Typically, a physician prescribes the recommended medicines in the average recommended dosage to his or her patient. If the medicine does not work, and the drug is approved for a range of doses, the physician may try a different dose or may switch to an alternative treatment. Time and money are wasted from unnecessary visits to the physician and the cost for ineffective medicine(s) either used or remaining unused (usually cannot be resold). It is becoming increasingly evident that much of the interindividual variation in response to drugs is inherited and it is clear that not all patients who appear to have the same indication benefit from the treatment. Whereas there are some estimates of the magnitude of the problem arising from adverse drug reactions, there is hardly any systematic prospective information on the scale of the problem arising from treatment failure. There are no well-controlled studies to demonstrate how ineffective many of the well-established therapies are. How many years and how many patients does one need to treat with "statins" to avoid one death from cardiovascular disease? Estimates available suggest certainly more than 10 patients for at least two years per one death avoided. If it were possible to predict with very high probability in which individuals these lipid-lowering drugs do not work at all (this may or may not be the case), not only would there accrue an enormous savings in resources but also many patients would be spared unrealistic high expectations of benefit. These patients may well benefit from alternative potentially effective treatments that may work for them.

3. Polymorphisms and the human genome

With recent advances in molecular genetics and genome sequencing, pharmacogenetic research has attracted enormous attention from both the scientific communities and the public. This is due to new technologies that permit rapid screening for specific polymorphisms, as well as recently gained knowledge of the genetic sequences of target genes such as those coding for enzymes, receptors, ion channels, and other types of pharmacological targets involved in drug response. As a result of the completion of the Human Genome Project and other public initiatives such as The SNP Consortium (single nucleotide polymorphisms, see http://snp.cshl.org), comprehensive maps of the human genome have been established including information on genetic variations associated with disease susceptibility as well as pharmacokinetics and pharmacodynamics. However, in general, identification of single nucleotide polymorphisms is ahead of the clinically more important task of correlating genotypes with phenotypes.

Research in pharmacogenomics and pharmacogenetics is developing in two main directions: firstly, identifying specific genes and gene products associated with various diseases which may act as targets for new drugs and/or diagnostic tools and, secondly, identifying genes and allelic variants of genes that affect the response to drug therapies.

Increasing numbers of research programmes have evolved from the Human Genome Project, including genome-wide screens to identify differences between individuals that arise from a single base pair alteration in their DNA or single nucleotide polymorphisms (SNPs). SNPs can be used to map and identify specific genes associated with various diseases such as cancer, diabetes, and arthritis. Many of the proteins encoded by these genes are expected to be new targets for drug therapy but may also improve our diagnostic capabilities and help to stratify otherwise heterogeneous diagnostic groups into more precise subgroups that may have different responses to the existing therapies. The fact that these genes were identified by polymorphism analysis indicates that drugs directed at such targets may have different effects in different patients. This leads to the concept of drug stratification or individualised drug treatment, in which the choice of drug, or the dose of a drug, is influenced by a patient's genetic status.

Genomic analysis has generated an enormous amount of information on human polymorphisms. There are over 4 million single nucleotide polymorphisms in public databases and more will probably be identified over the next few years. However, a greater challenge will be to determine the function of each polymorphic gene or, to be more exact, of the gene product and its variant forms. It should be noted however, that it might not always be necessary to know the function of a polymorphism as it relates to clinical utility. This is often seen in many drug development programmes, where compounds progress to demonstrate clinical utility, without its mode of action having been elucidated. In some circumstances, it may be necessary to determine the functional significance of a gene product for its toxicological importance and whether individual allelic variants are of therapeutic importance. Such expression and function profiling studies that enables the testing of genotype-phenotype correlations are expected to be extremely important for further advances in the field of pharmacogenetics.

In terms of current clinical practice, it is more relevant to determine individual genetic variations that will improve both the efficacy and safety of existing therapies. Because a relatively large number of patients receiving

a drug fail to gain the expected benefit, pharmacogenetics may identify the reasons for lack of benefit in certain individuals. However, adverse reactions are a major societal and economic healthcare problem and patients are more concerned about drugs doing harm to them. Therefore, the overall impact of pharmacogenetics in improving safety is equally important, if not more than in improving efficacy. Polymorphism in any one of many genes including those encoding drug receptors, drug transporters, and cell signalling pathways can be important factors in determining clinical response. It appears that among the polymorphisms of clinical relevance and of immediate utility are those involved in drug metabolism and disposition (e.g. CYP2D6, TPMT).

Functional polymorphisms in any one of these genes can lead to either a lack of therapeutic effect, unexpected clinical responses or an adverse reaction (Table 1).

Table 1
Potential effects of polymorphic drug metabolism on drug treatment

1. Adverse drug reactions
2. Extended pharmacological effect
3. Lack of prodrug activation
4. Metabolism by alternative, deleterious pathways
5. Ultrarapid metabolism (e.g. duplicated CYP2D6)
6. Modification of drug-drug interactions

The reader is referred to Chapters 2 and 3 on "Abnormal Drug Response" for additional discussions.

Polymorphisms have now been identified in more than 20 human drug metabolising enzymes, several with substantial inter-ethnic differences in their frequencies. The phenotypic consequences of some of these are critical determinants of therapeutic outcome [9-13]. Important examples are polymorphisms in the cytochrome P450 enzymes and in thiopurine S-methyltransferase (TPMT).

3.1 Cytochrome P450 drug metabolising enzymes

The cytochrome P450 drug metabolising enzymes (frequently referred to as CYP isoforms) are a multi-gene family of enzymes found predominantly in the liver (but present also in other tissues such as the brain). They are responsible for the metabolic elimination of a vast majority of

the drugs currently used in medicine. Genetically determined variability in the level of expression or function of some of these enzymes has a profound effect on drug response. In 'poor metabolisers' the genes encoding specific cytochrome P450s often contain inactivating mutations, which result in a complete lack of active enzyme and a severely compromised ability to metabolise drugs.

Thus, mutations in the gene encoding cytochrome CYP2D6 (known previously as debrisoquine hydroxylase) give rise to distinct phenotypes in a population – extensive and poor metabolisers. Case reports suggest that this polymorphism has clinical consequences for some individuals (see Chapter 3 on "Abnormal Drug Response"). Polymorphism not only affects drug disposition but can also be important in the conversion of prodrugs to their active form. Codeine is an old and widely used pro-analgesic that is metabolised to the analgesic morphine by CYP2D6, and the desired analgesic effect is not achieved in CYP2D6 poor metabolisers. CYP2D6 is highly polymorphic and is inactive or dysfunctional in about 6-9% of Caucasians of white origin [14]. Thus, millions of people worldwide may be potentially at risk of compromised metabolism or adverse drug reactions when prescribed drugs that are CYP2D6 substrates. Many CYP2D6 substrate drugs are used for treating chronic illnesses such as psychiatric, neurological, and cardiovascular diseases (Table 2). They have a narrow therapeutic window, commonly have side effects and are intended for long-term administration. Clinical problems can also arise from the co-administration of drugs that inhibit CYP2D6 or compete with its other substrate(s). A drug may interact with and inhibit CYP2D6 to the extent that the enzyme is no longer functionally active, resulting in a patient responding like a poor metaboliser even though he or she has an 'extensive metaboliser' genotype. Thus, quinidine, a powerful CYP2D6 inhibitor, may exaggerate the effects of other CYP2D6-metabolised drugs that are prescribed concomitantly or may prevent the metabolic activation of drugs such as codeine by CYP2D6.

Another variant results from amplification of the entire CYP2D6 gene, with some individuals inheriting up to 13 copies of the gene, arranged in tandem [15]. This amplification polymorphism results in affected people metabolising drugs that are CYP2D6 substrates so quickly that a therapeutic effect cannot be obtained at conventional doses. For example, it has been estimated that, while a daily dose of 10-20 mg nortriptyline would be sufficient for a patient who is a CYP2D6 poor metaboliser, an 'ultrarapid metaboliser' inheriting multiple copies of the gene could require as much as 500 mg a day [16]. These individuals develop rapidly accumu-

Table 2
Examples of drugs that are substrates of cytochrome P450 CYP2D6

Cardiovascular drugs	Neuro-psychiatric drugs	Analgesics	Miscellaneous
Alprenolol	Amitriptyline	Codeine	Atomoxetine
Bufuralol	Clomipramine	Hydrocodon	Chlorpheniramine
Carvedilol	Desipramine	Oxycodon	Dexfenfluramine
Encainde	Doxepin	Tramadol	Dextromethorphan
Flecainide	Duloxetine		Methadone
Indoramin	Fluoxetine		MDMA ("ecstasy")
Metoprolol	Haloperidol		Phenformin
Mexiletine	Imipramine		Sparteine
Nebivolol	Levomepromazine		Tolterodine
Oxprenolol	Maprotiline		Traxoprodil
Perhexiline	Mianserin		Tropisetron
Propafenone	Nortriptyline		
Propranolol	Paroxetine		
Timolol	Perphenazine		
	Risperidone		
	Sertindole		
	Thioridazine		
	Trimipramine		
	Venlafaxine		
	Zuclopenthixol		

lating metabolites that may prove toxic. For example, ultrarapid metaboliser may experience morphine toxicity following administration of codeine [17].

CYP2C9 is another member of the cytochrome P450 superfamily, which metabolises warfarin and phenytoin. Its activity influences patients' response to these well established drugs with narrow therapeutic index and their dose requirements [18-20].

3.2 Thiopurine S-methyltransferase

Another clinically important polymorphism occurs in the enzyme thiopurine S-methyltransferase (TPMT) [21, 22] that is responsible for the metabolism of the antitumour agents, azathioprine, 6-mercaptopurine and 6-thioguanine. Genetic mutations at the locus expressing this enzyme are associated with difficulty in avoiding toxicity whilst trying to achieve an effective concentration of these drugs in children with childhood acute lymphoblastic leukaemia [23]. Children with inherited TPMT deficiency exhibit severe haemopoietic toxicity when exposed to normal doses of drugs such as 6-mercaptopurine, whereas those with a high activity form of the enzyme require high doses of the drug to achieve any clinical benefit. TPMT polymorphism is relatively rare, with only about 1% of the white population being homozygous for it, but, since these individuals show exaggerated toxic responses to normal doses of these drugs, TPMT phenotype may be an important factor in the successful treatment of childhood leukaemia. Some centres already provide a diagnostic genotyping or phenotyping service to guide the clinical use of 6-mercaptopurine and azathioprine.

Other major polymorphic drug metabolising enzymes, including members of the cytochrome P450 family and phase II conjugating enzymes, have been recently reviewed [10].

3.3 Genetic polymorphisms and their potential for improving existing therapies

The following is a brief list of receptor and enzyme polymorphisms that are likely to affect response to existing therapies (selected examples of clinically important polymorphisms)

1. ß1-and ß2-adrenoreceptors
2. Angiotensin-converting enzyme (ACE)
3. Serotonin transporter (5-HTT)
4. 5-lipoxygenase (ALOX-5)
5. Cytochrome P450 enzymes (e.g. CYP2D6, CYP2C9, CYP2C19)
6. N-acetyltransferase 2 (NAT2)
7. Dihydropyrimidine dehydrogenase (DPD)
8. Cholesteryl ester transfer protein (CETP)
9. Multi-drug resistance protein (MDR-1) (P-glycoprotein)
10. Thiopurine S-methyltransferase (TPMT)
11. Leukotriene synthesising enzymes and receptor polymorphisms.

4. The current situation

Pharmacogenetic testing is currently used in a relatively limited number of teaching hospitals and specialist academic centres. The widely practised application of pharmacogenetic testing is the use of CYP2D6 genotyping to aid individual dose selection for drugs used to treat psychiatric illness.

Several independent testing laboratories have started to provide the pharmaceutical industry and medical practice with a high throughput, DNA-

based, testing service for a range of pharmacogenetic polymorphisms. It is, however, difficult to predict to what extent the pharmaceutical industry will routinely incorporate pharmacogenetic testing into prescribing schedules for drugs that are subject to polymorphic metabolism. This will depend to some extent on the attitude of the drug regulatory authorities. The reader is referred to Chapter 7 on "Regulatory Perspectives in Pharmacogenetics".

The clinical applicability and cost-effectiveness of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. Physicians need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and know how to use this knowledge. In addition, a reliable, DNA based, testing service needs to be made available. Pre-treatment genotyping may allow a more appropriate choice and doses of specific drugs, particularly those for treating psychiatric disorders. At present, adverse drug reactions occur in a substantial proportion of patients: a recent US study showed that, in patients prescribed psychiatric drugs that are CYP2D6 substrates, adverse drug reactions were observed in every patient with inherited mutations inactivating the CYP2D6 gene [24]. Others have questioned whether genotyping for CYP2D6 alone has much to offer in safe and effective use of neuroleptic drugs [25]. Nevertheless, Kirchheiner et al have provided a preliminary guidance for a number of drugs metabolised by CYP2D6 and CYP2C19 with a view to introducing genotype/phenotype-specific dose schedules [26].

5. The future

Pharmacogenetics is still an evolving discipline where for certain pharmacogenetic tests, there is ample mechanistic and epidemiological evidence demonstrating their value in improving risk/benefit. For other pharmacogenetic tests, the evidence is only suggestive, but not definitive, of clinical value. We are still a long way from having a pharmacogenetic DNA chip that general practitioners can use to identify all the drugs (or doses of a drug) to which any particular patient is responsive, non-responsive or intolerant.

However, there is increasing evidence that pharmacogenetics may become a valuable tool in health service. One day it may be considered unethical not to carry out such tests routinely to avoid exposing individuals to doses of drugs that could be ineffective or even harmful to them. The ability to identify sensitive individuals, either before drug treatment or after an adverse

drug response, would also be of economic importance as it would avoid the empiricism associated with matching the most appropriate drug at its optimal dose for each patient. It might also substantially reduce the need for hospitalisation, and its associated costs, because of adverse drug reactions.

Increase in knowledge of the mechanisms of drug action, identification of new drug targets and understanding of genetic factors that determine the response to drugs may allow us to design drugs that are specifically targeted towards particular responder populations, avoiding genetic variability in therapeutic response. The extent of genetic polymorphisms in the human population indicates that pharmacogenetic variability will probably be an issue for most new drugs.

The development of pharmacogenetics provides at least one mechanism for taking drug prescription away from its current empiricism and progressing towards a more patient-tailored 'individualised' drug treatment. Already, in the UK, the Department of Health has initiated an innovative GB£4 million start-up funding scheme for supporting research aimed at exploring the role of pharmacogenetics in improving existing therapies that patients are commonly taking now or are likely to be taking soon [27]. Proposals could involve the development of new services or new roles in existing therapies and applications for funding closed on 25 February 2004 [see http://www.doh.gov.uk/genetics/servicedev.htm] and six research projects investigating the value of pharmacogenetics in improving existing therapies have been funded.

5.1 Predicted developments

1. Changes in product information. Prescribing advice will start to relate dose to genotype and will highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.
2. Step-wise creation and implementation of prescribing guidelines, based on clinical studies, for drugs that are subject to substantial polymorphic metabolism.
3. Establishing and recording of individual patient genotypes and phenotypes i.e. 'personal pharmacogenetic expression profiles' as part of medical records.
4. Implementing pharmacogenetic testing may substantially reduce the need for hospitalisation following the use of existing therapies, and its associated costs, because of reduction in adverse drug reactions.
5. More public funds channelled to research concerning existing therapies as outcomes may save considerable public spending on existing drugs,

unlock finances for the development of new therapies and achieve better health outcomes for the populations.

Anticipated benefits of pharmacogenetics and pharmacogenomics for existing treatments:

1. Improving rational drug use and possible wider access to medicine – identify people most likely to respond to certain drugs and avoid using these drugs in those who may be at risk of serious adverse drug reactions
2. Reviewing for use in specific subgroup of patients those drugs that have been withdrawn and expanding indications for drugs already on the market
3. Step-wise elimination of "trial-and-error" or "one-size-fits-all" approach to prescribing
4. Saving resources.

5.2 Limitations and challenges

1. Motivation to fund research related to existing therapies may be low and compete with motivation to invest into new therapies
2. Public acceptance of genetic profiling may need time
3. For existing medicines, access to more targeted prescribing approach may be too costly to attract funds
4. Distinguishing environmental factors from genetic factors may be more difficult than expected and cause failure to achieve better treatment outcomes with pharmacogenetic approach
5. For existing medicine, complexities of interactions with drugs and other types of health products may not have been investigated and may complicate pharmacogenetic targeting approach.
6. Pharmacogenetic targeting may raise ethical issues that need to be identified and discussed (see Chapter 9 on "Ethical Issues").

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Chapter 7
Regulatory Perspectives in Pharmacogenetics

1. Introduction and background

Environmental and genetic factors, together with therapeutic interventions are the major determinants of public health. The sequencing of the human genome and the development of genetic and genomic technologies promise to improve public health and the economics of healthcare. The technologies can provide knowledge of how pharmacogenetic and pharmacogenomic information can be used to optimise the risk/benefit of many drugs and reduce the incidence of adverse drug reactions.

There is a diversity of opinion regarding the definitions of *pharmacogenetics* and *pharmacogenomics*. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. For example, polymorphic variations in the genes that encode the functions of drug metabolising enzymes, transporters, ion channels and receptors can result in wide interindividual differences in the dose-plasma concentration-response relationships for many important therapeutic agents. Pharmacogenetic studies include applications of single gene sequences or a set of multiple gene sequences to investigate variations in DNA sequence that may influence drug response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. In this context, pharmacogenomic studies include a whole spectrum of markers ranging from genome-wide scans, single nucleotide polymorphisms (SNP), candidate genes, haplotype markers and alterations in gene expression or inactivation that show promise to be predictive of drug action. Moreover, integrating pharmacogenetic and pharmacogenomic information following recent progress in human genetics and genomics has given new insights into (a) the basis for heterogeneity in disease states (e.g. subtypes of breast cancer), (b) predictive medicine (e.g. risk of developing or preventing Alzheimer's disease) and (c) dosage regimen selection for subgroups of patients (e.g. poor and extensive metabolisers of a drug metabolised by CYP2D6). Pharmacogenetics and pharmacogenomics promise to improve our understanding of the natural interindividual variability in disease susceptibility and drug response and have the potential to improve drug development and therapeutics in the future.

2. Drug development and regulatory assessment

Genome-based technologies have become more readily available, cost effective and reliable. As a result, pharmaceutical companies today are collecting pharmacogenetic or pharmacogenomic data in an increasing number of early and late clinical drug trials. However, many of these applications in drug development are exploratory and in most cases it is not yet apparent how to determine *a priori* how individuals would respond to a drug. Thus, there are only a few cases where pharmacogenetic or pharmacogenomic data have been incorporated into registration applications as a confirmatory test. In the future however, as our knowledge of hereditary factors and other determinants of drug response evolve, it is anticipated that the drug development process will lead to regulatory assessment, approval and marketing of drugs that would be genetically driven and individually tailored for optimal response.

The current regulatory framework in terms of guidelines that already recommend the sponsors of new drugs to explore pharmacogenetic influences during drug development and in terms of labeling of some drugs is described in Chapter 4 on "Exploring Pharmacogenetics in Drug Discovery and Development".

Regulatory agencies have the dual responsibility of protecting public health by assessing the risk/benefit, doses and dosing regimens of drugs and of promoting efficient and optimal drug development. Regulatory authorities worldwide share a common goal with the pharmaceutical industry to make available drugs that are effective, relatively free of serious adverse events, and have acceptable risk/benefit ratios. Thus, regulatory agencies and the pharmaceutical industry should encourage and facilitate exploration and utilization of pharmacogenetics and pharmacogenomics in the drug development process when and where it can make a perceptible difference in the practice of medicine.

There are three broad components of public health and drug therapy that are related to the use of pharmacogenetics and pharmacogenomics and are of interest to regulatory authorities:

2.1 Drug efficacy and effectiveness

Pharmacogenetic and pharmacogenomic data can be used to identify drug targets for specific subsets of a disease, or to identify a responder (or non-responder) to a drug in advance and thereby reduce the risk of therapeutic failure.

2.2 Drug safety and adverse events

Pharmacogenetic and pharmacogenomic data can be used to identify *a priori* subsets of the target patient population who are at greater risk of developing a drug-related adverse event, and thereby reduce the frequency of adverse reactions.

2.3 Drug dose and dosing regimens

Pharmacogenetic and pharmacogenomic data can be used to identify, prior to prescribing a drug, an appropriate dose for different subsets of patients that would improve the risk/benefit of the drug in these subsets in order to individually optimise therapy.

Thus, in many ways, regulatory agencies believe that pharmacogenetics and pharmacogenomics may provide a more effective tool in risk management.

3. The Pharmacogenetic/pharmacogenomic paradigm

The general approach to applying pharmacogenetics or pharmacogenomics in drug development is likely to be a three-step process.

3.1 Selection of a target disease or drug candidate

Usually the target disease is a common one whose pathophysiology is heterogeneous and where drug effects on clinical endpoints are highly variable between patients but where variability in response, for the most part, is unrelated to environmental or life-style factors. The candidate drug is likely to be one of several therapies available for a disease and its site and mechanism of action are well characterised.

3.2 Development of a predictive pharmacogenetic or pharmacogenomic test

The pharmacogenetic test usually is based on genetic variation in one or more biomarkers as evidenced by SNP or haplotypes, by basal gene expression levels (e.g. mRNA levels) or by predictive expression patterns in target pathogenic tissue (e.g. tumours), or in host tissue. The test is likely to predict responsive disease subsets of patients, the risk of disease progression or the likelihood of achieving efficacy, having adverse events or improving the selection of the dose of a drug for a given patient.

3.3 Determination of the analytical validity, clinical validity and clinical utility of a predictive pharmacogenetic or pharmacogenomic test

The analytical validity defines the accuracy and precision of the pharmacogenetic or pharmacogenomic test in measuring the genotype of interest. It is often expressed as analytical sensitivity and specificity and the performance of the test is commonly compared to a "gold standard".

The clinical validity describes how good the test is in predicting clinical outcome. It is frequently characterised as the clinical sensitivity and positive or negative predictive values of the pharmacogenetic or pharmacogenomic test for biomarkers of drug efficacy or safety. In order to establish clinical validity, the biomarkers may be identified early and determined later in clinical trials involving patients with the target disease that may develop an adverse reaction, or fail to respond to therapy. This often involves stratification of patient enrolment in clinical trials.

The clinical utility of a positive or negative pharmacogenetic or pharmacogenomic test determines how good the test and associated interventions are in improving health and/or preventing disease. The most rigorous assessment of clinical utility is through randomised, controlled clinical trials in which patients are randomly assigned to different interventions based on the results of the test.

4. Limitations and challenges of pharmacogenetics and pharmacogenomics

It is important that industry and regulatory authorities recognise the major limitations and challenges of using pharmacogenetic and pharmacogenomic information in clinical trials. Predictive pharmacogenetic and pharmacogenomic tests are complex in that their utility may be related to either disease biology (defining something about a patient's current or future disease condition) or drug response (defining the probability or likelihood of a clinical outcome both desirable and undesirable).

The limitations and challenges include the following:

- Patient populations are genetically heterogeneous; the phenotypes of the same common diseases, or many diseases with unmet medical need, are the result of complex interactions between genetic traits, and in some cases, the environment

- Because of population heterogeneity, a pharmacogenetic or pharmacogenomic test may identify only a small proportion of patients in which inherited mutations at one or more gene loci contribute significantly to the disease phenotype. This may lead to orphan drug status for an intervention; however, the threshold for an orphan drug differs between countries.
- Responses to drugs are highly variable between subjects, and are influenced by multiple genetic factors as well as non-genetic covariates such as drug interactions or co-morbidities
- Careful consideration must be given to the clinical and regulatory criteria in defining useful genotype-phenotype associations
- There is a need to develop efficient study designs and to adapt statistical methods and information technology paradigms for the accrual, analyses and reporting of pharmacogenetic/pharmacogenomic data

5. Current situation

At present, there are few examples of pharmacogenetic or pharmacogenomic predictive or diagnostic tests that have been approved by a regulatory agency for the purpose of individualising therapy.

Among the few exceptions are the immunohistochemical and DNA-based tests respectively to detect tumour HER-2 over expression in women with breast cancer who would benefit from trastuzumab (Herceptin® Roche), and the use of viral DNA tests to determine the level of drug resistance in patients that are HIV positive as an aid in the selection of a protease inhibitor. To date, much of the discussion between the pharmaceutical industry and regulatory agencies about pharmacogenetics and pharmacogenomics has focused on issues relating to emerging regulatory policy with respect to the validity, predictability, and usefulness of pharmacogenetic and pharmacogenomic data. In many ways, the development and use of pharmacogenetic or pharmacogenomic tests represent an "enrichment" tool for characterising safety or efficacy in clinical trials. Enrichment of target populations in drug development for efficacy promises to allow studies to be smaller and more efficient by excluding the enrolment of non-responders. However, one of the major unresolved concerns is how sufficient safety data will be acquired on a new drug when genotyping for efficacy is used to select patients for enrolment in a pharmacogenetic/pharmacogenomic clinical trial. Applications of pharmacogenetics/pharmacogenomics in the post-marketing surveillance setting may provide options for addressing this concern.

While inclusion or exclusion of particular genotypes or phenotypes (e.g. particular protein or mRNA expression patterns) is similar to other forms of enrichment that are well known to regulatory agencies and industry, there are several short-term considerations for regulatory agencies and the pharmaceutical industry as delineated below:

- Regulatory agencies worldwide have formed internal working groups to focus on issues of pharmacogenetics and pharmacogenomics with the intent of increasing an understanding of the science and to consider the need and feasibility of regulatory guidances or guidelines for industry. The achievement of a harmonised approach to pharmacogenetic/pharmacogenomic data is highly desirable to facilitate global consistency in the use of such data in drug development and regulatory assessment.
- Regulatory scientists anticipate seeing greater use of cytochrome P450-based genotype tests in drug development. This would lead to more information on the use and value of such tests in product information; for example to characterise clinical trial population into extensive and poor metaboliser genotypes and to include descriptions of any new pharmacogenetic or pharmacogenomic data (obtained from advanced technologies) from exploratory or confirmatory clinical trials in regulatory submissions. An important issue will be when and how to incorporate this information into labelling and package inserts.
- It is important to maintain an open dialogue between regulatory agencies, academic researchers and pharmaceutical company scientists to explore ways that encourage and facilitate the exploratory use of pharmacogenetic/pharmacogenomic technologies and exploit the clinical value of these sciences for improving public health, without penalizing companies that choose to do so.
- One possible cause of adverse drug reactions is genetic variation in how individuals metabolise, and in some cases, transport drugs. For those drugs that are metabolised by an enzyme that is polymorphic (e.g. CYP2D6), differences in systemic exposure from a given dose should be assessed early in drug development. If these differences can be shown to be associated with a higher risk of adverse events, or failure of usually recommended doses to provide efficacy in patient subsets, this information should be included in the product label and an appropriate dose should be recommended for the subset of at-risk patients defined by genotype. Consideration would need to be given not only to the prevalence of genetic variants in the intended target population but also the clinical significance of adverse reactions, the overall risk/benefit of the drug and genotyping a large number of potential recipients of the drug.

- If genetic tests were to be used prospectively for identifying drug responders or for identifying at-risk patients, the following evidence would be necessary for regulatory approval:
  - measures of the analytical quality of the test (analytical validation)
  - data from 'functional' studies (i.e. studies that relate DNA changes to alterations in protein function and/or levels) identifying predisposing genetic/genomic factors involved with disease pathogenesis to the extent of what is known about a disease, or genetic polymorphisms that may increase the benefits or lower the risk in patients receiving drugs. These data should be supportive of the genotype-phenotype association on which the test is based and
  - information on the clinical validity and clinical utility of the test for therapeutic applications and decision making. Consideration would need to be given to the design of the pivotal clinical trials to provide sufficient information to estimate the positive and negative predictive value of any genetic test (specificity and sensitivity), and the clinical benefit to drug use with and without the use of such a test;
- There will be a need for independent replication of outcomes in the regulation of pharmacogenetic tests, i.e., to have evidence of replication of the findings of an association between the test and clinical endpoints. It will be important to establish the reliability (sensitivity, specificity etc) of the genetic test in several clinical laboratories and to assure the clinical validity of the test (both positive and negative findings). Consideration will need to be given to whether the test specified in the label of a drug product is mandatory (most likely) or optional before prescribing the drug. These considerations will take into account the rationale and level of evidence supporting the clinical utility of the test. Ideally, the regulatory authorities will approve drug-specific predictive tests recommended in package inserts at the time of approval of the drug product.
- Use of case-control pharmacogenetic and pharmacogenomic studies to explore associations between genomic biomarkers and adverse events or effectiveness with drug therapy would be considered exploratory and hypothesis generating in most cases.

6. Summary and conclusions

Pharmacogenetics and pharmacogenomics should be considered in all phases of drug development. These sciences have considerable potential to improve our understanding of drug safety and efficacy and to improve our development of optimal drug doses and dosing regimens.

However, with this potential in mind, the application of genetic and genomic technologies should be based on good science and applied where it has the greatest chance to improve decision making not only in drug development, but also in regulatory assessments.

Continued dialogue between academic researchers, industry scientists and regulatory agencies is needed to reduce uncertainties in the rapidly evolving fields of pharmacogenetics and pharmacogenomics. Together, they can guide strategies for exploring these technologies and utilizing data in drug development and regulatory assessment in order to optimise the benefit/risk ratios of future drugs for society.

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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.

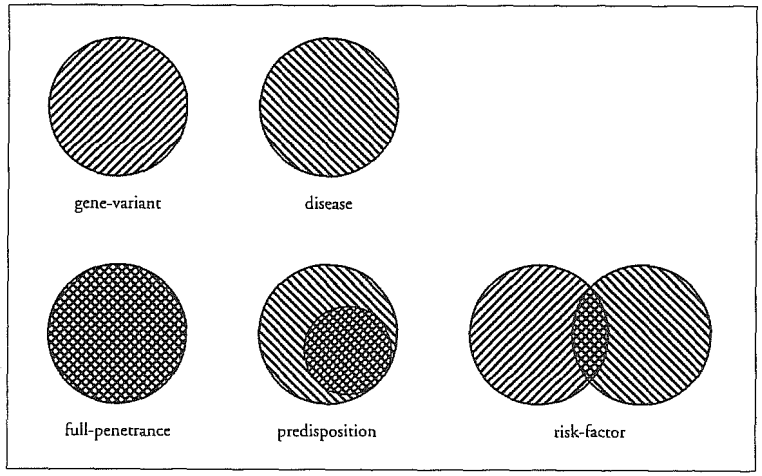
This will allow one to differentiate, among all genetic data, between information that may have particular consequences for the individual, based on its high degree of information content, and other data whose information content is smaller. Such an approach will provide a more measured and rational 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.

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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.