Chapter 8
Genetic Testing, Genetic Data and Genetic Information

1. Introduction

The discussion about genetic testing (including pharmacogenetic testing), genetic data, and genetic information has been impeded by the lack of a clear definition of the term "genetic" in this context. To construct an acceptable definition, it is necessary to consider the possible parameters or criteria that could influence this definition in the context of testing, data, and information.

Importantly, an appropriate definition of "genetic" should not only reflect the factual, scientific or intellectual viewpoint, but also the reasons that have intensified the associated debate. These reasons include ethical, societal and legal implications, as well as the public perceptions and sentiments, which the term "genetic" evokes.

With regard to the implications of genetic (and pharmacogenetic) testing, the most important characteristic of a test is its information content, rather than its genetic nature *per se*. Therefore, distinctions based on the more technical aspects, including a differentiation between genetic and non-genetic tests are not helpful in providing guidance as to how to safeguard and use the respective information.

2. Considerations of approaches towards a definition of genetic tests

A number of different approaches have been used to get at the essence of what constitutes genetic testing. Among these are (i) choice of the analyte (the biochemical entity the test directly measures), (ii) the heritable nature of the disease or parameter tested, and (iii) the understanding and meaning of the term within the spectrum of current public perceptions.

2.1 Definition based on analyte assayed

Two broad categories of analytes assayed can be discerned:

(a) *DNA (nucleic and mitochondrial) sequence (excluding RNA expression data):*
   - Arguments for:
     Encompasses only the information that can be transmitted to subsequent generations of offspring (germ-line) or cells (somatic)

but excludes all information influenced by non-inherited factors (except for somatic mutations)
- Arguments against:
  Does not encompass any other, non-DNA-based tests that are commonly used to test for single gene disorders and that are publicly perceived as "genetic" tests e.g. protein truncation test in familial adenomatous polyposis coli.

(b) *Nucleic acid based tests (including RNA expression):*
- Arguments for:
  Will capture certain mutations in regulatory regions based on their impact on gene expression even in the absence of knowledge of the relevant mutation
- Arguments against:
  Same as under (a) above, and will encounter great difficulty in discerning inherited variants from a host of not primarily inherited phenomena that affect transcriptional activity and/or message stability.

A definition of genetic testing based on analytes only, i.e. DNA or nucleic acid, is too narrow as it would exclude a number of tests that determine the consequences of underlying DNA sequence without directly measuring the DNA sequence. On the other hand, inclusion of all RNA-expression level data would constitute a definition that is excessively broad as it includes non-DNA-based, non-heritable modulation of gene expression.

2.2 Definition based on the heritable nature of the parameter/condition tested

This definition is the one most often encountered in various documents. It usually extends the definition of genetic test to genes, chromosomes, and can include proteins (or metabolic) products.

This approach is a reasonable one for rare monogeneic, high penetrance disorders, where non-DNA-based tests results provide essentially the same specific diagnostic or prognostic information as a DNA-based test. However, given that all common complex diseases also show some degree of heritability, most biochemical markers for such diseases will also reveal some genetic information. Therefore, their analysis would also constitute a genetic test of a sort. This approach would result in a definition that is too broad and too vague, because it can legitimately include almost any

and all tests/analytes, even those with quite poor correlation with underlying DNA variance.

Examples:
Extremely high plasma cholesterol levels, as encountered in familial hypercholesterolemia, would certainly qualify as a legitimate genetic test for this condition (they carry information that is basically diagnostic of the disorder). However, any cholesterol value may be considered as information that is (in part) genetic because even lower levels are influenced by a multitude of genetic variants of the protein components of various lipid pathways. However, since environmental factors also influence cholesterol levels, it would be very difficult or impossible to determine the genetic and non-genetic components, respectively, in such a case. Similarly it is impossible to correlate most variants of the gene encoding methyltetrahydrate folate reductase with measurements of plasma homocysteine levels (to which they contribute along with dietary factors), whereas the test is diagnostic in families with homocystinuria.

2.3 Definition based on the public perception of genetic testing

Since the public perception of a categorical difference between genetic and other medical tests is providing a major stimulus to the discussion of the topic, it would appear reasonable to consider what the public understands by the term 'genetic test' when developing a definition of genetic test.

The public has so far been confronted primarily with two kinds of genetic tests: tests for rare heritable diseases and DNA testing for identification purposes (e.g. in forensic and paternity testing). The experience with these two categories is likely to have substantially influenced the public perception of what a genetic test is, and what genetic data and information mean.

The public thus tends to consider as genetic tests
- Any test (regardless of whether based on DNA or other analytes) that diagnoses or predicts one of the classic, high-penetrance, monogeneic diseases; and
- Any test that is based on the analysis of DNA sequence variation (both germ-line and somatic), including paternity and forensic testing (the latter playing an important role in public sentiment).

Significantly, these two categories are characterised by
- Extremely high information content that is unusual in the spectrum of general medical tests, particularly with regard to predicting a serious illness, and with regard to rendering highly accurate personal identification data, respectively; and
- Information content that is exclusively determined by inherited factors.

Given that
- *the vast majority of currently available genetic tests with which the public has had any experience or to which the public is exposed pertain to* the two categories mentioned (i.e. they are tests that deliver very high information content) and
- *among all medical tests that have an extremely high information content with regard to future disease prediction, the vast majority are* genetic tests predictive of rare single gene diseases,

the public has come to equate genetic testing and genetic data with highly predictive, and thus sensitive, information.

Given also that tests predictive of a single gene disease and DNA-based identity tests are rather different from the majority of all other medical tests, it is understandable that equating these two categories with genetic tests in general can result in the perception that genetic tests are indeed categorically different and of potential threat to privacy and confidentiality.

It is appropriate to be concerned about data with high information content, as the potential for abuse of any data is proportional to the amount of information it contains. It is unfortunate, but understandable, that the current examples of genetic tests which the public is most familiar with have resulted in the perception that it is the genetic nature of the test, rather than its information content which accounts for the test's sensitive quality.

2.4 Synthesis of a definition

Tests that directly provide DNA-structure-derived information (regardless of its somatic or germinal nature) should be classified as genetic tests. Similarly tests that deliver data or information that are, directly indicative of inheritable properties should qualify as genetic tests. The definition of what defines a genetic test reverts to the definition of genetic data or genetic information, which, in common use of the language (the word 'genetic' being synonymous with 'inherited'), refers to heritable characteristics.

It is, therefore, proposed that the term "genetic testing" should include:
1. Any and all tests that directly determine mitochondrial or nuclear DNA structure (sequence and chemical characteristics, and including cytogenetic data) that is transmitted to subsequent generations (of cells or offspring), regardless of its medical consequences.
2. Any and all tests which procure information pertaining to traits and characteristics regardless of the nature of the analyte (such as RNA, proteins, metabolites etc) that allow unambiguous conclusions regarding the underlying DNA sequence.

It is further helpful to distinguish between:

2.4.1 Medical genetic testing

These describe the application of *Genetic Tests* to derive information relevant to healthcare, as it relates to
- disease diagnosis,
- disease treatment,
- disease risk prediction (i.e. test indicative of a particular condition that is not clinically evident at the time of testing and that is only discernible based on the genetic test), and
- reproductive health (predictive of the likelihood of particular conditions to be transmitted to or present in offspring prenatally).

It may be noted that the latter two categories are commonly the ones that raise the greatest concerns with regard to ethical, legal, and social considerations.

2.4.2 Non-medical genetic testing

These comprise the application of *Genetic Testing* for purposes other than medical decision making. Primarily, this relates to the use for identification purposes, e.g. paternity and forensic testing and identification of the presence of animal and plant materials.

3. Consideration of approaches towards a contextual definition of genetic testing

The current public perception of genetic testing/data/information relates to the experience the public has had so far with the actual practice of

genetic testing (see section 2.3 above), all of which is characterised by one particular property, namely a *very high information content* of the information generated.

High content of information translates directly into the personal sensitivity of the data, i.e. potential for misuse or abuse, thus increasing the concerns that characterise the public debate about genetic testing. The public debate around genetics and genetic data has been based on highly predictive tests. The public has not been sufficiently exposed to the great majority of genetic data, which have much lower information content.

It is the actual information content of any set of data that renders it more or less sensitive, rather than its genetic or non-genetic nature. Therefore it would appear reasonable to differentiate among genetic data, as defined above, on the basis of information content, to arrive at a balanced and rational assessment of any given set of genetic data. Thus, to the definition given above, a metric for information content needs to be added to assess and interpret the meaning of the information. It should be noted that the information content is contextual i.e. the same set of data may carry different information content depending on the question asked.

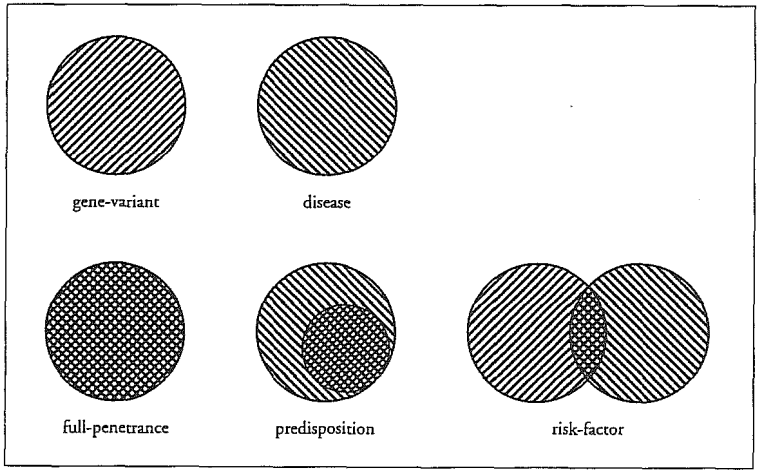
This will allow one to differentiate, among all genetic data, between information that may have particular consequences for the individual, based on its high degree of information content, and other data whose information content is smaller. Such an approach will provide a more measured and rational approach towards the use of these tests. *Notably, identical considerations apply to all other medical testing which, depending on the test, carry a spectrum of information content ranging from low and non-specific to high and very specific.*

4. Proposal for a differentiated assessment of genetic tests based on information content

Given the definition of genetic testing provided above, and in consideration of public perceptions of genetic testing, it is the information content of any given test that ultimately determines its meaning and possible ramifications for the individual. Medical science has a number of well-established parameters to measure and assess the quality of the information provided by a test, such as its positive and negative predictive value (PPV, NPV) for prospective studies, or specificity and sensitivity, for retrospective studies. It is the effective positive/negative predictive power,

or the specificity and sensitivity of a test, along with severity and medical-social impact of the disease or the clinical outcome in question which should determine its medical as well as potential social implications. These parameters are commonly affected by the nature of disease, in particular whether monogeneic or complex. Rather than using numerical values of PPV/NPV and *sensitivity/specificity* to establish a classification for genetic tests, it appears sensible to examine whether the biological mode by which these tests influence health outcomes may offer an opportunity of classifying them. Thus, it is possible to characterise broadly three categories of genetic tests that correlate with differential information content. These definitions have previously been published in a white paper on this topic [1] (see Fig 1).

Figure 1



4.1 Full penetrance tests

These apply to classic monogeneic conditions that are characterised by a very high correlation between gene variant and disease. Thus, the disease will virtually always occur if the gene variant is present (*full penetrance*), and will virtually never occur, if the gene variant is not present (i.e. there is no "imitation" of the disease based on other causes, so-called *phenocopy*). Testing for the variant gene, if positive, is highly diagnostic/predictive for the occurrence of the specific disease (high positive predictive value, PPV), while in the presence of a negative test, occurrence of the disease is

extremely unlikely (high negative predictive value, NPV). This is particularly true if the test is applied, as is usually the case, to members of families in whom the disease is known to occur (thus raising the *prior probability*, an important parameter of testing fidelity). Such tests are very unlikely to yield either a false negative or a false positive result, and therefore, display high sensitivity and specificity, respectively. Notably, predictive tests of this nature contribute a level of predictive accuracy that is almost deterministic, thus highly unusual in clinical medicine, and indeed encountered almost exclusively in these rare inherited disorders. This high degree of predictability is a consequence of the high penetrance of the genetic variant, and the usually unambiguous results of DNA-sequencing. In such conditions, all diagnostic technologies, regardless of the nature of the analyte used (nucleic acid sequence, protein concentration/structure/function, or other functional tests) may be considered *Genetic Tests* based on the definition introduced in 2.4., as long as these analytes show the same strong correlation with the disease, i.e. as long as their variance is determined by and indicative of the variance present at the level of the DNA template. Examples are Huntington's disease (testing done by DNA-sequence analysis) and phenylketonuria (testing done using a non-DNA-based assay).

4.2 Predisposition tests

These apply to familial conditions where penetrance is less than complete, but phenocopies tend not to occur. Thus, while the disease may not occur in all those who test positive (thus, modest PPV or specificity), its occurrence is considered a consequence of the presence of genetic variant when it arises in test-positive individuals. Likewise, if one tests negative, the disease is unlikely to be present or to occur. Therefore, these tests have – within the context of affected families – high sensitivity (no/few false negatives) and high NPV, but limited specificity (false positives occur). Because these constraints tend to be even greater in tests using other analytes (which reflect not only influence of DNA-based variance but are also influenced by many additional factors), only DNA-sequence based tests should be considered *Genetic Tests* in this category, in keeping with the definition provided under section 2.4. Examples are familial (BRCA1/2-related) breast cancer and hereditary hemochromatosis.

4.3 Risk factor tests

These apply to common complex diseases where penetrance for any gene variant is low, because several different genetic as well as environmental factors are generally necessary to come together to result in the appearance

of the disease, so one alone is hardly predictive. Since the same clinical presentations may arise based on various combinations of such factors, phenocopies are common. While a positive test for the presence of a particular genetic risk factor thus raises the odds of developing the disease, many of those who test positive will not develop the disease, whereas many of those who test negative may still develop the disease (based on a combination of other risk factors). Therefore, such tests are characterised by limited PPV and NPV (and/or limited sensitivity and specificity). As such, their impact on medical decision making is not different from that of many other, conventional medical tests (e.g. tests for blood pressure or cholesterol level). Therefore, again, only DNA-sequence-based tests should be considered *Genetic Tests* in this category. Examples are the Factor-V-Leiden variant and the ApoE4 alleles.

It is obvious that, as elsewhere in biology, this categorisation reflects a simplification of a spectrum of continuous variables. However, the categorisation outlined above provides a pragmatic approach towards genetic tests of quite different information content, and therefore of different potential medical and social impact on the individual. In practice, as new tests enter the clinical arena, it may be helpful to assign them to one of these categories, depending on the biological behaviour exhibited by the parameter they measure, on a case-by-case basis.

5. Pharmacogenetic tests and data

By definition, the consequences of pharmacogenetic tests will attain their full potential and application in the context of exposure to a pharmacological agent. Two conceptually quite different categories of tests, relating to interindividual differences in drug response, may be distinguished on the basis of the underlying biological variance:

(a) "Classical pharmacogenetic" tests probe for biological variation that is in itself not disease-causing or -contributory, but becomes clinically relevant *only* in response to exposure to the drug in question. These genetic variants affect either pharmacokinetic (absorption, distribution, metabolism and excretion of drugs) or pharmacodynamic interactions with a given drug.

(b) "Disease-mechanism-related pharmacogenetic" tests, in contrast, determine biological variation that is directly disease-related and *per se* of pathological importance. In this case, the test diagnoses a subgroup of the overall clinical disease/diagnostic entity. In this scenario, differential responses to a particular drug are related to whether the disease mech-

anism (pathophysiology), which the drug is tailored to target, contributes to the illness in a given patient (i.e. whether the patient belongs to that subgroup of the overall clinical disease entity for which the medicine is intended). Thus, the pharmacogenetic test may be viewed as defining the "molecular differential diagnosis" of the patient.

Although these two categories are conceptually rather different, they result in similar practical consequences with regard to the administration of a drug, namely stratification based on a particular DNA-encoded marker. While this stratification will mostly result in individually different dosing regimens in the former category, and in the determination of eligibility/ineligibility for the drug in the latter, it would still seem legitimate to include both under the umbrella term of "pharmacogenetics".

The information content for both of these categories of tests tends to be of modest magnitude, i.e. either one or both of the test-performance predicting parameters (PPV/specificity or NPV/sensitivity) will likely be in the range of the "risk factor test" category. It is important to realise that despite the commonly used terminology distinguishing, on the basis of such tests, "slow" and "fast" metabolisers (classical pharmacogenetic tests) or "responders" and "non-responders" (disease-mechanism-related tests), these tests will at best distinguish individuals *likely* to respond or not to respond in a particular fashion, given the limited information content of such tests.

6. Implications for medical practice and research

For 'risk factor tests' and, commonly, for 'predisposition tests', any classification into "genetic" and "non-genetic" (including the one proposed here) is an arbitrary one, because the (limited) quality of information that DNA-based tests yield is not materially different from the quality of information provided by any other biomedical test. Likewise (but at the other end of the spectrum), for 'full penetrance tests' there is hardly any difference in the (high) information content of the test regardless of whether the test is DNA-based test or non-DNA-based test. Thus, from the standpoint of medical information, all tests (regardless of the analyte examined) should be classified as "medical tests" and the information gleaned should be regarded as "private medical information".

6.1 Confidentiality

The information content of any medical data, including that derived from *Genetic Tests*, is highly contextual and dependent on the particular circumstances and the questions applied to them. Thus, a series of genetic markers may hold no predictive information content whatsoever with regard to any health-related issues. However, at the same time, their information content with regard to a forensic or paternity examination may be extremely high. *This mandates that any genetic data, regardless of their apparent information content, be treated with the same high standards of confidentiality as any other personal or medical data.* This mandate applies to both clinical practice and research.

6.2 Protection of human subjects

Based on the information content of a test in a particular setting, it may be prudent to examine whether special considerations should be afforded not to the test, but to individuals who are the carriers of highly predictive medical information, regardless of whether or not this information is genetic in nature.

6.3 Genetic counselling

The need for genetic counselling as part of a genetic testing procedure is dependent upon the impact of the results on the individual and/or his/her family. It may be appropriate therefore to make a distinction between 'full penetrance tests' and 'predisposition tests' and 'risk factor tests', respectively. The former category has primarily implications on reproductive decisions, and may also affect other family members in important ways. Therefore, genetic counselling is generally viewed as standard of care for carrier detection and prenatal testing for these conditions. The latter two categories should be the domain, principally, of the personal physician who is in charge of the treatment. For example, the magnitude of increased relative risk of carrying the Factor-V-Leiden variant is certainly comparable to being a smoker, and should be managed accordingly.

6.4 Quality control and regulatory supervision

As is the case with all medical testing, only stringent quality controls and assurance, and appropriate accreditation of laboratories will ensure reliable results for patients. The history of much of genetic testing – having evolved from research-based tests to clinically applied tests, without necessarily going through the appropriate establishment of standards compliant with the guidelines of Good Clinical Practice – makes it imperative that appropriate standards be set.

6.5 Testing for conditions without currently available treatment

Prenatal and postnatal testing for diagnostic purposes should be freely available, if these are indicated medically. Likewise, when requested by fully informed patients, postnatal predictive testing should be available (and offered) to them since negative test results may be as important as (or even more important than) positive ones. In addition, since most common complex diseases are multifactorial, they are also strongly influenced by environmental and life-style factors. More accurate assessment of the risk of a disease may empower people to make more informed healthcare choices, such as life-style changes that may favourably affect the overall risk. It should be noted, however, that predictive genetic testing for conditions for which no cure/prevention exists and which are likely to occur with delayed onset (e.g. Huntingdon's disease), there is general consensus that patients not preempt their children's independent decision, once they reach legal age, as to (or not to) having the test performed.

7. Social and legal aspects

7.1 "Controlled testing"

It is of course acknowledged that many believe that all genetic tests should only be available through the healthcare system. Today, however, DNA-based paternity testing and certain predisposition tests (e.g. for hereditary hemochromatosis) are freely available, often over the Internet. The right to know about one's own body is a fundamental right. Although it is clearly preferable that such testing should occur in the context of a medical consultation, it should not be denied if requested by a well-informed and consenting adult. Regulatory approval of laboratories offering such tests may include the requirement of physician consultation before undertaking such tests.

7.2 Data protection

All patients need assurance that all their medical data will be used only for the purposes authorised by them. However, many believe that patients should be free to relinquish control over the use of their personal samples and personal medical information for defined research purposes, particularly if confidentiality is assured by appropriate processes (such as after full anonymization of samples and data with appropriate systems auditing), and if data will only be used as part of an aggregate analysis.

7.3 Subject protection

To serve the intended purpose of delivering better healthcare to an individual, data derived from all medical tests, including genetic tests may need to be shared among a number of healthcare professionals involved in the care of the individual. This potentially opens the door to access of such data by unintended recipients, and misuse or abuse of the data in ways that are neither desirable nor authorised by the subject. Current concerns in this regard pertain mainly to possible discriminatory practices regarding employment and health and life insurance. To avoid such unintended use of genetic test data and, more broadly, of any private medical information, a societal consensus, including legal guidelines, will be necessary that should result in mandatory best practice principles regulating the legitimate use of such private medical data, and prohibiting its use in ways that are harmful to the individual.

8. Summary

The most important characteristic of a medical test is its information content, and distinctions between genetic and non-genetic tests lack scientific rationale and are not helpful in providing guidance as to how to use as well as safeguard the respective information and to protect the carrier from misuse of this information.

It is important, however, to be aware that the potential of discrimination based on genetic information is an issue that is of great public concern. Public apprehension about genetic tests and the potential for stigmatisation and abuse by third parties must be taken seriously and misperceptions addressed so that they do not become 'rate-limiting' to healthcare. Most importantly, society must afford its members protection from discrimination based on any medical, including genetic, data. As long as this is not provided, current public contention that all "genetic tests" may give rise to discrimination, regardless of their (mostly limited) information content, may well be justified, setting up a self-perpetuating situation that will defy factual considerations.

Genetic testing, as defined herein, offers potential new advantages for individual healthcare as well as public health. While recognising this potential, it is also important to understand its limitations. Ideally, all tests should be assessed on the basis of their merits with regard to their predictive/diagnostic power rather than to the analyte used in the test.

The public concerns with respect to DNA-based testing in general, however, are recognised and acknowledged.

Glossary of Terms:

Analyte	A biochemical or biological molecule whose qualitative or quantitative properties are analysed in a medical test.
Sensitivity	Likelihood that a person with disease will test positive. The higher the sensitivity, the lower the false negative rate.
Specificity	Likelihood that a person without the disease will test negative. The higher the specificity, the lower will be the false positive rate.
Positive Predictive Value (PPV)	Likelihood that a person with a positive test will have or develop the disease.
Negative Predictive Value (NPV)	Likelihood that a person with a negative test will not have or develop the disease.
Penetrance	Capacity of a gene variant to lead to the associated disease.
Phenocopy	Occurrence of the same disease, but not associated with the presence of a gene variant under consideration.

REFERENCE

[1] Miller F, Hurley J, Morgan S, et al.
Predictive genetic tests and healthcare costs.
Final Report Prepared for the Ontario Ministry of Health and Long Term Care.

Chapter 9
Ethical Issues

1. Introduction

Insight into the genetic variability among individuals and their response to drug treatments promises advances in the discovery, development, and use of drugs, as well as the potential to provide improved efficacy and greater safety. Understanding how patients will respond to a treatment, or if they will experience adverse events, will enable a targeted approach to treating or preventing illness. This information will result in the identification of genetically defined population subgroups that are likely to benefit most or least or even incur harm from a particular therapeutic intervention.

Because pharmacogenetics will influence both clinical research and medical practice, it is necessary to examine the ethical issues that may arise. Many documents and guidelines, both national and international, have addressed the pertinent issues of genetic data confidentiality [1], informed consent [2, 3], genetic profiling, clinical research and clinical practice [4], testing and sampling [5], patient data ownership and property rights [6].

The increase in public and private pharmacogenetic research has increased the visibility of the field and stimulated debate regarding potential ethical implications of pharmacogenetics in clinical research and medical practice. The discussion of some of the ethical issues is timely and relevant, given the public perceptions of genetic tests and genetic information in general.

2. Current ethical guidelines for medical research and practice

For the ethics of research involving human subjects [7], four basic principles have been defined that are widely accepted and used in biomedicine. These are (i) autonomy, the respect for individuals and their right to self-determination, (ii) beneficence, (iii) non-maleficence, and (iv) justice. In the Belmont Report, these principles have been defined with regard to clinical research on human subjects [8], and in the WHO's 1997 "*Report on Ethical Issues in Medical Genetics and Genetic Services*", the same principles are applied to genetic data in the context of both research and healthcare [9]. These principles may also be applied to pharmacogenetic data and research and their application to clinical practice.

- **Autonomy:**
  The principle of respect for individuals and their right to self-detemination acknowledges the subjects' beliefs and choices with regard to their participation in medical research or treatments. This principle includes the requirement for providing sufficient and unbiased information to enable them to make a considered decision. Additionally, subjects should understand the range of risk and the voluntary nature of their participation in the research or treatment plan, and the privacy protections regarding their medical data. This opportunity is provided when adequate standards for informed consent are satisfied.
- **Beneficence:**
  The principle of beneficence protects the subjects by maximising the possible benefits and minimising the potential harms of participating in clinical research or medical practice. Research sponsors, investigators and ethics committees have the responsibility to gather systematic and comprehensive information about the proposed research in order to assess if the potential benefits justify the risks posed by the research. This assessment will assist the prospective research subject or patient in the decision whether to participate in the research or treatment plan.
- **Non-maleficence:**
  The principle of non-maleficence protects research subjects and patients by minimising the potential harms of the proposed intervention. It embodies the spirit of the Hippocrates' Oath "*primum, non nocere*" (first, do no harm) and imposes on health professionals the duty to protect the patient from harm.
- **Justice:**
  The principle of justice guides the fairness in distribution of the benefits and burdens of research. The selection of subject populations and the subject as a potential beneficiary of subsequent applications of the research are considered.

While these key ethical principles apply equally to the application of pharmacogenetics in clinical research and medical practice as well as in all other areas of medicine, questions have been raised whether additional ethical considerations and guidelines are needed for pharmacogenetics. This view, implying that genetic testing and the use of genetic information are categorically different from other medical tests and medical information, has been termed "genetic exceptionalism".

3. Understanding pharmacogenetic information

Pharmacogenetic exceptionalism is the view that pharmacogenetic information is more sensitive than other types of medical information and has a higher potential for misuse and therefore requires additional measures to protect patient/subject confidentiality.

3.1 Genetic data categorisation

All genetic data, including pharmacogenetic data, should be considered as part of the overall spectrum of medical data and not classified separately. Information content, not the nature (genetic or otherwise) of test or the data, might be the only criterion that exposes genetic data to potential misuse. Procedures for protecting the confidentiality of genetic data and specimens need to be established and should accommodate variations in predictive information content and impact of the data. The following describe the current predictability choices:

- Predictive Value Unknown – the case for the majority of pharmacogenetic data where the science is evolving and the associations are not consistent or well-established
- Predictive Value Low – one risk factor in a common complex disease, e.g. the clotting Factor-V-Leiden variant in thrombosis
- Predictive Value Intermediate – markers of predisposition in certain familial forms of common diseases, e.g. BRCA1/2 in breast cancer
- Predictive Value High – for rare single-gene diseases, e.g. Huntington's disease

The information content of any medical data, including pharmacogenetic data, is contextual and dependent on the particular circumstances and questions applied to the data. Pharmacogenetic data do not have specific scientific characteristics that distinguish them from other medical data.

3.2 Considerations for public debate

As the vast majority of pharmacogenetic research is still in the exploratory stage, many questions arise as to how such information will ultimately be utilised by healthcare professionals and others. Many of these questions are fuelled by the current debate about the use of genetic information in general, and include:

- How should healthcare professionals and patients handle pharmacogenetic testing and data predictive of a drug response?

- Will the presence of pharmacogenetic information in the medical record compromise individual liberties, and expose individuals to invasion of privacy, or to discrimination?
- May an employer discriminate against current or prospective employees on the basis of their pharmacogenetic data?
- May a health insurer or provider discriminate against an individual on the basis of his or her pharmacogenetic data, or may a life insurance company reject an individual on the basis of his or her pharmacogenetic data?

In order for an informed debate to take place, it is evident that all stakeholders must have sufficient knowledge about the nature and potential application of pharmacogenetic information as applied to healthcare.

3.3 Reflecting perceptions and need for education and rational public policy

The current discussion about genetic information is influenced by the perception that all genetic data are deterministic, convey exceptionally high information content, and are highly relevant with regard to both the genetic marker carrier and his/her relatives. However, the vast majority of our physical and psychological characteristics are not simply a consequence of inherited properties but are also influenced by external factors (environment, life-style, optimisation of drug therapy, etc.).

While tests for certain rare, monogenetic disorders carry such high specificity and sensitivity that the perception of determinism may appear justified (such as in the case of Huntington's disease), there are tests for non-genetic disorders that carry similar information content (e.g. HIV). Pharmacogenetic tests are expected to be much less predictive than those of single gene disorders and to carry more probabilistic information, similar to determination of blood pressure or cholesterol levels. Inappropriate generalisation from the few, highly predictive genetic tests, to the much less predictive pharmacogenetic tests, has led to some perceptions about pharmacogenetic tests as carrying a higher potential for misuse, thus requiring a greater degree of protection. Education regarding the context and value of pharmacogenetic data needs to be developed for both general and medical audiences. This education will help dispel misunderstandings of genetic exceptionalism and counter any unwelcome tendencies toward discrimination based on pharmacogenetic information.

If society continues to embark on genetic exceptionalism or accepts any discrimination based on pharmacogenetic test results, then the recommendations based on information content, rather than on nature or source of data, will become irrelevant. It is extremely important to reinforce rational public policy and dispel public misunderstanding.

4. Autonomy issues and pharmacogenetics

4.1 Clinical research/study: Pre-approval

Based on the principle of self-determination, participation in pharmacogenetic research should be voluntary. Where possible, this includes not making participation in the actual clinical study contingent on participation in the pharmacogenetic sub-study. Early clinical research or studies conducted for exploratory, hypothesis-generating or hypothesis-testing purposes during pre-approval phase of new therapies should also be subject to this principle of self-determination and autonomy. Thus participation in pharmacogenetic testing, as in any clinical study, should be voluntary and independent of participation in the actual clinical study.

Clinical research or studies involve clinical decisions and well defined inclusion criteria or subject selection based on pharmacogenetic testing (i.e., core selection based on having a particular genotype). In instances, where pharmacogenetic test results provide for an inclusion or exclusion criterion, then the subject's agreement to participate in the clinical study will be linked with the subject's agreement to participate in pharmacogenetic testing; therefore, the subject's participation in the pharmacogenetic portion cannot be independent of the clinical study participation.

4.1.1 Confidentiality

Confidentiality is a complex concept that is both intrinsic and instrumental, involving several different, but overlapping personal interests [10]. Control over highly personal information is central to the goal of confidentiality within the pharmacogenetic setting. Patients should be informed about who will have access to their pharmacogenetic test results, and must be reassured that no parties, other than the authorised ones they are informed about, will have access to their pharmacogenetic test results. In particular, the sharing of samples among several research groups and across borders must be considered in accordance with international and local laws and practices.

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