

ETHICAL PERSPECTIVES ON PHARMACOGENOMIC PROFILING IN THE DRUG DEVELOPMENT PROCESS

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Pharmacogenomics, which is a field that encompasses the study of genetic polymorphisms that underlie individual differences in drug response, is rapidly advancing. The potential for the widespread use of pharmacogenomics in the drug development process merits an examination of its fundamental impact on clinical-trial design and practice. This article provides a critical analysis of some of the issues that pertain to pharmacogenomics in the drug development process. In particular, four areas will be discussed: clinical-trial design; subject stratification; some new social risks; and economic concerns. Recommendations are offered for addressing the issues that are discussed and anticipating the regulatory needs for pharmacogenomics-based trials.

GENETIC POLYMORPHISM

The difference in DNA sequence among individuals, groups or populations. Genetic variations that occur in more than 1% of a population would be considered useful polymorphisms for genetic-linkage analysis.

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Over the past several years, as a result of developments from the Human Genome Project (HGP), there have been unprecedented advances in our understanding of the role of GENETIC POLYMORPHISMS in the response to therapeutic drugs^{1–3}. Pharmacogenomics is a relatively new field that was spawned by these advances, which includes the study of genetic variations or polymorphisms between individuals, and how these variations influence responses to therapy. Although ‘pharmacogenomics’ and the older term ‘pharmacogenetics’ are often used interchangeably, pharmacogenomics is broader in scope, and refers to the complex interactions of genes across the genome. Pharmacogenomics includes identifying candidate genes and polymorphisms, correlating these polymorphisms with possible therapies, predicting drug response and clinical outcomes, reducing adverse events and selection, and selecting dosing of therapeutic drugs on the basis of GENOTYPE⁴. Individual variations in the response to drugs and drug toxicity is a common occurrence in the clinical setting and in drug development research protocols. Indeed, individual differences in drug response contribute to several adverse events that have long been recognized as being an important clinical problem^{5–8}.

One goal of pharmacogenomics is to customize drugs for defined sub-populations of patients, and,

eventually, perhaps even tailor therapies for specific individuals (FIG. 1). This application of pharmacogenomics has implications for predicting a patient’s response to medications, reducing adverse events and improving rational drug development. Increasingly, pharmaceutical companies, new biotechnology companies and industrial–academic partnerships are focusing on pharmacogenomics approaches^{9,10} (see the National Institutes of Health (NIH)–National Institute of General Medical Sciences (NIGMS) **Pharmacogenetics Research Network**), and testing human research subjects in clinical trials is well underway^{2,11–22} (TABLE 1). Indeed, most Phase II and III trials that are undertaken at present involve taking samples of genomic DNA for pharmacogenomics purposes^{2,3}.

Pharmacogenomics promises to provide numerous benefits (BOX 1). It will also profoundly change the way in which clinical drug trials are conducted, as well as influencing the drug development process. There are ethical and regulatory challenges to conducting genomics-based clinical-research protocols, and these are important for investigators and research ethics committees (Institutional Review Boards (IRBs) in the United States or Research Ethics Boards (REBs) in Canada) that evaluate and approve such protocols.

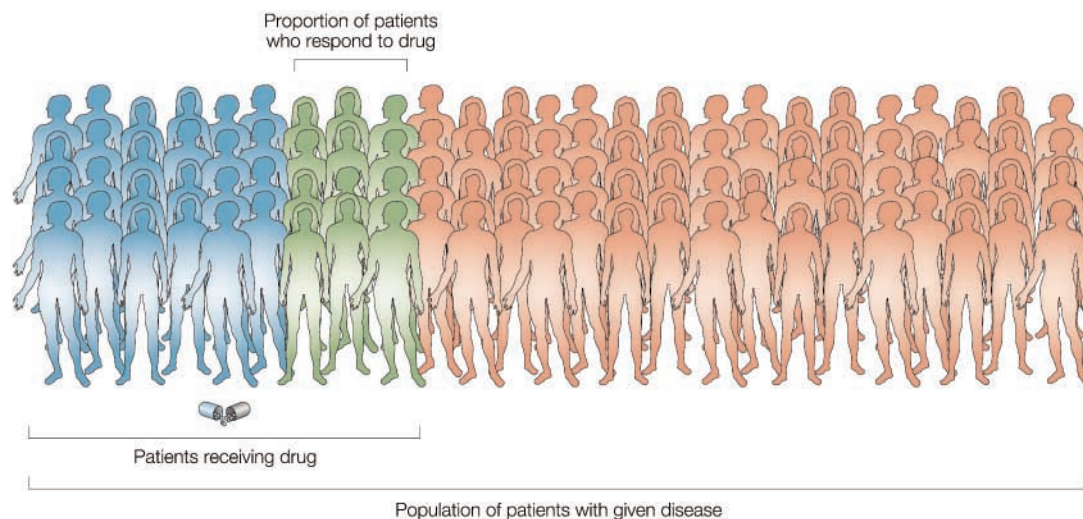
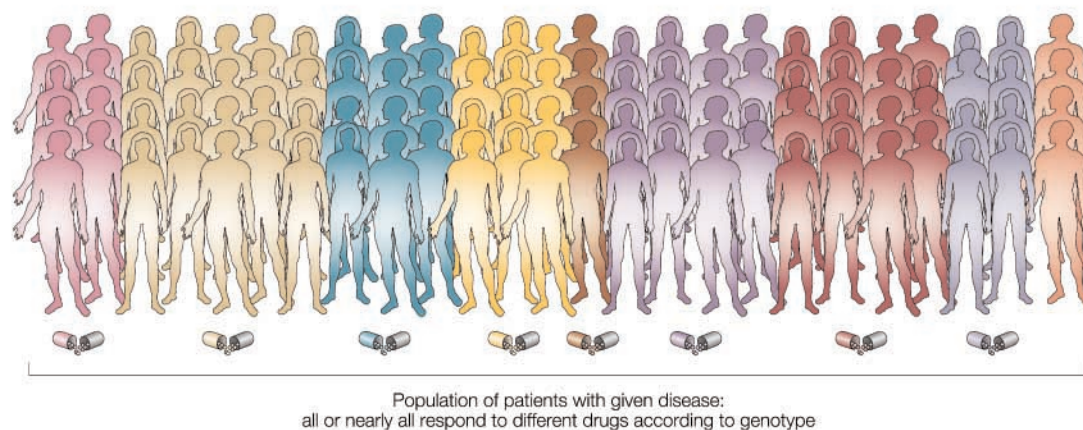
a Current state of drug development research**b Ideal future objective of drug development research**

Figure 1 | **An ultimate clinical goal of pharmacogenomics. a** | At present, only a limited number of patients are treated with a specific drug for any given disease due to adverse events. Of those patients who are receiving the drug, not all respond. **b** | One ideal goal that is anticipated from pharmacogenomics is to personalize or 'tailor' therapies, so that, on the basis of pre-genotyping, all patients who have a given disease will receive different drugs and respond to therapy with less risk of adverse events.

The speed of pharmacogenomics research raises new challenges for legislation and regulatory mechanisms — internationally as well as nationally and locally — that have yet to be addressed.

A large amount of attention in the research-ethics and health-policy literature has focused on issues that are related to privacy, confidentiality, ensuring adequate informed consent, and the collection and storage of genetic samples^{23–25}. Although pharmacogenomics research shares these concerns to varying degrees with other types of genetics research, it also raises new challenges, particularly with regards to pre-GENOTYPING to stratify or pre-select research subjects who have not yet received attention and need to be considered and addressed by the community of researchers, industry partners, research ethics committee members and regulatory authorities.

Certain ethical and social concerns in pharmacogenomics — such as those that revolve around informed consent and privacy — are now receiving some attention, but are likely to become much more central once it becomes part of standard clinical practice^{26–28}. However, it is important to consider the issues that arise within the context of using pharmacogenomics in clinical trials and drug development research. This paper addresses several ethical and policy issues that are grouped under four main categories: the design of clinical trials; research-subject stratification issues; new social risks; and economic issues that surround the introduction and use of pharmacogenomics in the drug development process. Some of these issues have the potential to radically alter how clinical trials are designed and conducted, and how the drug development process is regulated. The objective of this paper is

GENOTYPE

The genetic constitution of an organism, as distinguished from its physical appearance or characteristics (its phenotype).

GENOTYPING

The determination of relevant nucleotide base sequences in each of the two parental chromosomes.

PHENOTYPE

The physical characteristics of an organism or the presence of a disease that might or might not be genetic.

Table 1 | **Examples of clinical pharmacogenomic studies**

Clinical condition or disease	Drug(s)	Genetic polymorphism(s)	Outcome	References
Alzheimer's disease	Tacrine	<i>APOE4</i>	<i>APOE4</i> homozygotes have poor responses compared with research subjects with other <i>APOE</i> alleles	15–17
Schizophrenia	Clozapine	5-HT _{2A} receptor C102 allele	C102 homozygotes seem to respond better to the atypical antipsychotic clozapine	18–20
Coronary atherosclerosis	Pravastatin	Cholesteryl-ester transfer protein (<i>CETP</i>) with polymorphisms at the TaqB1 site (alleles B1 and B2); lipoprotein lipase (LDL); and β -fibrinogen	B1B1 homozygotes have a better response to pravastatin than either B1B2 heterozygotes or B2B2 homozygotes	21
Gastric or duodenal ulcers	Omeprazole and amoxicillin	<i>CYP2C19</i>	<i>CYP2C19</i> poor metabolizers responded more favourably to dual therapy than subjects with extensive metabolizer genotypes	11
Asthma	Zileuton and Montelukast	<i>ALOX5</i> genotype	Reduced response among heterozygotes	22

ALOX5, arachidonate 5-lipoxygenase; *APOE4*, apolipoprotein E4 allele.

to provide geneticists, clinical investigators, ethics committee members and policy makers with an improved understanding of some of the implications that pharmacogenomics has for clinical-trial designs and the drug research and development (R&D) process.

Principles of clinical-trial design

The practice of evidence-based clinical medicine depends on the conduct of clinical trials. A clinical trial is essentially a controlled prospective study that involves human participants or subjects, and is designed to determine the efficacy of a therapeutic intervention, preventative measure, diagnostic procedure or medical or surgical device²⁹. The fundamental characteristics of trial design to allow a meaningful interpretation of the data include sufficient sample size, statistical power and control of sampling bias. Clinical trials are usually classified according to four phases (BOX 2). Generally, the randomized clinical trial (RCT) and, in particular, the double-blind RCT (for which neither the investigator nor the research subject know to which arm of the trial the subject is assigned), is considered the 'gold standard' in determining treatment efficacies²⁹. Indeed, the objective of randomization is to reduce bias and variability as much as possible.

Pharmacogenomic profiling in clinical trials

At present, pharmacogenomic profiling is generally incorporated into trials either retrospectively or prospectively. Retrospective studies use genotyping and high-throughput-sequencing techniques to identify genotypes and attempt to correlate them with PHENOTYPES, such as disease or drug responsiveness. DNA libraries are now being established, and archived for future research. The use of pharmacogenomic profiling in prospective studies is focused on attempts to reduce pharmacokinetic variability or the incidence of adverse events. Typically, this consists of stratifying research subjects or excluding certain subjects from the trial on the basis of genotype.

BOX 3 depicts some of the possibilities for incorporating genotyping into different phases of a clinical trial. At present, in most of the trials reported in the literature, pharmacogenomic profiling is applied prospectively mainly during Phase I trials. Research subjects are enrolled into the trial on the basis of genotypes that predict metabolic capacity to respond to the drug(s) of interest, or genotypes that could prevent adverse events through particular pathways². At the Phase II level, the candidate-gene approach can be used in conjunction with genotyping to correlate particular polymorphisms with phenotypic differences in efficacy. In later Phase III trials, pharmacogenomic profiling can be used to distinguish responders from non-responders.

Sample size, ALLELE frequency and gene-effect size are some of the crucial parameters to take into consideration in the design and conduct of pharmacogenomic studies.

Scientific challenges of pharmacogenomic trials

In the United States, the Common Rule charges IRBs to ascertain that "Risks to subjects are minimized by using procedures which are consistent with sound research design..."²⁸, and this is an accepted provision of most of the codes that deal with research ethics^{30–32}. In a comprehensive framework for ethical clinical research, Ezekiel Emmanuel and colleagues³³ have argued that the first criteria for ethical research are scientific value and validity. These criteria take on a particular relevance for pharmacogenomics trials.

At present, drug trials proceed on the assumption that groups of research participants have little inter-individual variability, and are homogenous. However, one goal of pharmacogenomics research is to focus on inter-individual drug-related genetic variability, and pharmacogenomics trials therefore start with a different assumption about research-participant groups — that inter-individual heterogeneity is inherent. It is, therefore, important to consider how this assumption changes the way in which clinical trials are designed and statistically analysed.

ALLELE
An alternative form of a genetic locus — a single allele for each locus is inherited from each parent.

Box 1 | Potential opportunities to emerge from pharmacogenomics

- To predict a patient's response to drugs
- To develop 'customized' prescriptions
- To minimize or eliminate adverse events
- To improve efficacy and patient compliance
- To improve rational drug development
- To improve the accuracy of determining appropriate dosages of drugs
- To screen and monitor certain diseases
- To develop more powerful, safer vaccines
- To allow improvements in drug research and development (R&D) and the approval of new drugs

Clinical drug trials in the twenty-first century are primarily multicentre and multinational, and are conducted at various sites. Although this has many advantages for drug development research, design strategies need to recognize and take into consideration the inherent limitations that result from the variability that is found between different trial centres. For example, it will become increasingly important to be attentive to the ethnicity of trial subjects before pooling data from different sites. A perhaps less obvious issue that is related to the interpretation of data across several sites is a possible lack of consistency in controlling for pharmacokinetic variability. For example, a study that analysed cytochrome P450, subfamily 2, polypeptide 6 (*CYP2D6*) — one of the most studied genetic polymorphisms in drug biotransformation — at 15 clinical centres in the United States, showed a range of poor-metabolizer incidence from 0–15%, with some centres reporting 100% extensive metabolizers³⁴. Such variability can affect data interpretation from Phase I studies, which, in turn, can

SINGLE-NUCLEOTIDE POLYMORPHISM (SNP). The DNA sequence variations that occur when a single nucleotide (A, T, C or G) in the genome sequence is altered.

Box 2 | Key features of clinical-trial design*Phase I*

- Designed to provide information about pharmacokinetics and pharmacodynamics
- The first time that human participants are involved; focused on safety
- Not always randomized
- Useful in identifying minimal and maximal dosages

Phase II

- Focus on drug efficacy, safety and determining appropriate range of drug doses in patients with a disease or condition of interest
- Can be randomized

Phase III

- Large population sample
- Usually a comparison of new therapeutic intervention with standard treatment or placebo
- Generally a randomized and blinded study
- Often the final stage of testing before new drug approval can be granted

Phase IV

- Large-scale, long-term post-marketing studies
- Focused on identifying morbidity, mortality and adverse events
- Might identify new indications

influence decisions regarding dosages at the Phase II level, and hence the progression of drug development research on the basis of pharmacogenomic profiling. It is important, therefore, for clinical researchers to take concerns about multicentre variability into consideration in the design of pharmacogenomics-based drug development research.

Pharmacogenomics research is proceeding along two main paths: first, the identification of new genetic drug targets that are associated with various diseases; and second, the identification of specific genetic polymorphisms that are associated with responsiveness to particular drugs. In general, there are two types of experimental strategy that underlie pharmacogenomics protocols. The candidate-gene approach relies on a priori knowledge of disease pathogenesis, and/or the pharmacological mechanism of action of a given drug, to identify genes and compare the frequency of a given genotype of response or non-response to the drug of interest^{35,36}. This experimental strategy depends on, and is limited by, the validity of these assumptions. Although trials that use the candidate-gene approach are continuing, there is a growing concern about the ability of this approach to adequately answer the scientific questions — some of which are detailed in other recent reviews^{37–39}. The second pharmacogenomic strategy involves conducting genomic-association studies that use high-density markers — which are usually SINGLE-NUCLEOTIDE POLYMORPHISMS (SNPs) — to analyse the relationship between genetic alleles and drug-response phenotypes^{3,40}. Although the SNP approach might be advantageous in discovering new polymorphisms, it has been estimated that a study that requires genome-wide associations might involve analysing some 100,000 SNPs per individual. So, a clinical trial that involves 1,000 patients will involve ~100 million genotypes^{3,40}. Practical considerations regarding the large sample size of these trials, the cost of genotyping SNPs and data interpretation, have been highlighted⁴⁰. It has been estimated that genome-wide association trials would require at least a threefold increase in sample size compared with the candidate-gene approach⁴¹. Long and Langley⁴² examined the statistical power of five types of genomic association study to detect SNP–phenotypic associations, and concluded that a sample size of at least 500 individuals would be needed to achieve sufficient power. At present, there is no clear consensus on the ideal experimental design or statistical tools that are needed to arrive at valid conclusions. A series of studies that investigated the association between $\alpha 2$ -macroglobulin alleles and Alzheimer's disease, which were published in *Nature Genetics*^{43–46}, exemplify the limitations of the methodological heterogeneity that there now is in pharmacogenomics-based studies. Replication of the results and/or confirmation of the reported association has been difficult. Furthermore, the tendency to publish only positive results fuels concern about the number of false-positive associations. Indeed, the editors of *Nature Genetics* described in detail the limits of association studies and established more rigorous publication criteria for accepting genetic-association

Box 3 | **Pharmacogenomics in the drug development process****Genotyping at different stages of clinical trials:***Phase I*

- Genotyping might be carried out to try and identify and correlate polymorphisms with phenotypic elements (such as pharmacokinetic/pharmacodynamic properties, excretion and serum levels)
- Certain research subjects with particular genotypes might be excluded from the trial
- Certain research subjects with particular genotypes might be enrolled preferentially

Phase II

- Genotyping might be used for genotype–phenotype correlations
- Genotyping could be used to attempt to associate specific polymorphisms with differences in efficacy using the candidate-gene approach

Phase III

- Use results from Phase I and II trials to design an optimal large-scale Phase III study
- Test candidate genes for efficacy and metabolism
- Might be useful to conduct large-scale genotyping to discover new pharmacogenomic markers
- Identify which sub-populations show more adverse events to certain drugs
- Identify responders versus non-responders to certain drugs

Phase IV

Studies to assess the following:

- Rare adverse events and the relationship of such events to specific sub-populations
- Marketing considerations; that is, whether a diagnostic test might be capable of distinguishing the drug of interest from competitors, and whether the market for a given drug would justify the development of diagnostic testing

data⁴⁷. This empirical evidence of the scientific challenges that are associated with developing the appropriate pharmacogenomics techniques highlights the importance of consortia, such as the NIH–NIGMS Pharmacogenetics Research Network, to resolve these types of issue among researchers.

A challenge that needs to be addressed in developing genomics technologies is to establish and implement methods for searching and finding numerous genes. The classic ‘gene hunting’ approaches have not proved effective for complex diseases. Although it is hoped that high-throughput genomic studies will provide data to allow the possible association of a given reaction with numerous SNPs, there are no established methods that describe how to deal with the sets of data from clinical trials that are in the literature at present. It will be interesting to see how the new consortium of European research centres and institutions, which aims to integrate epidemiology with genomic tools to create a new sub-discipline of genomic epidemiology, might work to resolve these types of issue⁴⁸.

Stratification of human research subjects

Drug development strategies that incorporate pharmacogenomic profiling are based on the assumption that certain polymorphisms will be identified that can predict the response to a specific drug. This leads to the stratification of clinical-trial subjects into subgroups on the basis of genotype. Stratification poses several practical and ethical challenges.

Genotyping as either an inclusion or exclusion criteria to stratify research subjects might lead to a loss of the benefits of research participation, or to unfair representation in the trial, analogous to the historical under-representation in trials of population subgroups such as women, the elderly and children. This genotype-induced stratification could lead to subject-selection biases. An interesting example comes from clinical trials that involved patients with Alzheimer’s disease. A study over a 3.5-year period of two groups of patients with Alzheimer’s disease who were eligible for randomized clinical trials showed a markedly reduced risk of nursing-home placement among those who participated in the trials⁴⁹. This might be attributed to a long-term benefit of pharmacotherapy, as has been shown in a two-year follow-up study of Alzheimer’s disease patients who were given tacrine⁵⁰. The selection or stratification of subjects on the basis of their apolipoprotein E (*APOE*) genotype — because they might be less likely to respond to tacrine^{15–17} — might lead to unfair representation in trials⁵¹. Excluding individuals or groups from a trial on the basis of genotyping could, therefore, lead to a loss of benefits that they might otherwise accrue by participating in the trial. So, pharmacogenomics presents a new test case to re-evaluate human-subject research ethics in relation to recruitment practices and the eligibility of various groups.

Stratification of research subjects into smaller subgroups might confound the statistical analysis and interpretation of the results. For example, if 100 research

participants are stratified into groups of 10 each, it is conceivable that ‘statistically significant’ differences might be perceived. However, it is important to question whether these statistical differences are clinically relevant differences, as studies can be statistically significant but clinically insignificant. Although this debate about whether statistically significant data is necessarily a clinically important result has long been an issue for clinical-trial design^{52,53}, pharmacogenomic data that are obtained as a result of stratification of research subjects into smaller groups will probably considerably increase the possibility of spurious interpretations of statistical analyses.

Stratification also poses questions about the recruitment and enrolment of trial participants. Chen *et al.*⁵⁴ compared studies of *CYP2D6* genotyping in Phase I trials of two groups of healthy-volunteer participants, and found significant differences in genotype frequencies, which were due to sampling biases. This type of bias can be a serious challenge, as the drug-response and adverse-event profiles will not reflect those of the general population.

Bodenheimer⁵⁵ suggests that marketing considerations lead pharmaceutical companies to design trials in ways that are focused towards favouring certain drugs. In some cases, pharmaceutical companies might apply pharmacogenomic profiling to better position a particular drug in the market place. For example, a company that has had difficulty in getting a given drug onto hospital formularies might carry out further trials on only a genotypically selected sub-population of patients, and use the results of that study to portray the given drug in a more positive light. Conversely, if trials can be designed to accommodate smaller, but better-defined populations, this could lead to an improved analysis of risk–benefit ratios.

Stratification can also result in scientific and ethical challenges in trial design and data analysis because of the concept of **PENETRANCE**. The variable degree of the clinically relevant phenotypic expression of genetic variation could lead to false positives⁵⁶. This has important consequences for stratification of research participants into different arms of a trial, because some participants might not be offered the opportunity to receive trial medication if the given polymorphism in question is present, but is not highly penetrant. It is still too early to tell whether the use of transmission disequilibrium tests (TDT) — which certain authors^{56–58} claim would control for population stratification biases — would, in fact, be useful. At least one study indicates that TDT studies are not as statistically powerful as single-marker association studies⁴².

The clinical consequence of penetrance also presents challenges for regulatory authorities, such as the US Food and Drug Administration (FDA), in the approval and drug-labelling process. Will a given drug be restricted to patients with a particular polymorphism, even though individuals in the larger population might present with variable degrees of penetrance? More research is needed to determine the effects of penetrance on drug response and adverse events.

Economic considerations

Commercial interests are a principal force that drives the development and direction of pharmacogenomics research^{59,60}. Because a goal of pharmacogenomics is to tailor drugs to specific sub-populations, there is a concern that the market for certain drugs might be too small to justify costs that are incurred by the pharmaceutical industry in R&D and regulatory approval. One suggestion to resolve this problem is to make use of the US Orphan Drug Law⁶¹. According to the Orphan Drug Act — which has been in effect since 1983 — an ‘orphan disease’ is a condition that affects fewer than 200,000 people in the United States⁶², and there are more than 5,000 of these rare orphan conditions in ~20 million Americans⁶³. Before this legislation, very few pharmaceutical companies were interested in investing their R&D efforts in developing products for orphan diseases. The Act provides financial incentives, including tax credits, for companies to direct some of their efforts towards developing pharmaceutical agents for orphan conditions. Following in the footsteps of the United States, other nations, including Japan, the European Union, Singapore and Australia, have also now started orphan programmes⁶⁴. With respect to the possibility of using legislation that is similar to the Orphan Drug Act for pharmacogenomic-based therapeutics, it should be noted that there are limitations that are inherent within the law, and there are disagreements between the industry and the **Office of Orphan Products Development (OOPD)** regarding the size and definition of the target population⁶¹. So far, there are no legislation or regulatory requirements that are related to the assignment of orphan-drug status to pharmacogenomics-based drugs.

The development of pharmacogenomics-based drugs that are targeted to specific sub-populations will lead to a narrowing of the markets for drugs⁵⁹. Companies could create a demand for a given drug by offering tests to identify people who will respond to that drug. It is likely that entire populations might be given minimal attention in such market-driven drug development, which would result in ‘orphan populations’. Another key challenge that is likely to arise as a result of academic clinical-investigator partnerships with the commercial drug-trial sector will be conflicts of interest^{55,65}. Although not specific to pharmacogenomics *per se*, conflicts of interest in pharmacogenomics trials could yield greater difficulties than in other types of clinical trial. The control over trial design and conduct that companies might hold is a key concern. In this regard, regulatory guidelines will need to be established to prevent companies from either ‘trawling’ for patients, or avoiding offering genotyping that might limit their market for a particular drug.

The industry might also introduce genotyping for current generic drugs, thereby identifying sub-population-specific responsiveness or adverse events, or, alternatively, rescuing previously failed or shelved drugs, and therefore appropriating those drugs⁵⁹. This will be a daunting ethical and legal challenge for regulators and legislators — particularly those involved in patent law — which needs to be effectively addressed.

PENETRANCE

The probability of a gene or genetic trait being expressed. ‘Complete’ penetrance means that the gene or genes for a trait are expressed in all the population who have the genes. ‘Incomplete’ penetrance means that the genetic trait is expressed in only part of the population.

Box 4 | Challenges of pharmacogenomic profiling in drug discovery*Clinical-trial design*

- At present, there is no clear universal consensus within the scientific community as to the best design of pharmacogenomics trials
- More research is needed on the consequences of variable degrees of penetrance for drug response and adverse events

Stratification of research subjects

- Possible loss of benefits from trial participation
- Possible unfair representation of certain groups or populations in trials
- Possible confounding of statistical analysis and clinically relevant interpretation of results
- Possible sampling biases

Pharmacoeconomics

- Narrowing of drug markets
- Possible 'orphan drug' syndrome
- Possible 'orphan population' syndrome
- Questionable whether it is a good investment for venture capitalists

New social risks

- New 'hidden' disease categories and new labels
- Possible 'shifting of blame'
- Possible over-emphasis on 'pharmacogenomics cures'

It is also noteworthy that an economic analysis of industry pharmacogenomics applications indicates that it is questionable whether this technology is a good investment for venture capitalists⁶⁶. Market pressures and excessive enthusiasm for conducting pharmacogenomics trials might lead to research subjects being exposed to risks in trials that might then be abandoned due to volatile market trends and the uncertain longevity of specific patent holders.

Analysis of new social risks

In addition to the social risks that are shared with other types of genetics research, such as risks to confidentiality of information, privacy, insurability and discrimination, pharmacogenomics research presents several new challenges, which are summarized in BOX 4.

Pharmacogenomic profiling to stratify research subjects in clinical trials might create new perceived classifications or categories of conditions that will be sub-clinical (or 'hidden') in nature. So, individuals with no apparent health problems, on receiving information that they are harbouring a specific drug-associated genetic polymorphism, might label themselves as somehow ill. New disease labels and their legitimization are governed by social constructs that include, but are not limited to, individual personal histories, values and beliefs, interactions with family and health-care providers, and other relationships. Although the social construction of disease is not a new phenomenon *per se*⁶⁸, those that are created by pharmacogenomics are unique in that they are sub-clinical or 'hidden' without, necessarily, any visible manifestations. This is an important consideration for those who design and conduct clinical trials, as well as for

research-ethics committee members and policy makers who formulate policies related to informed consent for pharmacogenomics trials.

Given the present state of knowledge and technology, it is likely that, for a given condition, there will be several sub-populations who will respond differently to available medications. There might be a sub-population of patients who will not respond to any of the available agents. Rather than the ideal situation of having several pharmaceutical agents that are each tailored to a particular person's genotype, it seems more likely that an individual will be classified into one of two main categories: either as a 'responder' or as a 'non-responder' to a given therapy for a particular disease or condition. What should an individual think on learning that he or she is a 'non-responder'; for example, to a particular antihypertensive drug? The social consequences that arise from new disease labels and their legitimization would obviously involve interpersonal stigmatization or identity issues. In addition, a wider range of possible societal concerns, such as those related to access to insurance, employment and health-care resources, will probably emerge.

Another possible social consequence that might arise from pharmacogenomics-based therapeutics can be described as a paradigm shift in treatment choices, which is caused by the perception of 'uniqueness' that is often accorded to any type of genetics. For example, the possession of a polymorphism that is associated with non-responsiveness to a particular asthma medication or antihypertensive could lead to subtle subconscious 'shifting of blame' by the clinical investigator or the treating physician in a clinical setting.

This leads to another challenge — namely, the need for education to guard against the powerful lure of belief in 'one gene one response' — which, in reality, is too simplistic, and which might, along with other advances in genetics and genomics, lead to a form of cultural or societal genetic fatalism. Such a seductive belief could create a shift away from preventative medical approaches to health, such as lifestyle or behavioural modifications for certain conditions, to an emphasis on pharmacogenomics 'cures'.

The contribution of environmental factors in influencing the response to drugs is also important. Indeed, most common diseases are polygenic and multifactorial in nature, and are influenced by gene–gene and gene–environment interactions^{68,69}. Moreover, it has recently been suggested that in ~50% of cases, the pharmacogenetic polymorphism is not significantly associated with drug-response therapy⁷⁰. Without studies to investigate the influence of complex environmental interactions, we might fall prey to the reductionistic thinking that 'it's all in the genes'. More work needs to be done to investigate the effect of gene–gene and gene–environment interactions on the drug response.

Recommendations for future directions

The most pressing need is the development of appropriate study designs and statistical methods of analysis for pharmacogenomics trials. Standards are needed to

assess the quality of genotyping results and of the genotypic–phenotypic associations, so as to minimize false-positive or false-negative data. A broader scientific consensus is needed for phenotypic definitions, as well as appropriate guidelines to address the challenges of population and individual stratification.

A revision of the drug-approval process of the FDA (and other regulatory agencies internationally) should be undertaken to incorporate pharmacogenomics study designs and to reflect the continuing developments in this field, as well as the inherent limitations. The new pharmacogenomics guidelines should probably include the capability of using post-approval and post-marketing data (perhaps requiring certain types of Phase IV trial or requesting specific data outcomes) to reassess labelling specifics.

In collaboration with the appropriate legislators, academic and industrial partners should develop new regulations to address the ‘orphan drug’ and ‘orphan population’ issues that are raised by pharmacogenomics.

The pharmaceutical and genomics industry should participate with academic partners in conducting studies of cost-effectiveness that can guide policy decisions, and revising marketing incentives and strategies that take into consideration the potential reductions in markets, the rise and fall of marketing costs and R&D costs, and the possible changes in patent laws.

IRBs will need to work closely with the FDA, the Office for Human Research Protections (OHRP), researchers and industries, in the development of consensus guidelines and regulations for reviewing pharmacogenomics protocols. IRB members will need to proceed with caution when reviewing pharmacogenomics protocols, and, in particular, take scientific validity issues into consideration during their protocol-review decisions.

The continuing scientific developments in pharmacogenomics, and the potential clinical and economic impact of this technology, will eventually make genotyping in clinical practice routine. Before widespread clinical use becomes a reality, a host of pharmacogenomics-based clinical trials will be carried out. It is therefore essential that we plan now, so that these trials are designed and conducted in a scientifically and ethically optimal manner. This review has focused on certain key issues that are important for consideration and worthy of attention by researchers, research-ethics committee members and policy makers. The field continues to advance, and no doubt more issues will come to our attention. This discussion underscores the importance of community-wide discourse to ensure that potential risks are minimized, and that benefits are available to all. It is essential that ethics and policy develop in tandem with scientific advances in pharmacogenomics.

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A thorough review that discusses different designs of genetic-association studies and their inherent limitations. Lessons from these studies need to be considered in thinking about the future design of pharmacogenomics trials.

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FDA: <http://www.fda.gov/default.htm>
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