entitled 'Diminished Effectiveness in Poor Metabolizers' which included the following bullet points:

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.
- Tests are available to identify a patient's *CYP2C19* genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

The current prescribing information for clopidogrel in the EU includes similar elements, cautioning that *CYP2C19* PMs may form less of the active metabolite and therefore, experience reduced anti-platelet activity and generally exhibit higher cardiovascular event rates following a myocardial infarction (MI) than do patients with normal CYP2C19 function. It also advises that tests are available to identify a patient's *CYP2C19* genotype.

After reviewing all the available data, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) subsequently published a Clinical Alert in response to the new boxed warning included by the FDA [62]. It emphasised that information regarding the predictive value of pharmacogenetic testing is still very limited and the current evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. It is worth noting that there are no reported studies but if poor metabolism by CYP2C19 were to be an important determinant of clinical response to clopidogrel, the drug will be expected to be generally ineffective in certain Polynesian populations. Whereas only about 5% of western Caucasians and 12 to 22% of Orientals are PMs of *CYP2C19*, Kaneko *et al*. have reported an overall frequency of 61% PMs, with substantial variation among the 24 populations (38–79%) on 16 different islands of Vanuatu [63]. Mega *et al*. have reported that tripling the maintenance dose of clopidogrel to 225 mg daily in *CYP2C19*2* heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75 mg dose in non-carriers. In contrast, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition in *CYP2C19*2* homozygotes [64].

In evaluating the role of CYP2C19 with regard to clopidogrel therapy, it is important to make a clear distinction between its pharmacological effect on platelet reactivity and clinical outcomes (cardiovascular events). Although there is an association between the *CYP2C19* genotype and platelet responsiveness to clopidogrel, this does not necessarily translate into clinical outcomes. Two large meta-analyses of association studies do not indicate a substantial or consistent influence of *CYP2C19* polymorphisms, including the effect of the gain-of-function variant *CYP2C19*17*, on the rates of clinical cardiovascular events [65, 66]. Ma *et al*. have reviewed and highlighted the conflicting evidence from larger more recent studies that investigated association between *CYP2C19* genotype and clinical outcomes following clopidogrel therapy [67].

The prospects of personalized clopidogrel therapy guided only by the *CYP2C19* genotype of the patient are frustrated by the complexity of the pharmacology of clo-

pidogrel. In addition to CYP2C19, there are other enzymes involved in thienopyridine absorption, including the efflux pump P-glycoprotein encoded by the *ABCB1* gene. Two different analyses of data from the TRITON-TIMI 38 trial have shown that (i) carriers of a reduced-function *CYP2C19* allele had significantly lower concentrations of the active metabolite of clopidogrel, diminished platelet inhibition and a higher rate of major adverse cardiovascular events than did non-carriers [68] and (ii) *ABCB1* C3435T genotype was significantly associated with a risk for the primary endpoint of cardiovascular death, MI or stroke [69]. In a model containing both the *ABCB1* C3435T genotype and *CYP2C19* carrier status, both variants were significant, independent predictors of cardiovascular death, MI or stroke. Delaney *et al*. have also replicated the association between recurrent cardiovascular outcomes and *CYP2C19**2 and *ABCB1* polymorphisms [70].

The pharmacogenetics of clopidogrel is further complicated by some recent suggestion that *PON-1* may be an important determinant of the formation of the active metabolite, and therefore, the clinical outcomes. A common Q192R allele of *PON-1* had been reported to be associated with lower plasma concentrations of the active metabolite and platelet inhibition and higher rate of stent thrombosis [71]. However, other later studies have all failed to confirm the clinical significance of this allele [70, 72, 73].

Polasek *et al*. have summarized how incomplete our understanding is regarding the roles of various enzymes in the metabolism of clopidogrel and also the inconsistencies between *in vivo* and *in vitro* pharmacokinetic data [74]. On balance, therefore, personalized clopidogrel therapy may be a long way away and it is inappropriate to focus on one specific enzyme for genotype-guided therapy because the consequences of inappropriate dose for the patient can be serious. Faced with lack of high quality prospective data and conflicting recommendations from the FDA and the ACCF/AHA, the physician has a dilemma. Beitelshees *et al*. have suggested several courses of action that physicians pursue or can pursue, one being simply to use alternatives such as prasugrel [75].

Tamoxifen

Tamoxifen, a selective oestrogen receptor (ER) modulator, has been the standard treatment for ER+ breast cancer that results in a significant decrease in the annual recurrence rate, improvement in overall survival and reduction of breast cancer mortality rate by a third. It is extensively metabolized to 4-hydroxy-tamoxifen (by CYP2D6) and to N-desmethyl tamoxifen (by CYP3A4) which then undergoes secondary metabolism by CYP2D6 to 4-hydroxy-N-desmethyl tamoxifen, also known as endoxifen, the pharmacologically active metabolite of tamoxifen. Thus, the conversion of tamoxifen to endoxifen is catalyzed principally by CYP2D6. Both 4-hydroxy-tamoxifen and endoxifen have about 100-fold greater affinity than tamoxifen for the ER but the plasma concentrations of endoxifen are typically much higher than those of 4-hydroxy-tamoxifen. Mean plasma endoxifen concentrations are significantly lower in PM or intermediate metabolizers (IM) of *CYP2D6* compared with their extensive metabolizer (EM) counterparts, with no relationship to genetic variations of *CYP2C9, CYP3A5*, or *SULT1A1* [76]. Goetz *et al*. first reported an association between clinical outcomes and *CYP2D6* genotype in patients receiving tamoxifen monotherapy for 5 years [77].

The consensus of the Clinical Pharmacology Subcommittee of the FDA Advisory Committee of Pharmaceutical Sciences in October 2006 was that the US label of tamoxifen should be updated to reflect the increased risk for breast cancer along with the mechanistic data but there was disagreement on whether *CYP2D6* genotyping should be recommended. It was also concluded that there was no direct evidence of relationship between endoxifen concentration and clinical response [78]. Consequently, the US label for tamoxifen does not include any information on the relevance of *CYP2D6* polymorphism.

A later study in a cohort of 486 with a long follow-up showed that tamoxifen-treated patients carrying the variant *CYP2D6* alleles *4, *5, *10, and *41, all associated with impaired CYP2D6 activity, had significantly more adverse outcomes compared with carriers of functional alleles [79]. These findings were later confirmed in a retrospective analysis of a much larger cohort of patients treated with adjuvant tamoxifen for early stage breast cancer and classified as having EM ($n = 609$), IM ($n = 637$) or PM ($n = 79$) *CYP2D6* metabolizer status [80].

In the EU, the prescribing information was revised in October 2010 to include cautions that *CYP2D6* genotype may be associated with variability in clinical response to tamoxifen with PM genotype associated with reduced response, and that potent inhibitors of CYP2D6 should whenever possible be avoided during tamoxifen treatment, with pharmacokinetic explanations for these cautions. However, the November 2010 issue of Drug Safety Update bulletin from the UK Medicines and Healthcare products Regulatory Agency (MHRA) notes that the evidence linking various PM genotypes and tamoxifen treatment outcomes is mixed and inconclusive. Therefore it emphasized that there was no recommendation for genetic testing before treatment with tamoxifen [81].

A large prospective study has now suggested that *CYP2D6*6* may have only a weak effect on breast cancer specific survival in tamoxifen-treated patients but other variants had hardly any effect [82]. The absence of an association of survival with the more frequent variants (including *CYP2D6*4*) prompted these investigators to question the validity of the reported association between *CYP2D6* genotype and treatment response and recommended against pre-treatment genotyping. Thompson *et al*. studied the influence of comprehensive *vs*. limited *CYP2D6* genotyping for 33 *CYP2D6* alleles and reported that patients with at least one reduced function *CYP2D6* allele (60%) or no functional alleles (6%) had a non-significant

trend for worse recurrence-free survival [83]. However, recurrence-free survival analysis limited to four common *CYP2D6* allelic variants was no longer significant ($P = 0.39$), thus highlighting further the limitations of testing for only the common alleles. Kiyotani *et al*. have emphasised the greater significance of *CYP2D6*10* in Oriental populations [84, 85].

Kiyotani *et al*. have also reported that in breast cancer patients who received tamoxifen-combined therapy, they observed no significant association between *CYP2D6* genotype and recurrence-free survival. However, a subgroup analysis revealed a positive association in patients who received tamoxifen monotherapy [86]. This raises a spectre of drug-induced phenoconversion of genotypic EMs into phenotypic PMs [87]. In addition to co-medications, the inconsistency of clinical data may also be partly related to the complexity of tamoxifen metabolism in relation to the associations investigated. *In vitro* studies have reported involvement of both CYP3A4 and CYP2D6 in the formation of endoxifen [88]. Furthermore, CYP2D6 catalyzes 4-hydroxylation at low tamoxifen concentrations but CYP2B6 showed significant activity at high substrate concentrations [89]. Tamoxifen N-demethylation was mediated by CYP2D6, 1A1, 1A2 and 3A4, at low substrate concentrations, with contributions by CYP1B1, 2C9, 2C19 and 3A5 at high concentrations. Clearly, there are alternative, otherwise dormant, pathways in individuals with impaired CYP2D6-mediated metabolism of tamoxifen. Elimination of tamoxifen also involves transporters [90]. Two studies have identified a role for *ABCB1* in the transport of both endoxifen and 4-hydroxy-tamoxifen [91, 92]. The active metabolites of tamoxifen are further inactivated by sulphotransferase (SULT1A1) and uridine 5′-diphospho-glucuronosyltransferases (UGT2B15 and UGT1A4) and these polymorphisms too may determine the plasma concentrations of endoxifen. The reader is referred to a critical review by Kiyotani *et al*. of the complex and often conflicting clinical association data and the reasons thereof [85].

Schroth *et al*. reported that in addition to functional *CYP2D6* alleles, the *CYP2C19*17* variant identifies patients likely to benefit from tamoxifen [79]. This conclusion is questioned by a later finding that even in untreated patients, the presence of *CYP2C19*17* allele was significantly associated with a longer disease-free interval [93]. Compared with tamoxifen-treated patients who are homozygous for the wild-type *CYP2C19*1* allele, patients who carry one or two variants of *CYP2C19*2* have been reported to have longer time-to-treatment failure [93] or significantly longer breast cancer survival rate [94]. Collectively, however, these studies suggest that *CYP2C19* genotype may be a potentially important determinant of breast cancer prognosis following tamoxifen therapy. Significant associations between recurrence-free survival and 15 SNPs on nine chromosomal loci have been reported in a recently published tamoxifen GWAS [95]. Among them, rs10509373 in the *C10orf11* gene on 10q22 was significantly associated with recurrence-free survival in the replication study. In a combined analysis of rs10509373 genotype with *CYP2D6* and *ABCC2*, the number of risk alleles of these three genes had cumulative effects on recurrence-free survival in 345 patients receiving tamoxifen monotherapy. The risks of basing tamoxifen dose solely on the basis of *CYP2D6* genotype are self-evident.

Irinotecan

Irinotecan is a DNA topoisomerase I inhibitor, approved for the treatment of metastatic colorectal cancer. It is a prodrug requiring activation to its active metabolite, SN-38. Clinical use of irinotecan is associated with severe side effects, such as neutropenia and diarrhoea in 30–45% of patients, which are related to SN-38 concentrations. SN-38 is inactivated by glucuronidation by the UGT1A1 isoform. UGT1A1-related metabolic activity varies widely in human livers, with a 17-fold difference in the rates of SN-38 glucuronidation [96]. *UGT1A1* genotype was shown to be strongly associated with severe neutropenia, with patients hosting the **28/*28* genotype having a 9.3-fold higher risk of developing severe neutropenia compared with the rest of the patients [97]. In this study, *UGT1A1*93*, a variant closely linked to the **28* allele, was suggested as a better predictor for toxicities than the **28* allele in Caucasians.

The irinotecan label in the US was revised in July 2005 to include a brief description of *UGT1A1* polymorphism and the consequences for individuals who are homozygous for the *UGT1A1*28* allele (increased risk of neutropenia), and it recommended that a reduced initial dose should be considered for patients known to be homozygous for the *UGT1A1*28* allele. However, it cautioned that the precise dose reduction in this patient population was not known and subsequent dose modifications should be considered based on individual patient's tolerance to treatment. Heterozygous patients may be at increased risk of neutropenia. However, clinical results have been variable and such patients have been shown to tolerate normal starting doses. After careful consideration of the evidence for and against the use of pre-treatment genotyping for *UGT1A1*28*, the FDA concluded that the test should not be used in isolation for guiding therapy [98]. The irinotecan label in the EU does not include any pharmacogenetic information.

Pre-treatment genotyping for irinotecan therapy is complicated by the fact that genotyping of patients for *UGT1A1*28* alone has a poor predictive value for development of irinotecan-induced myelotoxicity and diarrhoea [98]. *UGT1A1*28* genotype has a positive predictive value of only 50% and a negative predictive value of 90–95% for its toxicity. It is questionable if this is sufficiently predictive in the field of oncology, since 50% of patients with this variant allele not at risk may be prescribed sub-therapeutic doses. Consequently, there are concerns regarding the risk of lower efficacy in carriers of the *UGT1A1*28* allele if the

dose of irinotecan was reduced in these individuals simply because of their genotype. In one prospective study, *UGT1A1*28* genotype was associated with a higher risk of severe myelotoxicity which was only relevant for the first cycle, and was not seen throughout the entire period of 72 treatments for patients with two variant alleles (**28/*28*) compared with wild-type alleles (**1/*1*). The response rate was also higher in **28/*28* patients compared with **1/*1* patients, with a non-significant survival advantage for **28/*28* genotype, leading to the conclusion that irinotecan dose reduction in patients carrying a *UGT1A1*28* allele could not be supported [99]. The reader is referred to a review by Palomaki *et al*. who, having reviewed all the evidence, suggested that an alternative is to increase irinotecan dose in patients with wild-type genotype to improve tumour response with minimal increases in adverse drug events [100].

While the majority of the evidence implicating the potential clinical importance of *UGT1A1*28* has been obtained in Caucasian patients, recent studies in Asian patients show involvement of a low-activity *UGT1A1*6* allele, which is specific to the East Asian population. The *UGT1A1*6* allele has now been shown to be of greater relevance for the severe toxicity of irinotecan in the Japanese population [101]. Arising mainly from the genetic differences in the frequency of alleles and lack of quantitative evidence in the Japanese population, there are significant differences between the US and Japanese labels in terms of pharmacogenetic information [14].

The poor efficiency of the *UGT1A1* test may not be altogether surprising, since variants of other genes encoding drug-metabolizing enzymes or transporters also influence the pharmacokinetics of irinotecan and SN-38 and therefore, also play a crucial role in their pharmacological profile [102]. These other enzymes and transporters also manifest inter-ethnic differences. For example, a variation in *SLCO1B1* gene also has a significant effect on the disposition of irinotecan in Asian patients [103] and *SLCO1B1* and other variants of *UGT1A1* are now believed to be independent risk factors for irinotecan toxicity [104]. The presence of *MDR1/ABCB1* haplotypes including C1236T, G2677T and C3435T reduces the renal clearance of irinotecan and its metabolites [105] and the C1236T allele is associated with increased exposure to SN-38 as well as irinotecan itself. In Oriental populations, the frequencies of C1236T, G2677T and C3435T alleles are about 62%, 40% and 35%, respectively [106] which are substantially different from those in the Caucasians [107, 108].

The complexity of irinotecan pharmacogenetics has been reviewed in detail by other authors [109, 110]. It involves not only UGT but also other transmembrane transporters (ABCB1, ABCC1, ABCG2 and SLCO1B1) and this may explain the difficulties in personalizing therapy with irinotecan. It is also evident that identifying patients at risk of severe toxicity without the associated risk of compromising efficacy may present challenges.

The five drugs discussed above illustrate some common features that may frustrate the prospects of personalized therapy with them, and probably many other drugs. The main ones are:

- Focus of labelling on pharmacokinetic variability due to one polymorphic pathway despite the influence of multiple other pathways or factors
- Inadequate relationship between pharmacokinetic variability and resulting pharmacological effects
- Inadequate relationship between pharmacological effects and clinical outcomes
- Many factors alter the disposition of the parent compound and its pharmacologically active metabolites
- Phenoconversion arising from drug interactions may limit the durability of genotype-based dosing. This is further discussed later.

In one recent survey of over 10 000 US physicians [111], 58.5% of the respondents answered 'no' and 41.5% answered 'yes' to the question 'D*o you rely on FDA-approved labeling (package inserts) for information regarding genetic testing to predict or improve the response to drugs?*' An overwhelming majority did not believe that pharmacogenomic tests had benefited their patients in terms of improving efficacy (90.6% of respondents) or reducing drug toxicity (89.7%).

Perhexiline

We choose to discuss perhexiline because, although it is a highly effective anti-anginal agent, its use is associated with severe and unacceptable frequency (up to 20%) of hepatotoxicity and neuropathy. Therefore, it was withdrawn from the market in the UK in 1985 and from the rest of the world in 1988 (except in Australia and New Zealand, where it remains available subject to phenotyping or therapeutic drug monitoring of patients). Since perhexiline is metabolized almost exclusively by CYP2D6 [112], *CYP2D6* genotype testing may offer a reliable pharmacogenetic tool for its potential rescue.

Patients with neuropathy, compared with those without, have higher plasma concentrations, slower hepatic metabolism and longer plasma half-life of perhexiline [113]. A vast majority (80%) of the 20 patients with neuropathy were shown to be PMs or IMs of *CYP2D6* and there were no PMs among the 14 patients without neuropathy [114]. Similarly, PMs were also shown to be at risk of hepatotoxicity [115]. The optimum therapeutic concentration of perhexiline is in the range of 0.15–0.6 mg l^{-1} and these concentrations can be achieved by genotype-specific dosing schedule that has been established, with PMs of *CYP2D6* requiring 10–25 mg daily, EMs requiring 100–250 mg daily and UMs requiring 300–500 mg daily [116]. Populations with very low hydroxy-perhexiline : perhexiline ratios of $\leq$0.3 at steady-state contain those patients who are PMs of CYP2D6 and this approach of identifying at risk patients has been just as effective as

genotyping patients for *CYP2D6* [116, 117]. Pre-treatment phenotyping or genotyping of patients for their CYP2D6 activity and/or their on-treatment therapeutic drug monitoring in Australia have resulted in a dramatic decline in perhexiline-induced hepatotoxicity or neuropathy [118–120]. Eighty-five percent of the world's total usage is at Queen Elizabeth Hospital, Adelaide, Australia. Without actually identifying the centre for obvious reasons, Gardiner & Begg have reported that '*one centre performed CYP2D6 phenotyping frequently (approximately 4200 times in 2003) for perhexiline*' [121]. It seems clear that when the data support the clinical benefits of pre-treatment genetic testing of patients, physicians do test patients.

In contrast to the five drugs discussed earlier, perhexiline illustrates the potential value of pre-treatment phenotyping (or genotyping in absence of CYP2D6 inhibiting drugs) of patients when the drug is metabolized virtually exclusively by a single polymorphic pathway, efficacious concentrations are established and shown to be sufficiently lower than the toxic concentrations, clinical response may not be easy to monitor and the toxic effect appears insidiously over a long period. Thiopurines, discussed below, are another example of similar drugs although their toxic effects are more readily apparent.

Thiopurines

Thiopurines, such as 6-mercaptopurine and its prodrug, azathioprine, are used widely in the treatment of various cancers, organ transplants and auto-immune diseases. Their use is frequently associated with severe myelotoxicity. In haematopoietic tissues, these agents are inactivated by the highly polymorphic thiopurine S-methyltransferase (TPMT). At the normal recommended dose, TPMT-deficient patients develop myelotoxicity by greater production of the cytotoxic end product, 6-thioguanine, generated through the therapeutically relevant alternative metabolic activation pathway.

Following a review of the data available, the FDA labels of 6-mercaptopurine and azathioprine were revised in July 2004 and July 2005, respectively, to describe the pharmacogenetics of, and inter-ethnic differences in, its metabolism. The label goes on to state that patients with intermediate TPMT activity may *be*, and patients with low or absent TPMT activity *are*, at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of azathioprine. The label recommends that consideration should be given to either genotype or phenotype patients for TPMT by commercially available tests.

A recent meta-analysis concluded that compared with non-carriers, heterozygous and homozygous genotypes for low TPMT activity were both associated with leucopenia with an odds ratios of 4.29 (95% CI 2.67 to 6.89) and 20.84 (95% CI 3.42 to 126.89), respectively. Compared with intermediate or normal activity, low TPMT enzymatic activity was significantly associated with myelotoxicity and leucopenia [122]. Although there are conflicting reports on the cost-effectiveness of testing for TPMT, this test is the first pharmacogenetic test that has been incorporated into routine clinical practice. In the UK, TPMT genotyping is not available as part of routine clinical practice. TPMT phenotyping, on the other hand, is available routinely to clinicians and is the most widely used approach to individualizing thiopurine doses [123, 124]. Genotyping for TPMT status is usually undertaken to confirm deficient TPMT status or in patients recently transfused (within 90+ days), patients who have had a previous severe reaction to thiopurine drugs and those with change in TPMT status on repeat testing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline on TPMT testing notes that some of the clinical data on which dosing recommendations are based rely on measures of TPMT phenotype rather than genotype but advocates that because *TPMT* genotype is so strongly linked to TPMT phenotype, the dosing recommendations therein should apply regardless of the method used to assess TPMT status [125]. However, this recommendation fails to recognise that genotype–phenotype mismatch is possible if the patient is in receipt of TPMT inhibiting drugs and it is the phenotype that determines the drug response. Crucially, the important point is that 6-thioguanine mediates not only the myelotoxicity but also the therapeutic efficacy of thiopurines and thus, the risk of myelotoxicity may be intricately linked to the clinical efficacy of thiopurines. In one study, the therapeutic response rate after 4 months of continuous azathioprine therapy was 69% in those patients with below average TPMT activity, and 29% in patients with enzyme activity levels above average [126]. The issue of whether efficacy is compromised as a result of dose reduction in TPMT deficient patients to mitigate the risks of myelotoxicity has not been adequately investigated.

The discussion above on perhexiline and thiopurines is not to suggest that personalized medicine with drugs metabolized by multiple pathways will never be possible. But most drugs in common use are metabolized by more than one pathway and the genome is far more complex than is sometimes believed, with multiple forms of unexpected interactions. Nature has provided compensatory pathways for their elimination when one of the pathways is defective. At present, with the availability of current pharmacogenetic tests that identify (only some of the) variants of only one or two gene products (e.g. AmpliChip for CYP2D6 and CYPC19, Infiniti CYP2C19 assay and Invader UGT1A1 assay), it seems that, pending progress in other fields and until it is possible to do multivariable pathway analysis studies, personalized medicine may enjoy its greatest success in relation to drugs that are metabolized virtually exclusively by a single polymorphic pathway.

Abacavir

We discuss abacavir because it illustrates how personalized therapy with some drugs may be possible without

understanding fully the mechanisms of toxicity or invoking any underlying pharmacogenetic basis. Abacavir, used in the treatment of HIV/AIDS infection, probably represents the best example of personalized medicine. Its use is associated with serious and potentially fatal hypersensitivity reactions (HSR) in about 8% of patients. In early studies, this reaction was reported to be associated with the presence of HLA-B*5701 antigen [127–129]. In a prospective screening of ethnically diverse French HIV patients for HLA-B*5701, the incidence of HSR decreased from 12% before screening to 0% after screening, and the rate of unwarranted interruptions of abacavir therapy decreased from 10.2% to 0.73%. The investigators concluded that the implementation of HLA-B*5701 screening was cost-effective [130].

Following results from a number of studies associating HSR with the presence of the HLA-B*5701 allele, the FDA label was revised in July 2008 to include the following statement:

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue [abacavir] if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Since the above early studies, the strength of this association has been repeatedly confirmed in large studies and the test shown to be highly predictive [131–134]. Although one may question HLA-B*5701 as a pharmacogenetic marker in its classical sense of altering the pharmacological profile of a drug, genotyping patients for the presence of HLA-B*5701 has resulted in:

- Elimination of immunologically confirmed HSR
- Reduction in clinically diagnosed HSR

The test has acceptable sensitivity and specificity across ethnic groups as follows:

- In immunologically confirmed HSR, HLA-B*5701 has a sensitivity of 100% in White as well as in Black patients.
- In clinically suspected HSR, HLA-B*5701 has a sensitivity of 44% in White and 14% in Black patients.
- The specificity in White and Black control subjects was 96% and 99%, respectively

Current clinical guidelines on HIV treatment have been revised to reflect the recommendation that HLA-B*5701 screening be incorporated into routine care of patients who may require abacavir [135, 136]. This is another example of physicians not being averse to pre-treatment genetic testing of patients.

A GWAS has revealed that HLA-B*5701 is also associated strongly with flucloxacillin-induced hepatitis (odds ratio of 80.6; 95% CI 22.8, 284.9) [137]. These empirically found associations of HLA-B*5701 with specific adverse responses to abacavir (HSR) and flucloxacillin (hepatitis) further highlight the limitations of the application of pharmacogenetics (candidate gene association studies) to personalized medicine.

Clinical uptake of genetic testing and payer perspective

Meckley & Neumann have concluded that the promise and hype of personalized medicine has outpaced the supporting evidence and that in order to achieve favourable coverage and reimbursement and to support premium prices for personalized medicine, manufacturers will need to bring better clinical evidence to the marketplace and better establish the value of their products [138]. In contrast, others believe that the slow uptake of pharmacogenetics in clinical practice is partly due to the lack of specific guidelines on how to select drugs and adjust their doses on the basis of the genetic test results [17]. In one large survey of physicians that included cardiologists, oncologists and family physicians, the top reasons for not implementing pharmacogenetic testing were lack of clinical guidelines (60% of 341 respondents), limited provider knowledge or awareness (57%), lack of evidence-based clinical information (53%), cost of tests considered prohibitive (48%), lack of time or resources to educate patients (37%) and results taking too long for a treatment decision (33%) [139]. The CPIC was created to address the need for very specific guidance to clinicians and laboratories so that pharmacogenetic tests, when already available, can be used wisely in the clinic [17].

The label of none of the above drugs explicitly requires (as opposed to recommended) pre-treatment genotyping as a condition for prescribing the drug. In terms of patient preference, in another large survey most respondents expressed interest in pharmacogenetic testing to predict mild or serious side effects (73 $\pm$ 3.29 and 85 $\pm$ 2.91%, respectively), guide dosing (91%) and assist with drug selection (92%) [140]. Thus, the patient preferences are very clear. The payer perspective regarding pre-treatment genotyping can be regarded as an important determinant of, rather than a barrier to, whether pharmacogenetics can be translated into personalized medicine by clinical uptake of pharmacogenetic testing. Warfarin provides an interesting case study.

Although the payers have the most to gain from individually-tailored warfarin therapy by increasing its

effectiveness and reducing expensive bleeding-related hospital admissions, they have insisted on taking a more conservative stance having recognized the limitations and inconsistencies of the available data. The Centres for Medicare and Medicaid Services provide insurance-based reimbursement to the majority of patients in the US. Despite the label change by the FDA, these insurers decided not to pay for the genetic tests, although the cost of the test kit at that time was relatively low at approximately US$500 [141]. An Expert Group on behalf of the American College of Medical Genetics also determined that there was insufficient evidence to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients [142]. The California Technology Assessment Forum also concluded in March 2008 that the evidence has not demonstrated that the use of genetic information changes management in ways that reduce warfarin-induced bleeding events, nor have the studies convincingly demonstrated a large improvement in potential surrogate markers (e.g. aspects of International Normalized Ratio (INR)) for bleeding [143]. Evidence from modelling studies suggests that with costs of US $400 to US $550 for detecting variants of *CYP2C9* and *VKORC1*, genotyping before warfarin initiation will be cost-effective for patients with atrial fibrillation only if it reduces out-of-range INR by more than 5 to 9 percentage points compared with usual care [144]. After reviewing the available data, Johnson *et al*. conclude that (i) the cost of genotype-guided dosing is substantial, (ii) none of the studies to date has shown a cost-benefit of using pharmacogenetic warfarin dosing in clinical practice and (iii) although pharmacogenetics-guided warfarin dosing has been discussed for many years, the currently available data suggest that the case for pharmacogenetics remains unproven for use in clinical warfarin prescription [30].

In an interesting study of payer perspective, Epstein *et al*. reported some interesting findings from their survey [145]. When presented with hypothetical data on a 20% improvement on outcomes, the payers were initially impressed but this interest declined when presented with an absolute reduction of risk of adverse events from 1.2 to 1.0%. Clearly, absolute risk reduction was correctly perceived by many payers as more important than relative risk reduction. Payers were also more concerned with the proportion of patients in terms of efficacy or safety benefits, rather than mean effects in groups of patients. Interestingly enough, they were of the view that if the data were robust enough, the label should state that the test is strongly recommended.

Medico-legal implications of pharmacogenetic information in drug labelling

Consistent with the spirit of legislation, regulatory authorities typically approve drugs on the basis of population-based pre-approval data and are reluctant to approve drugs on the basis of efficacy as evidenced by subgroup analysis. The use of some drugs requires the patient to carry specific pre-determined markers associated with efficacy (e.g. being ER+ for treatment with tamoxifen discussed above). Although safety in a subgroup is important for non-approval of a drug, or contraindicating it in a subpopulation perceived to be at serious risk, the issue is how this population at risk is identified and how robust is the evidence of risk in that population. Pre-approval clinical trials rarely, if ever, provide sufficient data on safety issues related to pharmacogenetic factors and usually, the subgroup at risk is identified by references to age, gender, previous medical or family history, co-medications or specific laboratory abnormalities, supported by reliable pharmacological or clinical data. In turn, the patients have legitimate expectations that the physician will test for, or exclude, the presence of a marker of risk or non-response, and as a result, meaningfully discuss treatment options. Prescribing information generally includes various scenarios or variables that may impact on the safe and effective use of the product, for example, dosing schedules in special populations, contraindications and warning and precautions during use. Deviations from these by the physician are likely to attract malpractice litigation if there are adverse consequences as a result.

In order to refine further the safety, efficacy and risk : benefit of a drug during its post approval period, regulatory authorities have now begun to include pharmacogenetic information in the label. It should be noted that if a drug is indicated, contraindicated or requires adjustment of its initial starting dose in a particular genotype or phenotype, pre-treatment testing of the patient becomes *de facto* mandatory, even if this may not be explicitly stated in the label. In this context, there is a serious public health issue if the genotype-outcome association data are less than adequate and therefore, the predictive value of the genetic test is also poor. This is usually the case when there are other enzymes also involved in the disposition of the drug (multiple genes with small effect each). In contrast, the predictive value of a test (focussing on even one specific marker) is expected to be high when a single metabolic pathway or marker is the sole determinant of outcome (equivalent to monogeneic disease susceptibility) (single gene with large effect). Since most of the pharmacogenetic information in drug labels concerns associations between polymorphic drug metabolizing enzymes and safety or efficacy outcomes of the corresponding drug [10–12, 14], this may be an opportune moment to reflect on the medico-legal implications of the labelled information. There are very few publications that address the medico-legal implications of (i) pharmacogenetic information in drug labels and (ii) application of pharmacogenetics to personalize medicine in routine clinical medicine. We draw heavily on the thoughtful and detailed commentaries by Evans [146, 147] and by

Marchant *et al*. [148] that deal with these complex issues and add our own perspectives.

Tort suits include product liability suits against manufacturers and negligence suits against physicians and other providers of health-related services [146]. When it comes to product liability or clinical negligence, prescribing information of the product concerned assumes considerable legal significance in determining whether (i) the marketing authorization holder acted responsibly in developing the drug and diligently in communicating newly emerging safety or efficacy data through the prescribing information or (ii) the physician acted with due care.

Manufacturers can only be sued for risks that they fail to disclose in labelling. Therefore, the manufacturers usually comply if regulatory authority requests them to include pharmacogenetic information in the label. They may find themselves in a difficult position if not satisfied with the veracity of the data that underpin such a request. However, as long as the manufacturer includes in the product labelling the risk or the information requested by authorities, the liability subsequently shifts to the physicians.

Against the background of high expectations of personalized medicine, inclusion of pharmacogenetic information in the label places the physician in a dilemma, especially when, to all intent and purposes, reliable evidence-based information on genotype-related dosing schedules from adequate clinical trials is non-existent. Although all involved in the personalized medicine 'promotion chain', including the manufacturers of test kits, may be at risk of litigation, the prescribing physician is at the greatest risk [148]. This is especially the case if drug labelling is accepted as providing recommendations for normal or accepted standards of care. In this setting, the outcome of a malpractice suit may well be determined by considerations of how reasonable physicians *should* act rather than how most physicians *actually* act. If this were not the case, all concerned (including the patient) must question the purpose of including pharmacogenetic information in the label.

Consideration of what constitutes an appropriate standard of care may be heavily influenced by the label if the pharmacogenetic information was particularly highlighted, such as the boxed warning in clopidogrel label. Guidelines from expert bodies such as the CPIC may also assume considerable significance, although it is uncertain how much one can rely on these guidelines. Interestingly enough, the CPIC has found it necessary to distance itself from any 're*sponsibility for any injury or damage to persons or property arising out of or related to any use of its guidelines, or for any errors or omissions*.' These guidelines also include a broad disclaimer that they are limited in scope and do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. These guidelines emphasise that it remains the responsibility of the health care provider to determine the best course of treatment for a patient and that adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. Such all-encompassing broad disclaimers cannot possibly be conducive to achieving their desired goals.

Another issue is whether pharmacogenetic information is included to promote efficacy by identifying non-responders or to promote safety by identifying those at risk of harm; the risk of litigation for these two scenarios may differ markedly. Under the current practice, drug-related injuries are, but efficacy failures generally are not, compensable [146]. However, even in terms of efficacy, one need not look beyond trastuzumab (Herceptin®) to consider the fallout. Denying this drug to many patients with breast cancer has attracted a number of legal challenges with successful outcomes in favour of the patient. The same may apply to other drugs if a patient, with an allegedly non-responder genotype, is prepared to take that drug because the genotype-based predictions lack the required sensitivity and specificity. This is especially important if either there is no alternative drug available or the drug concerned is devoid of a safety risk associated with the available alternative. When a disease is progressive, serious or potentially fatal if left untreated, failure of efficacy is in itself a safety issue. Evidently, there is only a small risk of being sued if a drug demanded by the patient proves ineffective but there is a greater perceived risk of being sued by a patient whose condition worsens after a treatment, strongly desired by the patient, has been withheld [146].

When it comes to safety, the risk of liability is even greater and it seems that the physician may be at risk regardless of whether he genotypes the patient or not. For a successful litigation against a physician, the patient will be required to prove that (i) the physician had a duty of care to him, (ii) the physician breached that duty, (iii) the patient incurred an injury and that (iv) the physician's breach caused the patient's injury [148]. The burden to prove this may be greatly reduced if the genetic information is specially highlighted in the label. Risk of litigation is self evident if the physician chooses not to genotype a patient potentially at risk. Under the pressure of genotype-related litigation, it may be easy to lose sight of the fact that inter-individual differences in susceptibility to adverse side effects from drugs arise from a vast array of non-genetic factors such as age, gender, hepatic and renal status, nutrition, smoking and alcohol intake and drug–drug interactions. Notwithstanding, a patient with a relevant genetic variant (the presence of which needs to be demonstrated), who was not tested and reacted adversely to a drug, may have a viable lawsuit against the prescribing physician [148]. If, on the other hand, the physician chooses to genotype the patient who agrees to be genotyped, the potential risk of litigation may not be much lower. Despite the 'negative' test and fully complying with all the clinical warnings and precautions, the occurrence of a serious side effect that was intended to be mitigated must surely concern the patient, especially if the side effect was asso-

ciated with hospitalization and/or long term financial or physical hardships. The argument here would be that the patient may have declined the drug had he known that despite the 'negative' test, there was still a likelihood of the risk. In this setting, it may be interesting to contemplate who the liable party is. Ideally, therefore, a 100% level of success in genotype–phenotype association studies is what physicians require for personalized medicine or individualized drug therapy to be successful [149].

There is an additional dimension to genotype-based prescribing that has received little attention, in which the risk of litigation may be indefinite. Consider an EM patient (the majority of the population) who has been stabilized on a relatively safe and effective dose of a medication for chronic use. The risk of injury and liability may change dramatically if the patient was at some future date prescribed an inhibitor of the enzyme responsible for metabolizing the drug concerned, converting the patient with EM genotype into one of PM phenotype (phenoconversion). Drug–drug interactions are genotype-dependent and only patients with IM and EM genotypes are susceptible to inhibition of drug metabolizing activity whereas those with PM or UM genotype are relatively immune. Many drugs switched to availability over-the-counter are also known to be inhibitors of drug elimination (e.g. inhibition of renal *OCT2*-encoded cation transporter by cimetidine, CYP2C19 by omeprazole and CYP2D6 by diphenhydramine, a structural analogue of fluoxetine).

Risk of litigation may also arise from issues related to informed consent and communication [148]. Physicians may be held to be negligent if they fail to inform the patient about the availability of pharmacogenetic tests, the results of which could have influenced the patient in determining his treatment options and choice. In the context of the implications of a genetic test and informed consent, the patient would also have to be informed of the consequences of the results of the test (anxieties of developing any potentially genotype-related diseases or implications for insurance cover). Different jurisdictions may take different views but physicians may also be held to be negligent if they fail to inform the patients' close relatives that they may share the 'at risk' trait. This later issue is intricately linked with data protection and confidentiality legislation. However, in the US, at least two courts have held physicians responsible for failing to tell patients' relatives that they may share a risk-conferring mutation with the patient, even in situations in which neither the physician nor the patient has a relationship with those relatives [148].

Challenges facing personalized medicine

Promotion of personalized medicine needs to be tempered by the known epidemiology of drug safety. Some important data concerning those ADRs that have the greatest clinical impact are lacking. These include (i) lack of data on what proportion of ADRs in the wider community is primarily due to genetic susceptibility, (ii) lack of an understanding of the mechanisms that underpin many ADRs and (iii) the presence of an intricate relationship between safety and efficacy such that it may not be possible to improve on safety without a corresponding loss of efficacy. This is generally the case for drugs where the ADR is an undesirable exaggeration of a desired pharmacologic effect (warfarin and bleeding) or an off-target effect related to the primary pharmacology of the drug (e.g. myelotoxicity after irinotecan and thiopurines).

Limitations of pharmacokinetic genetic tests

Understandably, the current focus on translating pharmacogenetics into personalized medicine has been mainly in the area of genetically-mediated variability in pharmacokinetics of a drug. Frequently, frustrations have been expressed that the clinicians have been slow to exploit pharmacogenetic information to improve patient care. Poor education and/or awareness among clinicians are advanced as potential explanations for poor uptake of pharmacogenetic testing in clinical medicine [111, 150, 151]. However, given the complexity and the inconsistency of the data reviewed above, it is easy to understand why clinicians are at present reluctant to embrace pharmacogenetics. Evidence suggests that for most drugs, pharmacokinetic differences do not necessarily translate into differences in clinical outcomes, unless there is close concentration–response relationship, inter-genotype difference is large and the drug concerned has a narrow therapeutic index. Drugs with large inter-genotype differences are typically those that are metabolized by one single pathway with no dormant alternative routes. When multiple genes are involved, each single gene usually has a small effect in terms of pharmacokinetics and/or drug response. Often, as illustrated by warfarin, even the combined effect of all the genes involved does not fully account for a sufficient proportion of the known variability.

Since the pharmacokinetic profile (dose–concentration relationship) of a drug is usually influenced by many factors (see below) and drug response also depends on variability in responsiveness of the pharmacological target (concentration–response relationship), the challenges to personalized medicine which is based almost exclusively on genetically-determined changes in pharmacokinetics are self-evident. Therefore, there was considerable optimism that personalized medicine based on pharmacodynamic pharmacogenetics may have better prospects of success than that based on pharmacokinetic pharmacogenetics alone. In broad terms, studies on pharmacodynamic polymorphisms have aimed at investigating whether the presence of a variant is associated with (i) susceptibility to and severity of the related diseases and/or (ii) modification of the clinical response to a drug. The three most widely investigated pharmacological targets in this respect are the variations in the genes encoding for promoter region

of the serotonin transporter *(SLC6A4)* for antidepressant therapy with selective serotonin re-uptake inhibitors, potassium channels (*KCNH2, KCNE1, KCNE2* and *KCNQ1*) for drug-induced QT interval prolongation and β-adrenoreceptors (*ADRB1* and *ADRB2*) for the treatment of heart failure with β-adrenoceptor blockers. Unfortunately, the data available at present, although still limited, does not support the optimism that pharmacodynamic pharmacogenetics may fare any better than pharmacokinetic pharmacogenetics.

Role of non-genetic factors in drug safety

A number of non-genetic age and gender-related factors may also influence drug disposition, regardless of the genotype of the patient and ADRs are frequently caused by the presence of non-genetic factors that alter the pharmacokinetics or pharmacodynamics of a drug, such as diet, social habits and renal or hepatic dysfunction. The role of these factors is sufficiently well characterized that all new drugs require investigation of the influence of these factors on their pharmacokinetics and risks associated with them in clinical use. Where appropriate, the labels include contraindications, dose adjustments and precautions during use. Even taking a drug in the presence or absence of food in the stomach can result in marked increase or decrease in plasma concentrations of certain drugs and potentially trigger an ADR or loss of efficacy. Account also needs to be taken of the interesting observation that serious ADRs such as torsades de pointes or hepatotoxicity are much more frequent in females whereas rhabdomyolysis is more frequent in males [152–155], although there is no evidence at present to suggest gender-specific differences in genotypes of drug metabolizing enzymes or pharmacological targets.

Ethnicity and influence of minor allele frequency

Ethnic differences in allele frequency often mean that genotype–phenotype correlations cannot be easily extrapolated from one population to another. In multiethnic societies where genetic admixture is increasingly becoming the norm, the predictive values of pharmacogenetic tests will come under greater scrutiny. Limdi *et al*. have explained inter-ethnic difference in the impact of *VKORC1* polymorphism on warfarin dose requirements by population differences in minor allele frequency [46]. For example, Shahin *et al*. have reported data that suggest that minor allele frequencies among Egyptians cannot be assumed to be close to a specific continental population [44]. As stated earlier, novel SNPs in *VKORC1* and *CYP2C9* that significantly affect warfarin dose in African Americans have been identified [47]. Also, as discussed earlier, the *CYP2D6*10* allele has been reported to be of greater significance in Oriental populations when considering tamoxifen pharmacogenetics [84, 85] whereas the *UGT1A1*6* allele has now been shown to be of greater relevance for the severe toxicity of irinotecan in the Japanese population [101]. Although a specific genotype will predict similar dose requirements across different ethnic groups, future pharmacogenetic studies will have to address the potential for inter-ethnic differences in genotype-phenotype association arising from influences of differences in minor allele frequencies. For example, in Italians and Asians, approximately 7% and 11%, respectively, of the warfarin dose variation was explained by V433M variant of *CYP4F2* [41, 42] whereas in Egyptians, *CYP4F2* (V33M) polymorphism was not significant despite its high frequency (42%) [44].

Drug-induced phenoconversion as a major complicating factor

Perhaps, drug interactions pose the greatest challenge to any potential success of personalized medicine. Co-administration of a drug that inhibits a drug-metabolizing enzyme mimics a genetic deficiency of that enzyme, thus converting an EM genotype into a PM phenotype and intricately linking the success of pharmacogenetics in personalizing medicine to the burden of drug interactions. In this context, it is not only the prescription drugs that matter, but also over-the-counter drugs and herbal remedies. Arising from the presence of transporters at various interfaces, drug interactions can influence absorption, distribution and hepatic or renal excretion of drugs. These interactions would mitigate any benefits of genotype-based therapy, especially if there is genotype–phenotype mismatch. Even the successful genotype-based personalized therapy with perhexiline has on rare occasions run into problems associated with drug interactions. There are reports of three cases of drug interactions with perhexiline with paroxetine, fluoxetine and citalopram, resulting in raised perhexiline concentrations and/or symptomatic perhexiline toxicity [156, 157]. According to the data reported by Klein *et al*., co-administration of amiodarone, an inhibitor of CYP2C9, can reduce the weekly maintenance dose of warfarin by as much as 20–35%, depending on the genotype of the patient [31].

Not surprisingly, drug–drug, drug–herb and drug–disease interactions continue to pose a major challenge not only in terms of drug safety generally but also personalized medicine specifically. Clinically important drug–drug interactions that are associated with impaired bioactivation of prodrugs appear to be more easily neglected in clinical practice compared with drugs not requiring bioactivation [158]. Given that *CYP2D6* features so prominently in drug labels, it must be a matter of concern that in one study, 39 (8%) of the 461 patients receiving fluoxetine and/or paroxetine (converting a genotypic EM into a phenotypic PM) were also receiving a CYP2D6 substrate/drug with a narrow therapeutic index [159].

Conclusions

When multiple markers are potentially involved, association of an outcome with combination of different

polymorphisms (haplotypes) rather than a single polymorphism has a greater chance of success. For example, it seems that for warfarin, a combination of *CYP2C9*3/*3* and *VKORC1* A1639A genotypes is generally associated with a very low dose requirement but only approximately 1 in 600 patients in the UK will have this genotype, making it difficult to assess this association in any large clinical trial. Study population and phenotypes of toxicity should be better defined and correct comparisons should be made to study the strength of the genotype–phenotype associations, bearing in mind the complications arising from phenoconversion.

Careful scrutiny by expert bodies of the data relied on to support the inclusion of pharmacogenetic information in the drug labels has often revealed this information to be premature and in sharp contrast to the high quality data typically required from the sponsors from well-designed clinical trials to support their claims concerning efficacy, lack of drug interactions or improved safety. Available data also support the view that the use of pharmacogenetic markers may improve overall population-based risk : benefit of some drugs by decreasing the number of patients experiencing toxicity and/or increasing the number who benefit. However, most pharmacokinetic genetic markers included in the label do not have sufficient positive and negative predictive values to enable improvement in risk- : benefit of therapy at the individual patient level. Given the potential risks of litigation, labelling should be more cautious in describing what to expect. Advertising the availability of a pharmacogenetic test in the labelling is counter to this wisdom. Furthermore, personalized therapy may not be possible for all drugs or at all times. Instead of fuelling their unrealistic expectations, the public should be adequately educated on the prospects of personalized medicine until future adequately powered studies provide conclusive evidence one way or the other.

This review is not intended to suggest that personalized medicine is not an attainable goal. Rather, it highlights the complexity of the subject, even before one considers genetically-determined variability in the responsiveness of the pharmacological targets and the influence of minor frequency alleles. With increasing advances in science and technology and better understanding of the complex mechanisms that underpin drug response, personalized medicine may become a reality one day but these are very early days and we are no where near achieving that goal. For some drugs, the role of non-genetic factors may be so important that for these drugs, it may not be possible to personalize therapy. Overall review of the available data suggests a need (i) to subdue the current exuberance in how personalized medicine is promoted without much regard to the available data, (ii) to impart a sense of realism to the expectations and limitations of personalized medicine and (iii) to emphasize that pre-treatment genotyping is anticipated simply to improve risk : benefit at individual level without expecting to eliminate risks completely. The Royal Society report entitled 'Personalized medicines: hopes and realities' summarized the position in September 2005 by concluding that pharmacogenetics is unlikely to revolutionize or personalize medical practice in the immediate future [9]. Seven years after that report, the statement remains as true today as it was then. In their review of progress in pharmacogenetics and pharmacogenomics, Nebert *et al*. also believe that 'individualized drug therapy is impossible now, or in the foreseeable future' [160]. They conclude 'From all that has been discussed above, it should be clear by now that drawing a conclusion from a study of 200 or 1000 patients is one thing; drawing a conclusion from a DNA test on an individual patient walking into your office is quite another.' The reader is urged to read a recent editorial by Nebert [149].

The promotion of personalized medicine should emphasize five key messages; namely, (i) all drugs have toxicity and beneficial effects which are their intrinsic properties, (ii) pharmacogenetic testing can only improve the likelihood, but without the guarantee, of a beneficial outcome in terms of safety and/or efficacy, (iii) determining a patient's genotype may reduce the time required to identify the correct drug and its dose and minimize exposure to potentially ineffective medicines, (iv) application of pharmacogenetics to clinical medicine may improve population-based risk : benefit ratio of a drug (societal benefit) but improvement in risk : benefit at the individual patient level cannot be guaranteed and (v) the notion of right drug at the right dose the first time on flashing a plastic card is nothing more than a fantasy.

Contributions by the authors

This review is partially based on sections of a dissertation submitted by DRS in 2009 to the University of Surrey, Guildford for the award of the degree of MSc in Pharmaceutical Medicine. RRS wrote the first draft and DRS contributed equally to subsequent revisions and referencing.

Competing Interests

The authors have not received any financial support for writing this review. RRS was formerly a Senior Clinical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), London, UK, and now provides expert consultancy services on the development of new drugs to a number of pharmaceutical companies. DRS is a final year medical student and has no conflicts of interest.

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