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The impact of pharmacogenetics and pharmacogenomics

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Abstract

Pharmacogenetics is widely proclaimed as about to revolutionise the face of medicine. In a more realistic assessment, the implementation of molecular genetics and biology will continue to provide, as it has done already, better ways to diagnose and treat illnesses, but it will do so at a steady and evolutionary pace based on an improved understanding of the nature of disease, allowing more specific treatments, better risk prediction, and the implementation of preventive strategies. As such, future progress in biomedicine will travel the same well-trodden paths of improved differential diagnosis and risk prediction along which it has advanced over the past decades and centuries. So, while meaningful biomedical research today depends, by and large, on the use of the newly developed tools of genetics and genomics, and the insights gained through them, it is unlikely to fundamentally change the direction of medical progress.

INTRODUCTION

The advances made over the past 30 years in molecular biology, molecular genetics and genomics, and the development and refinement of associated methods and technologies, have had a major impact on our understanding of biology, including the action of drugs and other biologically active xenobiotics. The tools that have been developed to allow these advances, and the knowledge of fundamental principles underlying cellular function thus derived, have become quintessential and indeed indispensable for all areas of biological research, including future progress in biomedicine and healthcare.

It is important to realise that – with regard to pharmacology and drug discovery – these accomplishments have led gradually, and starting sometime in the last third or quarter of the last century, to a rather fundamental shift from the ‘chemical paradigm’ to a ‘biological paradigm’. Previously, medicinal chemistry drove new developments in drug discovery, with biology almost an ancillary service that examined new molecules for biological function. Now,

biology, based on a new-found understanding of physiological effects of biomolecules and pathways, has now taken the lead, requesting from the chemist compounds that modulate the function of these biomolecules or pathways, with a – at least theoretically – predictable functional impact in the setting of integrated physiology.

One particular aspect from the broad scope across which progress in biology has been achieved, namely our understanding of genetics, and, especially, our cataloguing of genome sequences, has uniquely captured the imagination of both scientists and the public. Although understandable given the austere beauty of Mendel's laws, the compelling aesthetics of the double helix structure, and the awe-inspiring accomplishment – coupled with an unprecedented public relations campaign – of the Human Genome Project, the public excitement about genetics and genomics, and the high expectations regarding the impact they will have on the practice of health care, are almost certainly unrealistic. Thus, at the interface between genetics/

genomics and pharmacology, pharmacogenetics and pharmacogenomics (usually in the most loosely defined terms) are commonly touted as heralding a 'revolution' in medicine, yet as soon as one begins to probe more carefully, little substance is yet to be found to support these enthusiastic claims.

Indeed, as pointed out above, the major change in how we discover drugs – from the chemical to the biological paradigm – occurred some time ago. What the current advances, in due time, will allow us to do is to move from a physiology-based to a (molecular) pathology-based approach towards drug discovery, promising the advancement from a largely palliative to a more cause/contribution-targeting pharmacopoeia.

This paper is intended to provide a necessarily somewhat subjective view of what the disciplines of genetics and genomics stand to contribute – and how they have actually contributed for many years – to drug discovery and development, and more broadly to the practice of healthcare. Particular emphasis will be placed on examining the role of genetics – acquired or inherited variations at the level of DNA-encoded information – in 'real life', ie with regard to common complex disease; a realistic understanding of this role is absolutely essential for a balanced assessment of the impact of 'genetics' on healthcare in the future. Definitions for some of the terms that are in wide and often unreflected use today – almost always sorely missing from both academic and public policy-related documents on the topic – will be provided, with an understanding that much of the field is still in flux, and that these may well change. Particular emphasis will be given to pharmacogenetics, where a more systematic classification than generally found will be attempted. It is important to remain mindful that what will be discussed is – to a large extent – still uncharted territory, so by necessity many of the positions taken, reasoned on today's understanding and knowledge, must be

viewed as somewhat speculative in nature. Where appropriate and possible, select examples will be provided, although it should be pointed out that much of the literature in the area of genetic epidemiology and pharmacogenetics lacks the stringent standards normally applied to peer-reviewed research, and replicate data are generally absent.

DEFINITION OF TERMS

There is widespread indiscriminate use of, and thus confusion about, the terms 'pharmacogenetics' and 'pharmacogenomics'. While no universally accepted definition exists, there is an emerging consensus on the differential meaning and use of the two terms (see Table 1).

Pharmacogenetics

The term '-genetics' relates etymologically to the presence of individual properties, and inter-individual differences in these properties, as a consequence of having inherited (or acquired) them. Thus, the term 'pharmacogenetics' describes the interactions between a drug and the characteristics of an individual (or perhaps more accurately groups of individuals) as they relate to differences in the DNA-based information. Pharmacogenetics, therefore, refers to the assessment of clinical efficacy and/or the safety and tolerability profile – the pharmacological, or response-phenotype – of a drug in groups of individuals that differ with regard to certain DNA-encoded characteristics. It tests the hypothesis that these differences – if indeed associated with a differential response-phenotype – may allow prediction of individual drug response. The DNA-encoded characteristics are most commonly assessed based on the presence or absence of polymorphisms at the level of the nuclear DNA, but may be assessed at different levels where such DNA variation translates into different characteristics, such as differential mRNA expression or splicing, protein levels or functional

Pharmacogenetics will lead to improved cause-targeted pharmacopoeia

Pharmacogenetics defined

Table I: Terminology

Pharmacogenetics • Differential effects of a drug – <i>in vivo</i> – in different patients, dependent on the presence of inherited gene variants. • Assessed primarily genetic (SNP) and genomic (expression) approaches. • A concept to provide more patient/disease-specific healthcare. • One drug, many genomes (ie different patients). • Focus: patient variability.
Pharmacogenomics • Differential effects of compounds – <i>in vivo</i> or <i>in vitro</i> – on gene expression, among the entirety of expressed genes. • Assessed by expression profiling. • A tool for compound selection/drug discovery. • Many 'drugs' (ie early-stage compounds), one genome (ie 'normative' genome [database, technology platform]). • Focus: compound variability.

characteristics, or even physiological phenotypes – all of which would be seen as surrogate, or more integrated, markers of the underlying genetic variant. (It should be noted that some authors continue to subsume all applications of expression profiling under the term 'pharmacogenomics', in a definition of the terms that is more driven by the technology used rather than by functional context.)

Pharmacogenomics

In contrast, the terms 'pharmacogenomics' and its close relative 'toxicogenomics' are etymologically linked to 'genomics', the study of the genome and of the entirety of expressed and non-expressed genes in any given physiological state. These two fields of study are concerned with a comprehensive, genome-wide assessment of the effects of pharmacological agents, including toxins/toxicants on gene expression patterns. Pharmacogenomic studies are thus used to evaluate the differential effects of a number of chemical compounds – in the process of drug discovery commonly applied to lead selection – with regard to inducing or suppressing the expression of transcription of genes in an experimental setting. Except for situations in which pharmacogenetic considerations are

'front-loaded' into the discovery process, inter-individual variations in gene sequence are not usually taken into account in this process. In contrast to pharmacogenetics, pharmacogenomics therefore does not focus on differences among individuals with regard to the drug's effects, but rather examines differences among several (prospective) drugs or compounds with regard to their biological effects using a 'generic' set of expressed or non-expressed genes. The bases of comparison are quantitative measures of expression, using a number of more-or-less comprehensive gene expression profiling methods, commonly based on microarray formats. By extrapolation from the experimental results to – theoretically – desirable patterns of activation or inactivation of expression of genes in the setting of integrative pathophysiology this approach is hoped to provide a faster, more comprehensive, and perhaps even more reliable way to assess the likelihood of finding an ultimately successful drug than previously available schemes involving mostly *in vivo* animal experimentation.

Thus, although both pharmacogenetics and pharmacogenomics refer to the evaluation of drug effects using (primarily) nucleic acid markers and technology, the directionalities of their approaches are distinctly different: pharmacogenetics represents the study of *differences among a number of individuals with regard to clinical response to a particular drug* ('one drug, many genomes'), whereas pharmacogenomics represents the study of *differences among a number of compounds with regard to gene expression response in a single (normative) genome/expressome* ('many drugs, one genome'). Accordingly, the fields of intended use are distinct: the former will help in the clinical setting to find the medicine most likely to be optimal for a patient (or the patients most likely to respond to a drug), the latter will aid in the setting of pharmaceutical research to find the 'best' drug candidate from a given series of compounds under evaluation.

Pharmacogenomics defined

PHARMACOGENOMICS: FINDING NEW MEDICINES QUICKER AND MORE EFFICIENTLY

Once a screen (assay) has been set up in a drug discovery project, and lead compounds are identified, the major task becomes the identification of an optimised clinical candidate molecule among the many compounds synthesised by medicinal chemists. Conventionally, such compounds are screened in a number of animal or cell models for efficacy and toxicity, experiments that – while having the advantage of being conducted in the *in vivo* setting – commonly take significant amounts of time and depend entirely on the similarity between the experimental animal condition/setting and its human counterpart, ie the validity of the model.

Although such experiments will never be entirely replaced by expression profiling on either the nucleic acid (genomics) or the protein (proteomics) level, this technique offers powerful advantages and complementary information. First, efficacy and profile of induced changes can be assessed in a comprehensive fashion (within the limitations – primarily sensitivity and completeness of transcript representation – of the technology platform used). Second, these assessments of differential efficacy can be carried out much more expeditiously than in conventionally used, (patho-) physiology-based animal models. Third, the complex pattern of expression changes revealed by such experiments may provide new insights into possible biological interactions between the actual drug target and other biomolecules, and thus reveal new elements, or branch-points, of a biological pathway that may be useful as surrogate markers, novel diagnostic analytes or additional drug targets. Fourth, increasingly important, these tools serve to determine specificity of action among members of gene families that may be highly important for both efficacy and safety of a new drug. It must

be borne in mind that any and all such experiments are limited by the coefficient of correlation with which the expression patterns determined are linked to the desired *in vivo* physiological action of the compound.

A word of caution regarding microarray-based expression profiling: the power of comprehensive (almost) genome-wide assessment of expression patterns has led to what may justly be described as somewhat of an infatuation with this technology that at times leaves a certain degree of critical scepticism to be desired. In particular, the pairwise comparison algorithms used in much of this work (competition staining of a case and a control sample on the same physical array) raise a number of questions regarding selection bias which take on particular significance since the overall sample sizes are commonly (very) small. Biostatistical analytical approaches are commonly less than sophisticated, if used at all. Additionally, it is important to remain aware of the fact that all microarray expression data are of only associative character, and must be interpreted mindful of this limitation.

As a subcategory of this approach, toxicogenomics is increasingly evolving as a powerful adjuvant to classic toxicological testing. As pertinent databases are being created from experiments with known toxicants, revealing expression patterns that may potentially be predictive of longer-term toxic liabilities of compounds, future drug discovery efforts should benefit by insights allowing earlier 'killing' of compounds likely to cause such complications.

When using these approaches in drug discovery – even if implemented with proper biostatistics and analytical rigour – it is imperative to understand the probabilistic nature of such experiments: a promising profile on pharmacogenomic and toxicogenomic screens will enhance the likelihood of having selected an ultimately successful compound, and will

Conventional screening methods for drug candidates are expensive and depend on the validity of the model

Expression profiling and proteomics will complement and enhance traditional screening methods

Novel surrogate markers, diagnostic analytes and drug targets may also be revealed with pharmacogenomics techniques

A reduction in the number of animal experiments

achieve this goal quicker than conventional animal experimentation, but will do so only with a certain likelihood of success. The less reductionist approach of the animal experiment will still be needed. It is to be anticipated, however, that such approaches will constitute an important time- and resource-saving first evaluation or screening step, which will help to focus and reduce the number of animal experiments that will ultimately need to be conducted.

**PHARMACOGENETICS:
MORE TARGETED, MORE
EFFECTIVE MEDICINES
Genes and environment**

It is common knowledge that today's pharmacopea – in as much as it represents enormous progress compared with what our physicians had only 15 or 20 years ago – is far from perfect. Many people respond only partially, or fail to respond altogether, to the drugs they are given, and others suffer adverse events that range from unpleasant to serious and life threatening.

Complex diseases are multifactorial

There is an emerging consensus that all common complex diseases (ie the health problems that are by far the main contributors to society's disease burden as well as to public and private health spending) are 'multifactorial' in nature, ie that they are brought upon by the coincidence of certain intrinsic (inborn or acquired) predispositions and susceptibilities on the one hand, and extrinsic, environment-derived influences on the other, with the relative importance of these two influences varying across a broad spectrum. In some diseases external factors appear to be more important, while in others intrinsic predispositions prevail. In almost all cases, a number of both intrinsic (genetic) as well as extrinsic factors appear to contribute, although it is not clear from the currently available literature how much this reflects the requirement of several intrinsic and extrinsic factors to coincide in any one individual, or how much this reflects the causative heterogeneity of each of today's

Intrinsic variation to drug response may be predicted more easily with pharmacogenetics

conventional, clinical diagnoses – a fact for which there is similar consensus. In either case, the disease-causing (or better: disease-contributing) role that intrinsic, genetically encoded properties play with regard to the occurrence of the disease is fundamentally different in these common, complex diseases from those in the classic, monogenic, 'Mendelian' diseases. While in the latter the impact of the genetic variant is typically categorical in nature, ie deterministic, in the former case the presence of a disease-associated genetic variant is merely of probabilistic influence, raising (or lowering) the likelihood of disease occurrence to some extent, but never predicting it in a black-and-white fashion.

If we regard a pharmacological agent as an extrinsic, environmental factor with a potential to affect the health status of the individual to whom it is administered, then individually differing responses to such an agent would – under the paradigm just elaborated upon – be expected to be based on differences regarding the 'intrinsic' characteristics of these patients, as long as we can exclude variation in the exposure to the drug. This is important, as in clinical practice non-adherence to prescribed regimens of administration, or drug-drug interactions interfering with bioavailability of the drug, are perhaps the most likely culprits when such differences in response-phenotype are observed. The influence of such intrinsic variation on drug response may be predicted to be more easily recognisable, and more relevant the steeper the dose-response curve of a given drug is. The argument for the greater likelihood of observing environmental factor/gene interactions with drugs as compared with, say, foodstuffs, goes along the same lines.

Clearly, a better, more fundamental and mechanistic understanding of the molecular pathology of disease in general and of the role of intrinsic, biological properties regarding the predisposition to contract such diseases, as well as of drug action on the molecular level, will be

essential for future progress in healthcare. Current progress in molecular biology and genetics has indeed provided us with some of the prerequisite tools that should help us reach the goal of such a more refined understanding.

An attempt at a systematic classification of pharmacogenetics

Two conceptually quite different scenarios of inter-individually differential drug response may be distinguished on the basis of the underlying biological variance (see Table 2):

- In the first case, the underlying biological variation is *in itself not disease-causing* or disease-contributing, and becomes clinically relevant *only* in response to the exposure to the drug in question ('classical pharmacogenetics').
- In the second case, the biological variation is *directly disease-related*, is *per se* of pathological importance, and represents a subgroup of the overall clinical disease/diagnostic entity. The differential response to a drug is thus related to how well this drug addresses, or is matched to, the presence or relative importance of the pathomechanism it targets, in different patients, ie the 'molecular differential diagnosis' of the patient ('disease

mechanism-related pharmacogenetics').

Although these two scenarios are conceptually rather different, they result in similar practical consequences with regard to the administration of a drug, namely stratification based on a particular, DNA-encoded marker. It seems therefore legitimate to subsume both under the umbrella of 'pharmacogenetics'.

'Classical pharmacogenetics'

This category includes differential *pharmacokinetics* and *pharmacodynamics*.

Pharmacokinetic effects are due to inter-individual differences in absorption, distribution, metabolism (with regard to both activation of pro-drugs, inactivation of the active molecule, and generation of derivative molecules with biological activity) or excretion of the drug. In any of these cases, differential effects observed are due to the presence at the intended site of action either of inappropriate concentrations of the pharmaceutical agent, or of inappropriate metabolites, or of both, resulting either in lack of efficacy or toxic effects. Pharmacogenetics, as it relates to pharmacokinetics, has been recognised as an entity for more than 100 years, going back to the observation, commonly credited to Archibald Garrod, that a subset of psychiatric patients treated with the hypnotic sulphonal developed porphyria. We have since then come to understand the underlying genetic causes for many of the previously known differences in enzymatic activity, most prominently with regard to the P450 enzyme family, and these have been the subject of recent reviews (Table 3).^{1,2} However, such pharmacokinetic effects are also seen with membrane transporters, such as in the case of differential activity of genetic variants of MDR-1 that affects the effective intracellular concentration of antiretrovirals,³ or of the purine analogue-metabolising enzyme, thiomethyl-purine-transferase.⁴

Notably, despite the widespread recognition of isoenzymes with

Table 2: Pharmacogenetics systematic classification

'Classical' pharmacogenetics Pharmacokinetics • Absorption • Metabolism – Activation of prodrugs – De-activation – Generation of biologically active metabolites • Distribution • Elimination Pharmacodynamics Palliative drug action (modulation of disease-symptoms or disease-signs by targeting physiologically relevant systems, without addressing those mechanism that cause or causally contribute to the disease) 'Molecular differential-diagnosis-related' pharmacogenetics Causative drug action (modulation of actual causative or contributory mechanisms)
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Table 3: Pharmacogenetics; chronology and systematics

Pharmacogenetic phenotype	Described	Underlying gene/mutation	Identified
Sulphonal-porphyria	ca. 1890	Porphobilinogen-deaminase?	1985
Suxamethonium-hypersensitivity	1957–60	Pseudocholinesterase	1990–92
Primaquin hypersensitivity; favism	1958	G-6-PD	1988
Long QT-syndrome	1957–60	<i>Herg</i> etc	1991–97
Isoniazid slow/fast acetylation	1959–60	<i>N</i> -acetyltransferase	1989–93
Malignant hyperthermia	1960–62	Ryanodine receptor	1991–97
Fructose-intolerance	1963	Aldolase B	1988–95
Vasopressin insensitivity	1969	Vasopressin receptor2	1992
Alcohol susceptibility	1969	Aldehyde-dehydrogenase	1988
Debrisoquine-hypersensitivity	1977	CYP2D6	1988–93
Retinoic acid resistance	1970	PML-RARA fusion-gene	1991–93
6-Mercaptopurin-toxicity	1980	Thiopurine-methyltransferase	1995
Mephenytoin resistance	1984	CYP2C19	1993–94
Insulin-insensitivity	1988	Insulin receptor	1988–93
Testing substance			
Phase I enzyme			
Aldehyde-dehydrogenase		Acetaldehyde	
Alcohol-dehydrogenase		Ethanol	
CYP1A2		Caffeine	
CYP2A6		Nicotine, coumarin	
CYP2C9		Warfarin	
CYP2C19		Mephenytoin, omeprazole	
CYP2D6		Dextromethorphan, dbrisoquine, sparteine	
CYP2E1		Chloroxazone, caffeine	
CYP3A4		Erythromycin	
CYP3A5		Midazolam	
Serum cholinesterase		Benzoylcholine, butrylcholine	
Paraoxonase/arylesterase		Paraoxon	
Phase II enzyme			
Acetyltransferase (NAT1)		<i>para</i> -Aminosalicylic acid	
Acetyltransferase (NAT2)		Isoniazid, sulfamethazine, caffeine	
Dihydropyrimidin-dehydrogenase		5-Fluorouracil	
Glutathione-transferase (GST-M1)		<i>trans</i> -Stilbene-oxide	
Thiomethyltransferase		2-Mercaptoethanol, D-penicillamine, captopril	
Thiopurine-methyltransferase		6-Mercaptopurine, 6-thioguanine, 8-azathioprine	
UDP-glucuronosyl-transferase (UGT1A)		Bilirubin	
UDP-glucuronosyl-transferase (UGT2B7)		Oxazepam, ketoprofen, oestradiol, morphine	

differential metabolising potential since the middle of the 20th century, the practical application and implementation of this knowledge has been minimal so far. This may be the consequence, on one hand, of the irrelevance of such differences in the presence of relatively flat dose–effect curves (ie a sufficiently wide therapeutic window), as well as, on the other hand, the fact that many drugs are subject to complex, parallel metabolising pathways, where in the case of underperformance of one enzyme, another one may compensate. Such compensatory pathways may well have somewhat different substrate affinities, but allow plasma levels to remain within therapeutic concentrations. Thus, the

number of such polymorphisms that have found practical applicability is rather limited and, by and large, is restricted to determinations of the presence of functionally deficient variants of the enzyme, thiopurine-methyl-transferase, in patients prior to treatment with purine analogue chemotherapeutics.

Pharmacodynamic effects, in contrast, may lead to inter-individual differences in a drug's effects despite the presence of appropriate concentrations of the intended active (or activated) drug compound at the intended site of action. Here, DNA-based variation in how the target molecule, or another (downstream) member of the target molecule's mechanistic pathway, can respond to the

medicine modulates the effects of the drug. This will apply primarily to palliatively working medicines that improve a condition symptomatically by modulating pathways relevant to disease phenotype (but not to disease cause) that are not dysfunctional but can be used to counterbalance the effect of a dysfunctional, disease-causing pathway, and therefore allow mitigation of symptoms. A classical example of such an approach is the acute treatment of thyrotoxicity with beta-adrenergic blocking agents: even though the sympathetic nervous system does in this case not contribute causally to tachycardia and hypertension, dampening even its baseline tonus through this class of drugs relieves the cardiovascular symptoms and signs of this condition, before the causal treatment (in this case available through

partial chemical ablation of the hyperactive thyroid gland) can take effect. Notably, the majority of today's pharmacopoeia actually belongs to this class of palliatively acting medicines.

A schematic (Figure 1) is provided to help clarify these somewhat complex concepts, in which a hypothetical case of a complex trait/disease is depicted where excessive, dysregulated function of one of the trait-controlling/contributing pathways (Figure 1, A and B) causes symptomatic disease – the example used refers to blood pressure as the trait, and hypertension as the disease in question, respectively (for the case of a defective or diminished function of a pathway, an analogous schematic could be constructed, and again for a deviant function). A palliative treatment would be one that addresses one of the pathways that – while not dysregulated – contributes to the overall deviant physiology (Figure 1, F), while the respective pharmacogenetic–pharmacodynamic scenario would occur if this particular pathway was, owing to a genetic variant, not responsive to the drug chosen (Figure 1, G). A palliative treatment may also be ineffective if the particular mechanism targeted by the palliative drug, owing to the presence of a molecular variant, provides less than the physiologically expected baseline contribution to the relevant phenotype (Figure 1, H). In such a case, modulating an *a priori* unimportant pathway in the disease scenario will not yield successful palliative treatment results (Figure 1, I and J).

One of the most persuasive examples accumulated to date for such palliative–drug-related pharmacogenetic effects has been observed in the field of asthma. The treatment of asthma relies on an array of drugs aimed at modulating different 'generic' pathways, thus mediating bronchodilation or anti-inflammatory effects, often without regard to the possible causative contribution of the targeted mechanism to the disease. One of the mainstays of the treatment of asthma is

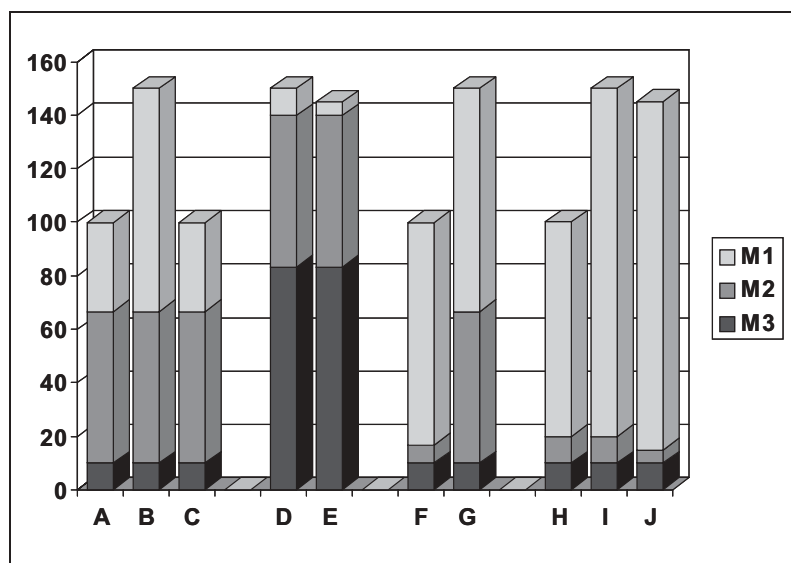


Figure 1: (A) normal physiology – three molecular mechanisms (M1, M2, M3) contribute to a trait; (B) diseased physiology D1 – derailment (cause/contribution) of molecular mechanism 1 (M1); (C) diseased physiology D1 – causal treatment T1 (aimed at M1); (D) diseased physiology D3 – derailment (cause/contribution) of molecular mechanism 3 (M3); (E) diseased physiology D3, treatment T1 – treatment does not address cause; (F) diseased physiology D1, palliative treatment T2 (aimed at M2); (G) diseased physiology D1, palliative treatment T2 – T2-refractory gene variant in M2; (H) normal physiology variant – differential contribution of M1 and M2 to normal trait; (I) diseased physiology D1-variant – derailment of mechanism M1; (J) diseased physiology D1-variant: treatment with T2. Solid colours indicate normal function, stippling indicates pathological dysfunction, hatching indicates therapeutic modulation

**A persuasive example
for pharmacogenetics is
asthma – different
responses are seen to
beta-2-agonists**

activation of the beta-2-adrenoceptor by specific agonists, which leads to relaxation of bronchial smooth muscles and, consequently, bronchodilation. Recently, several molecular variants of the beta-2-adrenoceptor have been shown associated with differential treatment response to such beta-2-agonists.^{5,6} Individuals carrying one or two copies of a variant allele that contains a glycine in place of arginine in position 16 were found to have a 3- and 5-fold reduced response to the agonist, respectively. This was shown in both *in vitro*^{7,8} and *in vivo*⁸ studies to correlate with an enhanced rate of agonist-induced receptor–receptor down-regulation, but not with any difference in transcriptional or translational activity of the gene, or with agonist binding. In contrast, a second polymorphism affecting position 19 of the beta upstream peptide was shown to affect translation (but not transcription) of the receptor itself, with a 50 per cent decrease in receptor numbers associated with the variant allele – which happens to be in strong linkage disequilibrium with a variant allele position 16 in the receptor. The simultaneous presence of both mutations would thus be predicted to result in low expression and enhanced down-regulation of an otherwise functionally normal receptor, depriving patients carrying such alleles of the benefits of effective bronchodilation as a ‘palliative’ (ie non-causal) counter-measure to their pathological airway hyper-reactivity. Importantly, there is no evidence that any of the allelic variants encountered are associated with the prevalence or incidence, and thus potentially the aetiology of the underlying disease.^{9,10} This would reflect the scenario depicted in Figure 1, H.

**Inhibition of leukotriene
synthesis is dependent
on the 5-lipoxygenase
promoter region**

Inhibition of leukotriene synthesis, another palliative approach toward the treatment of asthma, proved clinically ineffective in a small fraction of patients who carried only non-wild-type alleles of the 5-lipoxygenase promoter region.¹¹ These allelic variants had previously been shown to be associated with decreased

transcriptional activity of the gene.¹² It stands to reason – consistent with the clinical observations – that in the presence of already reduced 5-lipoxygenase activity pharmacological inhibition may be less effective (Figure 1, H, I, J). Of note, again, there is no evidence for a primary, disease-causing or contributing role of any 5-lipoxygenase variants; all of them were observed at equal frequencies in disease-affected and non-affected individuals.¹²

Pharmacogenetic effects may not only account for differential efficacy, but also contribute to differential occurrence of adverse effects. An example for this scenario is provided by the well-documented ‘pharmacogenetic’ association between molecular sequence variants of the 12S rRNA, a mitochondrion-encoded gene, and aminoglycoside-induced ototoxicity.¹³ Intriguingly, the mutation that is associated with susceptibility to ototoxicity renders the sequence of the human 12S rRNA similar to that of the bacterial 12S rRNA gene, and thus effectively turns the human 12S rRNA into the (bacterial) target for aminoglycoside drug action – presumably mimicking the structure of the bacterial binding site of the drug.¹⁴ As in the other examples, presence of the 12S rRNA mutation *per se* has no primary, drug-treatment-independent pathologic effect *per se*.

One may speculate that, analogously, such ‘molecular mimicry’ may occur within one species: adverse events may arise if the selectivity of a drug is lost because a gene that belongs to the same gene-family as the primary target, loses its ‘identity’ vis-à-vis the drug and attains, based on its structural similarity with the principal target, similar or at least increased affinity to the drug. Depending on the biological role of the ‘impostor’ molecule, adverse events may occur – even though the variant molecule, again, may be quite silent with regard to any contribution to disease causation. Although we currently have no obvious

examples for this scenario, a non-selective drug-effect based on such molecular mimicry is certainly imaginable for various classes of receptors and enzymes.

Pharmacogenetics as a consequence of molecular differential diagnosis

As alluded to earlier, there is general agreement today that any of the major clinical diagnoses in the field of common complex disease, such as diabetes, hypertension or cancer, constitute a number of aetiologically (ie at the molecular level) more or less distinct subcategories. In the case of a causally acting drug this may imply that the agent will only be appropriate, or will work best, in that fraction of all the patients who carry the (all-inclusive and imprecise) clinical diagnosis in whom the dominant molecular aetiology, or at least one of the contributing aetiological factors, matches the mechanism of action of the drug in question (Figure 1, C). If the mechanism of action of the drug addresses a pathway that is not disease-relevant – perhaps already down-regulated as an appropriate physiological response to the disease, then the drug may – logically – be expected not to show efficacy (Figure 1, D, E).

Thus, unrecognised and undiagnosed disease heterogeneity – disclosed indirectly by presence or absence of response to a drug targeting a mechanism that contributes only to one of several molecular subgroups of the disease – provides an important explanation for differential drug response and probably represents a substantial fraction of what we today somewhat indiscriminately subsume under the term ‘pharmacogenetics’.

Currently, the most frequently cited example for this category of ‘pharmacogenetics’ is trastuzumab (HERCEPTIN®), a humanised monoclonal antibody directed against the *her-2* oncogene. This breast cancer treatment is prescribed based on the level of *her-2* oncogene expression in the patient’s tumour tissue. Differential

diagnosis at the molecular level not only provides an added level of diagnostic sophistication, but also actually represents the prerequisite for choosing the appropriate therapy. Because trastuzumab specifically inhibits a ‘gain-of-function’ (ie enhanced expression) variant of the oncogene, it is ineffective in the two-thirds of patients who do not ‘over-express’ the drug’s target, whereas it significantly improves survival in the one-third of patients that constitute the ‘sub-entity’ of the broader diagnosis ‘breast cancer’ in whom the gene is expressed.¹⁵ Some have argued against this being an example of ‘pharmacogenetics’, because the parameter for patient stratification (ie for differential diagnosis) is the somatic gene expression level rather than a particular ‘genotype’ data.¹⁶ This is a difficult argument to follow, since in the case of a treatment-effect-modifying germline mutation it would obviously not be the nuclear gene variant *per se*, but also its specific impact on either structure/function or on expression of the respective gene/gene product that would represent the actual physiological corollary underlying the differential drug action. Conversely, an *a priori* observed expression difference is highly likely to reflect a – potentially as yet undiscovered – sequence variant. Indeed, as pointed out earlier, there are a number of examples in the field of pharmacogenomics where the connection between genotypic variant and altered expression has already been demonstrated.^{12,17}

Another example, although still hypothetical, of how proper molecular diagnosis of relevant pathomechanisms will significantly influence drug efficacy, is in the evolving class of anti-AIDS/HIV drugs that target the CCR5 cell-surface receptor.^{18–20} These drugs would be predicted to be ineffective in those rare patients who carry the delta-32 variant, but who nevertheless have contracted AIDS or test HIV-positive (most probably due to infection with an SI-virus phenotype that utilises CXCR4).^{21,22}

Aetiological factors are an important factor for drug efficacy

Disease heterogeneity may explain differential drug response

It should be noted that the pharmacogenetically relevant molecular variant need not affect the primary drug target, but may equally well be located in another molecule belonging to the system or pathway in question, both up- and downstream in the biological cascade with respect to the primary drug target.

Different classes of markers

Pharmacogenetic phenomena, as pointed out previously, need not be restricted to the observation of a direct association between allelic sequence variation and phenotype, but may extend to a broad variety of indirect manifestations of underlying but often (as yet) unrecognised sequence variation. Thus, differential methylation of the promoter-region of O6-methylguanine-DNA-methylase has recently been reported to be associated with differential efficacy of chemotherapy with alkylating agents. If methylation is present, expression of the enzyme that rapidly reverses alkylation and induces drug-resistance is inhibited, and therapeutic efficacy is greatly enhanced.²³

Complexity is to be expected

In the real world, it is likely that not only one of the scenarios depicted, but a combination of several ones may affect how well a patient responds to a given treatment, or how likely it is that he or she will suffer an adverse event. Thus, a fast-metabolising patient with poor-responder pharmacodynamics may be particularly unlikely to gain any benefit from taking the drug in question, while a slow-metabolising status may counterbalance in another patient the same inopportune pharmacodynamics, while a third patient, who is a slow metaboliser and displaying normal pharmacodynamics, may be more likely to suffer adverse events. In all of them, both the pharmacokinetic and pharmacodynamics properties may result from the interaction of several of the mechanisms described above. In addition, it is known, of course, that co-administration of other drugs, or even the

consumption of certain foods, may affect and further complicate the picture for any given treatment.

INCORPORATING PHARMACOGENETICS INTO DRUG DEVELOPMENT STRATEGY

It is important to note that despite the public hyperbole and the high-strung expectations surrounding the use of pharmacogenetics to provide 'personalised care', these approaches are likely to be applicable only to a fraction of medicines that are being developed. Further, if and when such approaches will be used, they will represent no radical new direction or concept in drug development but simply a stratification strategy as we have been using it all along.

An increasingly sophisticated and precise diagnosis of disease, arising from a deeper, more differentiated understanding of pathology at the molecular level, that will increasingly subdivide today's clinical diagnoses into molecular subtypes, will foster medical advances which, if considered from the viewpoint of today's clinical diagnosis, will appear as 'pharmacogenetic' phenomena, as described above. However, the sequence of events that is today often presented as characteristic for a 'pharmacogenetic scenario' – namely, exposing patients to the drug, recognising a differential (ie quasi-bimodal) response pattern, discovering a marker that predicting this response, and creating a diagnostic product to be co-marketed with the drug henceforth – is likely to be reversed. Rather, in the case of 'pharmacogenetics' owing to a match between drug action and dysregulation of a disease-contributing mechanism we will probably search for a new drug specifically, and *a priori*, based on a new mechanistic understanding of disease causation or contribution (ie a newly found ability to diagnose a molecular sub-entity of a previously more encompassing, broader, and less precise clinical disease definition). Thus, pharmacogenetics will not be so

Chemotherapy efficacy can be affected by pharmacogenetic phenomena

Fast-metabolising patient vs. slow-metabolising patient

Pharmacogenetics will present greater challenges in drug regulation, business development and marketing

much about finding the 'right medicine for the right patient', but about finding the 'right medicine for the disease (-subtype)', as we have aspired to do all along throughout the history of medical progress. This is, in fact, good news: the conventional 'pharmacogenetic scenario' would invariably present major challenges from both a regulatory and a business development and marketing standpoint, as it will confront development teams with a critical change in the drug's profile at a very late point during the development process. In addition, the timely development of an approvable diagnostic in this situation is difficult at best, and its marketing as an 'add-on' to the drug a less than attractive proposition to diagnostics business. Thus, the 'practice' of pharmacogenetics will, in many instances, be marked by progress along the very same path that has been one of the main avenues of medical progress for the last several hundred years: differential diagnosis first, followed by the development of appropriate, more specific treatment modalities.

Thus, the sequence of events in this case would probably involve, first, the development of an *in vitro* diagnostic test as a stand-alone product that may be marketed on its own merits, allowing the physician to establish an accurate, state-of-the-art diagnosis of the molecular subtype of the patient's disease. Sometimes such a diagnostic may prove helpful even in the absence of specific therapy by guiding the choice of existing medicines and/or of non-drug treatment modalities such as specific changes in diet or lifestyle. Availability of such a diagnostic – as part of the more sophisticated understanding of disease – will undoubtedly foster and stimulate the search for new, more specific drugs; and once such drugs are found, availability of the specific diagnostic will be important for carrying out the appropriate clinical trials. This will allow a prospectively planned, much more systematic approach towards clinical and business development, with a commensurate

greater chance of actual realisation and success.

In practice, some extent of guesswork will remain, owing to the nature of common complex disease. First, all diagnostic approaches – including those based on DNA analysis in common complex disease, as stressed above – will ultimately only provide a measure of probability, not of certainty. Thus, although the variances of drug response among patients who do (or do not) carry the drug-specific sub-diagnosis will be smaller, there will still be a distribution of differential responses. Although by and large the drug will work better in the 'responder' group, there will be some patients in this subgroup who will respond less or not at all and, conversely, not everyone belonging to the 'non-responder' group will completely fail to respond, depending perhaps on the relative magnitude with which the particular mechanism contributes to the disease. It is important to keep in mind, therefore, that even in the case of fairly obvious bimodality patient responses will still show distribution patterns, and that all predictions as to responder or non-responder status will only have a certain likelihood of being indeed accurate (Figure 2). The terms 'responder' and 'non-responder' as applied to groups of patients stratified based on a DNA marker represent, therefore, misnomers inspired by Mendelian thinking that should be replaced by more appropriate terms that reflect the probabilistic nature of any such classification, eg 'probable (non-)responder'.

In addition, based on our current understanding of the polygenic and heterogeneous nature of these disorders, we will – even in an ideal world where we would know about all possible susceptibility gene variants for a given disease and have treatments for them – be able to exclude, in any one patient, only those that do not appear to contribute to the disease, and therefore deselect certain treatments. We will, however, most likely find ourselves left with a small number –

Customised drug therapy

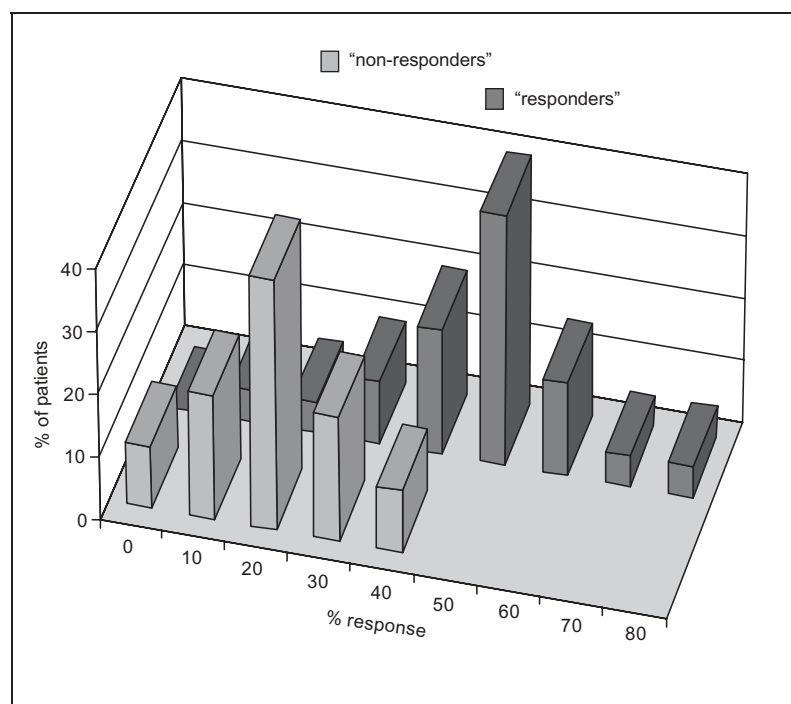


Figure 2: Hypothetical example of bimodal distribution according to marker that indicates 'non-responder' or 'responder' status. Note that in both cases a distribution is present, with overlaps, thus, the categorisation into 'responders' or 'non-responders' based on the marker must be understood to convey only the probability to belong to one or the other

two to four, perhaps – of potentially disease-contributing gene variants whose relative contribution to the disease will be very difficult, if not impossible, to rank in an individual patient. Trial and error, and this great intangible quantity 'physician experience', will probably still play an important role, albeit on a more limited and selective basis.

The alternative scenario, where differential drug response and/or safety occurs as a consequence of a pathologically not relevant, purely drug-response related pharmacogenetics scenario, is more likely to present greater difficulty in planning and executing a clinical development programme because, presumably, it will be more difficult to anticipate or predict differential responses *a priori*. When such a differential response occurs, it will also potentially be more difficult to find the relevant marker(s), unless it happens to be among the 'obvious' candidate genes implicated in

the disease physiopathology or the treatment's mode of action. Although screening for molecular variants of these genes, and testing for their possible associations with differential drug response, is a logical first step, if unsuccessful, it may be necessary to embark on an unbiased genome-wide screen for such a marker or markers. Despite recent progress in high-throughput genotyping, the obstacles that will have to be overcome on the technical, data analysis and cost levels are formidable. They will limit the deployment of such programmes, at least for the foreseeable future, to select cases in which there are very solid indications for doing so, based on clinical data showing a near-categorical (eg bimodal) distribution of treatment outcomes. Even then, we may expect to encounter for every success – that will be owed to a favourably strong linkage disequilibrium across considerable genomic distance in the relevant chromosomal region – as many or more failures, in cases where the culpable gene variant cannot be found because of the higher recombination rate or other characteristics of the stretch of genome that it is located on.

REGULATORY ASPECTS

Regulatory agencies in both Europe and the USA are beginning to show keen interest in the potential role that pharmacogenetics approaches may play in the development and clinical use of new drugs, and the potential challenges that such approaches may present to the regulatory approval process. While no formal guidelines have been issued, the pharmaceutical industry has already been reproached – albeit in a rather non-specific manner – for not being more proactive in the use of pharmacogenetic markers. It will be of key importance for all concerned to engage in an intensive dialogue at the end of which – it is hoped – will emerge a joint understanding that stratification according to DNA-based markers is fundamentally nothing new, and not different from stratification

Ethical impact of pharmacogenetics

according to any other clinical or demographic parameter, as has been used all along.

Based on the (in the case of common complex diseases scientifically unjustified) perception that DNA-based markers represent a different class of stratification parameters, a number of important questions will need to be addressed and answered – always, it is hoped, in analogy to ‘conventional’ stratification parameters, including those referring to ethical aspects. Among the most important ones are questions concerning:

- the need and/or ethical justification (or lack thereof) to include likely non-responders in a trial for the sake of meeting safety criteria, which, given the restricted indication of the drug, may indeed be excessively broad;
- the need to use active controls if the patient/disease stratum is different from that in which the active control was originally tested;
- the strategies to develop and gain approval for the applicable first-generation diagnostic, as well as for the regulatory approval of subsequent generations of tests to be used to determine eligibility for prescription of the drug; as well as
- a number of ethical-legal questions relating to the unique requirements regarding privacy and confidentiality for ‘genetic testing’ that may raise novel problems with regard to regulatory audits of patient data (see below).

Genetic exceptionalism

A concerted effort to avoid what has been termed ‘genetic exceptionalism’ – the differential treatment of DNA-based markers as compared with other personal medical data – should be made so that the already very difficult process of obtaining regulatory approval is not further unnecessarily complicated. This seems justified based on the recognised fact that

in the field of common complex disease DNA-based markers are not at all different from ‘conventional’ medical data in all relevant aspects – namely specificity, sensitivity and predictive value.

PHARMACOGENETIC TESTING FOR DRUG EFFICACY V SAFETY

In principle, pharmacogenetic approaches may be useful both to raise efficacy and to avoid adverse events, by stratifying patient eligibility for a drug according to appropriate markers. In both cases, clinical decisions and recommendations must be supported by data that have undergone rigorous biostatistical scrutiny. Based on the substantially different prerequisites for and opportunities to acquiring such data, and to applying them to clinical decision-making, the use of pharmacogenetics for enhanced efficacy is expected to be considerably more common than for the avoidance of adverse events.

The likelihood that adequate data on efficacy in a subgroup may be generated is reasonably high, given the fact that unless the drug is viable in a reasonably sizeable number of patients, it will probably not be developed for lack of a viable business case, or at least only under the protected environment of orphan drug guidelines. Implementation of pharmacogenetic testing to stratify for efficacy, provided that safety in the non-responder group is not an issue, will primarily be a matter of physician preference and sophistication, and potentially of third-party payer directives, but would appear less likely to become a matter of regulatory mandate, unless a drug has been developed selectively in a particular stratum of the overall indication (in which case a contra-indication label for other strata is likely to be issued). Indeed, an argument can be made against depriving those who carry the ‘‘likely’’ non-responder’ genotype regarding eligibility for the drug, but who individually, of course, may respond to the drug with a certain, albeit lower, probability. From a regulatory aspect, use of pharmacogenetics for efficacy, if

It is unlikely that pharmacogenetic approaches will improve safety

Genetic testing

adequate safety data exist, appears largely unproblematic – the worst-case scenario (a genotypically inappropriate patient receiving the drug) would result in treatment without expected beneficial effect, but with no increased odds to suffer adverse consequences, ie much of what one would expect under conventional paradigms.

The utility and clinical application of pharmacogenetic approaches towards improving safety, in particular with regard to serious adverse events, will meet with considerably greater hurdles and is therefore less likely expected to become reality. A number of reasons are cited for this.

First, in the event of serious adverse events associated with the use of a widely prescribed medicine, withdrawal of the drug from the market is usually based almost entirely on anecdotal evidence from a rather small number of cases – in accordance with the Hippocratic mandate '*primum non nocere*'. If the sample size is insufficient to demonstrate a statistically significant association between drug exposure and event, as is typically the case, it will most certainly be insufficient to allow meaningful testing for genotype–phenotype correlations; the biostatistical hurdles become progressively more difficult as many markers are tested and the number of degrees of freedom applicable to the analysis for association continues to rise. Therefore, the fraction of attributable risk shown to be associated with a given at-risk (combination of) genotype(s) would have to be very substantial for regulators to accept such data. Indeed, the low prior probability of the adverse event, by definition, can be expected to yield an equally low positive (or negative) predictive value.

Second, the very nature of safety issues raises the hurdles substantially because in this situation the worst-case scenario – administration of the drug to the 'wrong' patient – will result in higher odds to harm to the patient. Therefore, it is likely that the practical application of successfully investigating and applying

pharmacogenetics towards limiting adverse events will probably be restricted to diseases with dire prognosis, where a high medical need exists, where the drug in question offers unique potential advantages (usually bearing the characteristics of a 'life-saving' drug), and where, therefore, the tolerance even for relatively severe side effects is much greater than for other drugs. This applies primarily to areas such as oncology or HIV/AIDS. In most other indications, the sobering biostatistical and regulatory considerations discussed represent barriers that are unlikely to be overcome easily; and the proposed, conceptually highly attractive, routine deployment of pharmacogenetics as a generalised drug surveillance or pharmaco-vigilance practice following the introduction of a new pharmaceutical agent²⁴ faces these scientific as well as formidable economic hurdles.

ETHICAL-SOCIETAL ASPECTS OF PHARMACOGENETICS

No discussion about the use of genetic/genomic techniques and approaches to healthcare can be complete without considering their impact on the ethical, societal and legal level.

Much of the discussion about ethical and legal issues relating to pharmacogenetics is centred on the issue of 'genetic testing', a topic that has recently also been the focus of a number of guidelines, advisories, White Papers, etc, issued by a number of committees in both Europe and the USA. It is interesting to note that the one characteristic that almost all these documents share is a studious avoidance of defining what exactly a 'genetic test' is. Where definitions are given, they tend to be very broad, including not only the analysis of DNA but also of transcription and translation products affected by inherited variation. The most sensible solution to this dilemma will ultimately, it is hoped, be a consensus to treat all personal medical data in a similar fashion

regardless of the degree to which DNA-encoded information affects it (noting that there really is not any medical data that are not to some extent affected by intrinsic patient properties). It may, however, for the time being, be helpful to let the definition of what constitutes 'genetic data' be guided by the public perception of 'genetic data' – in as much as the whole discussion of this topic is prompted by these public perceptions.

Definition of a genetic test

In the public eye, 'genetic test' is usually understood either (i) as any kind of test that establishes the diagnosis (or predisposition) of a classic monogenic, heritable disease, or (ii) as any kind of test based on nucleic acid analysis. This includes the (non-DNA-based) Guthrie test for phenylketonuria, forensic and paternity testing, and a DNA-based test for Lp(a), but not the plasma-protein-based test for the same marker (even though the information derived is identical). Since monogenic disease is, in effect, excluded from this discussion, it stands to reason to restrict the definition of 'genetic testing' to the analysis of (human) DNA sequence.

Based on the perceived particular sensitivity of 'genetic' data, institutional review boards commonly apply a specific set of rules to granting permission to test for DNA-based markers in the course of drug trials or other clinical research, including (variably) separate informed consent forms, the anonymisation of samples and data, specific stipulations about availability of genetic counselling, provision to be able to withdraw samples at any time in the future, etc.

Genetic testing for primary disease risk assessment unlikely to be a sensitive issue

Arguments have been advanced²⁴ that genotype determinations for pharmacogenetic characterisation, in contrast to 'genetic' testing for primary disease risk assessment, are less likely to raise potentially sensitive issues with regard to patient confidentiality, the misuse of genotyping data or other nucleic acid-derived information, and the possibility of stigmatisation. While this is certainly true when pharmacogenetic testing is compared to predictive

genotyping for highly penetrant Mendelian disorders, it is not apparent why in common complex disorders issues surrounding predictors of primary disease risk would be any more or less sensitive than those pertaining to predictors of probable treatment success/failure. Indeed, two lines of reasoning may actually indicate an increased potential for ethical issues and complex confrontations among the various stakeholders to arise from pharmacogenetic data.

First, while access to genotyping and other nucleic acid-derived data related to disease susceptibility can be strictly limited, the very nature of pharmacogenetic data calls for a rather more liberal position regarding use: if this information is to serve its intended purpose, ie improving the patient's chance for successful treatment, then it is essential that it is shared among at least a somewhat wider circle of participants in the healthcare process. Thus, the prescription for a drug that is limited to a group of patients with a particular genotype will inevitably disclose the receiving patient's genotype to anyone of a large number of individuals involved in the patient's care at the medical and administrative level. The only way to limit this quasi-public disclosure of this patient's genotype data would be if he or she were to sacrifice the benefits of the indicated treatment for the sake of data confidentiality.

Second, patients profiled to carry a high disease probability along with a high likelihood for treatment response may be viewed, from the standpoint of, for example, insurance risk, as quite comparable to patients displaying the opposite profile, ie a low risk to develop the disease, but a high likelihood not to respond to medical treatment, if the disease indeed occurs. For any given disease risk, then, patients less likely to respond to treatment would be seen as a more unfavourable insurance risk, particularly if non-responder status is associated with chronic, costly illness

Complex-disease mosaic

rather than with early mortality, the first case having much more far-reaching economic consequences. The pharmacogenetic profile may thus, under certain circumstances, even become a more important (financial) risk-assessment parameter than primary disease susceptibility, and would be expected – in as much as it represents but one stone in the complex-disease mosaic – to be treated with similar weight, or lack thereof, as other genetic and environmental risk factors.

Practically speaking, the critical issue is not only, and perhaps not even predominantly, the sensitive nature of the information, and how it is, if at all, disseminated and disclosed, but how and to what end it is used. Obviously, generation and acquisition of personal medical information must always be contingent on the individual's free choice and consent, as must be all application of such data for specific purposes. Beyond this, however, there is today an urgent need for the requisite dialogue and discourse among all stakeholders within society to develop and endorse a set of criteria by which the use of genetic and indeed all personal medical information should occur. It will be critically important that society as a whole endorses, in an act of solidarity with those destined to develop a certain disease, guidelines that support the beneficial and legitimate use of the data in the patient's interest while at the same time prohibiting their use in ways that may harm the individual, personally, financially or otherwise. As long as we trust our political decision processes to reflect societal consensus, and as long as such consensus reflects the principles of justice and equality, the resulting set of principles should assert such proper use of medical information. Indeed, both aspects – data protection and patient/subject protection – are seminal components of the mandates included in the WHO's 'Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services'²⁵ which mandate

autonomy, beneficence, no maleficence and justice.

SUMMARY

Pharmacogenetics, in the different scenarios included in this term, will represent an important new avenue towards understanding disease pathology and drug action, and will offer new opportunities of stratifying patients to achieve optimal treatment success. As such, it represents a logical, consequent step in the history of medicine – evolution, rather than revolution. Its implementation will take time, and will not apply to all diseases and all treatments equally. If society finds ways to sanction the proper use of this information, thus allowing and protecting its use for the patient's benefit, important progress in healthcare will be made.

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Data protection of genetic data

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