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

4.1.2 Informed consent

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

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

- **A statement of clear rationale:**
  Provides justification for conducting the study, usually including an introduction to the concept of pharmacogenetics.
- **Fields of study for sample use:**
  The field may be *narrow*, and restricted to a certain diagnosis, indication, or medicine, as defined by the single protocol or *broad*, and permitting research in several or all-possible indications. Likewise the scope of pharmacogenetic analysis may vary from specified polymorphisms to genome wide scans. Generally, the narrower the scope of the consent, the fewer potential issues it will raise. Some ethicists have questioned the permissibility of obtaining broad consent, arguing that society must protect individuals from consenting to outcomes that cannot yet be foreseen. Others have maintained that narrow scope results in limitations to the advance of medical knowledge and takes no account of future relevant advances that may occur in this emerging field [11, 12].
- **Length of time the samples will be stored:**
  The time range for storage of the samples may be for the duration of the study to many years thereafter, in order to address questions at a later point in the development programme, as long as applicable regional rules and regulations are met.
- **Sample coding:**
  The degree of sample coding is strongly associated with the degree of data and privacy protections provided; thus, sample coding has been structured, by consensus, into five categories. These categories have been adopted by the regulatory authorities [13] as well as by industry [14]. The table below provides the industry (Pharmacogenomic Working Group, PWG) and the regulatory (European Medicines Agency, EMEA) terminology. These are the current, established comparisons:

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

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

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

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

- **Expected benefits to the patient or others (if any):**
  In most cases, the benefits to patients are currently undergoing hypothesis testing or exploration, and the benefits of the drug and pharmacogenetic differentiation for improving the potential therapeutic outcomes, still need to be established. This point must be clearly stated in the informed consent.
- **Potential risks:**
  These might include the direct additional risks of obtaining the pharmacogenetic sample, which are generally minor (the risks of a phlebotomy) and the indirect risks associated with breach of privacy. These risks must be clearly indicated in the informed consent.
- **Treatment of and participant's access to the study results:**
  Informed consent forms should clearly state whether or not results of pharmacogenetic tests will be conveyed to participants. Communication of preliminary pharmacogenetic test results to study participants is often not very meaningful, in particular if the clinical relevance of the test has not yet been established. Also, if samples are anonymized, feedback of results to participants is not possible. However, in the case of industrial sponsorship, publication of the aggregate results of studies is usually included in reports issued to research physicians. Still, some advocate that all test results must be made available to participants, and that informed consent forms, which require participants to waive this option, are not acceptable. Even if patients are given access to the results, a provision must be included granting those participants who do not want to learn of their results, the right *not to know*. However, in the case of individual results as opposed to group results, many argue that relaying of non-validated information poses a risk to the participant due to data misinterpretation or misuse; also, such non-validated information or preliminary research data has no meaning to the participant. Given that pharmacogenetics is in its infancy, only occasionally will precise, useful, validated information be obtained as a result of pharmacogenetic research.
- **Handling of intellectual property generated from the use of samples:**
  While generally not a topic relevant to clinical trials, the issue of sharing benefit with individuals or the community following the provision of a DNA sample has been raised. This would be inappropriate, as it is not a feature of clinical studies, which have relied on altruism. The notion of sharing is derived from research on minority populations, not the framework of global research undertaken for pharmacogenetics. This should be made clear in the informed consent process and documents.
- **Ownership or custodianship of sample:**
  There are divided opinions about who, if anyone, should own the sample – investigator, study participant, intermediary, etc. One compromise solution suggested is based on *English Common Law* under which ownership of the body and its parts is not possible, thus rendering whoever holds the sample a good-faith custodian. The consent should make clear the details of ownership or custodianship, as appropriate.
- **Ownership or custodianship of data:**
  The informed consent should clearly state the ownership of data derived from pharmacogenetic testing along with a clear statement regarding potential intellectual property derived from the data.
- **Access to samples and data:**
  Collected samples and data are handled by a variety of processes, including analysis, storage, audit trails, third parties, submission to regulatory authorities, etc. The informed consent document should describe sample storage and access, along with any applicable restrictions and legal requirements.
- **Liability of the investigator:**
  As with all other clinical trials, it should be clearly specified the extent to which the investigator and/or sponsor conducting the trial will be held responsible if the participant suffers bodily harm or other damage. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability or negligence.

4.1.3 Possible exceptions to informed consent

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

4.2 Medical practice: Post-approval

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

4.2.1 Confidentiality

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

4.2.2 Informed consent

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

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

5. Beneficence and pharmacogenetics

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

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

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

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

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

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

6. Non-maleficence aspects of pharmacogenetics

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

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

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

6.1 Privacy

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

6.2 Discrimination

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

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

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

6.3 Requirement for protection from discrimination based on pharmacogenetic testing

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

7. Justice and pharmacogenetics

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

7.1 Fairness of distribution and potential beneficiary concerns

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

7.1.1 Ethnicity

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

7.1.2 Disease subgroups

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

7.2 Emerging economies and developing nations

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

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

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

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

8. Recommendations

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

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

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

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

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

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

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Chapter 10
Pharmacoeconomic Considerations in Pharmacogenetics

1. Introduction

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

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

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

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

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

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

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

2. Health outcome assessment

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

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

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

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

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

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

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

3. Factors affecting the economic impact of pharmacogenetics

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

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

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

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

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

3.1 Direct costs

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

3.1.1 Drug pricing

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

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

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

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

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

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

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

3.1.2 Pharmacogenetic tests

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

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

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

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

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

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

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

3.1.3 Cost for data storage and management of pharmacogenetic information

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

3.2 Indirect costs

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