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

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

3.1.3 Cost for data storage and management of pharmacogenetic information

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

3.2 Indirect costs

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

3.3 Intangible costs

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

3.4 External costs (informal costs)

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

4. Factors affecting economic benefits of pharmacogenetics

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

4.1 Direct costs

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

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

4.2 Indirect costs

Savings in indirect costs may include:

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

4.3 Intangible costs

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

4.4 External costs

See section 4.2 ("Indirect costs").

5. Pharmacoeconomic assessment

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

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

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

5.1 Cost-per-outcome analyses

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

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

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

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

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

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

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

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

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

5.2 Pharmacoeconomic study design in pharmacogenetics

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

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

Table 1

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

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

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

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

The case of a pharmacogenetic test that is applied for finding the individually adjusted appropriate dose of a drug, as compared to not using such a test, requires different considerations. Here the relevant factors, in a strictly accounting analysis of direct cost, include, but are not necessarily limited to those shown in Table 2.

Table 2

Cost of running the test on all patients that are treated with the drug in question	*versus*	Cost of additional follow-up visits with the physician to adjust the dose (based on clinical efficacy) that could have been avoided ***plus*** Cost of additional morbidity potentially associated with a delayed finding of optimal dosing (e.g. in rapid metabolisers) ***plus*** Cost of ADRs potentially associated with improper dosing (e.g. in slow metabolisers)

The same considerations apply regarding a pharmacoeconomic comparison of the above two alternatives as previously presented for Table 1. Again, the performance of the pharmacogenetic test is a critical parameter influencing the viability of the pharmacogenetic option regarding cost-benefit or cost-effectiveness ratios.

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

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

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

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

6. Development of modelling and multi-criteria approaches

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

7. Payer attitude toward pharmacogenetics

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

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

7.1 Cost control

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

7.1.1 Top-down "directive" approach

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

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

7.1.2 Incentive-based approach

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

7.2. Pricing

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

7.3. Payment system

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

8. Conclusions

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

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

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

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

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

9. Recommendations

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

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Chapter 11
Communication and Education

1. Introduction

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

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

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

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

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

2. Identifying communication and educational needs

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

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

2.1 Genetic polymorphism – one major cause of variable drug response

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

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

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

2.2 What is 'personalised medicine'?

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

2.3 Pharmacogenetics: Revolution or evolution?

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

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

2.4 Better safety and efficacy and economic benefits

2.4.1 Impact on purchaser

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

2.4.2 Impact on developer

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

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

2.5 Data protection and confidentiality

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

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

2.6 Medical research versus clinical application

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

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

3. Issues for the Educator

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

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

3.2 Societal, legal and ethical implications

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

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

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

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

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

3.3 Need for information to all stakeholders

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

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

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

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

3.4 Educational approach

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

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

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

3.5 Language

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

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

3.6 The message

Educators must convey clearly the following messages:

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

4. Role of the regulatory authorities

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

4.1 Genetic tests

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

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

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

4.2 Product information

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

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

5. Role of the media

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

6. Communication and education strategy

6.1 Goals

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

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

These goals should remain at the forefront:

- Create awareness of how the applications of pharmacogenetic research will impact human health, including patient treatment and care
- Communicate research initiatives and findings to educate and update stakeholders especially on their relevance to clinical practice
- Organize and harmonise realistic policy on provision of information (wording and content) by all players (at least within groups such as physicians and companies developing drugs and/or diagnostic kits).

6.2 Implementation

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

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

6.3 Development of key messages

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

Key message development should:

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

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

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

SOME USEFUL WEBSITES

A. National Institute of Health – USA:
http://www.nigms.nih.gov/pharmacogenetics/

B. Human Genetics Commission – UK
http://www.hgc.gov.uk

C. Human Genetics Advisory Commission – UK
http://www.doh.gov.uk/genetics/hgac.htm

D. Nuffield Council on Bioethics
http://www.nuffieldbioethics.org

E. Pharma Genomics:
http://genomics.phrma.org/

F. Pharma Genomics:
http://genomics.phrma.org/pharmacogenomics.html

G. UK Dept of Health Genetics White Paper
http://www.doh.gov.uk/genetics/whitepaper.htm

H. Public Health Genetics Unit (PHGU), Cambridge
http://www.cgkp.org.uk/index.php

I. The Human Genome Organization (HUGO)
http://www.gene.ucl.ac.uk/hugo/

J. Council of Europe Steering Committee on Bioethics.
Working document on the applications of genetics for health purposes
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Chapter 12
Unresolved Issues and Barriers to Progress

1. Introduction

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

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

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

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

2. Biological complexity

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

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

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

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

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

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

3. Technological obstacles

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

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

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

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

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

4. Business-related obstacles

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

4.1 Drug development

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

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

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

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

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

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

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

4.2 Regulatory obstacles

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

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

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

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

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

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

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

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

4.3 Commercial obstacles

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

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

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

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

5. Obstacles in medical practice

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

6. Public perceptions

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

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

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

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

7. Looking forward

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

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

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Annex 1

Process and Membership of CIOMS Working Group on Pharmacogenetics

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

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

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

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

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