

**PHARMACOGENOMICS IN CLINICAL RESEARCH AND
PRACTICE: AN ETHICAL CONSIDERATION**

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Summary

Pharmacogenomics is the study of variation in drug response caused by genetic inheritance. It allows us to identify sources of an individual's profile of drug response and predict the best possible treatment option for this individual. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, has opened new possibilities in drug discovery and development. However, these developments, although bearing scientific promise, raise new ethical challenges, in particular in the fields of research and therapy. The developments of guidelines, policies and legal standards have not kept pace with the rapid scientific progress. This review article discusses some of the ethical considerations that are related to the use of pharmacogenomics in clinical research and practice. In near future pharmacogenomics is likely to fulfil the dreams of individualized medicine.

Keywords: Clinical research, Ethics, Human genome, Pharmacogenomics.

Introduction

Today the drug therapy in practice is based on a trial-and-error method of matching patients with the right drugs and right dosage, but people often respond differently to the same medicine. There are only few medicines having same therapeutic effect on every patient. These inter and intra-individual variability mainly attribute to pharmacokinetic and pharmacodynamic differences that are influenced by genetic polymorphisms (variations in DNA sequence among individuals). (1) 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. (2) The prediction and identification of polymorphisms may lead to a better understanding and design of rational drug regimens.

Pharmacogenomics is a relatively new field that was developed by these advances, which 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 genotype. 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. (3)

The continuing scientific developments in pharmacogenomics and the potential clinical and economic impact of this technology will make genotyping in both clinical research trials and, eventually, clinical practice routine. The pharmaceutical industry has begun to use this knowledge in drug development protocols, and genotyping human research subjects in clinical trials to associate particular genotypes with possible adverse drug reactions is becoming more common⁴. The ability to streamline clinical trials by genotyping will enable researchers to 'rescue' drugs that could not be approved under conventional models of research trials. Pharmacogenomics will not only produce better drugs but also yield greater efficiency in the allocation of resources in drug development. (5)

The speed of pharmacogenomics research raises new challenges for legislation and regulatory mechanisms —internationally as well as nationally and locally — that have not yet received extensive consideration. 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.

There are ethical and regulatory challenges to conducting genomics-based clinical-research protocols and these are important for investigators and research ethics committees that evaluate and approve such protocols. (3) This review provides an overview of some ethical issues, which arise with the integration of pharmacogenomics into the discovery of drugs and the practice of preventive and therapeutic medicine.

Research and development

The first criteria for ethical research are scientific value and validity, and these criteria take on a particular relevance for pharmacogenomics research. (6) In the context of drug discovery and development, clinical pharmacogenomics is the use of genetic information, from a population or from an individual, to predict the efficacy, safety, and toxicity of drugs, either as part of a drug development program or as part of an individual's diagnosis and treatment regimen. It encompasses genetically determined variability in drug response in and across populations. Much of this variability is because of both polymorphisms in drug metabolism (i.e. pharmacokinetic effects), and polymorphisms in drug receptors and other effectors (i.e. pharmacodynamic effects). (7)

Drug discovery

Substantial investments have currently been made in the pharmaceutical and biotechnological industries to use genomic strategies for the discovery of novel targets. Two broad pharmacogenomic strategies are used to identify disease-related genes and to search for protein products that can be used as drug targets: discovery genomics and discovery genetics. Discovery genomics attempts to identify all kind of genes that code for receptors and enzymes, and their role in disease process. Discovery genetics, on the other hand, identifies genes and their function involved in the susceptibility to major common diseases.

A first issue that arises as a result of such development is how to decide which disease should be considered first for drug discovery. It is expected that the first future drug discoveries based on pharmacogenomics research will be found in the field of frequently occurring diseases such as cancer, cardiovascular diseases and asthma. Secondly, such new strategies in drug discovery combined with increasing possibilities to genotype patients might contribute to a more or less tailor-made pharmacy. Patients might be divided into subgroups with similar genotypes, for which drugs could be developed to specifically fit patients with that genetic profile. However, there will always be patients who turn out to have a rare genetic profile that

does not fit in any of the 'common' subgroups: possibly, many small groups might emerge for whom no tailor-made drugs will be developed because the target group is just too small to make it commercially profitable. Individuals, who are not responding to any of available drug may be categorised either as a responder or as a non responder to a given therapy. This might raise problems of equity and fair distribution: patients who genetically fit into one of the subgroups could be treated with a tailor-made drug, while other patients would receive the 'bulk drug' that is known not to be the ideal medicine for them, due to the lack of a specific alternative. (8)

Clinical drug trials

The development of pharmacogenomics has started changing the process of clinical trials. The pharmacogenomic profiling is generally incorporated into trials either retrospectively or prospectively. At present, in most of the trials reported in the literature, pharmacogenomic profiling is applied prospectively mainly during Phase I trials. The 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 drug events through particular pathways. 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 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.

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 subjects into subgroups on the basis of genotype. Genotyping as either an inclusion or exclusion criteria to stratify research subjects might lead to subjects election biases. Also the pharmacogenomic profiling may lead to the classification of new categories of conditions which are subclinical in nature. Here by we mean to say that individuals on which genetic profiling is done may come to know that they are carrying a specific disease associated gene which may show its consequences in near future. Thus they may label themselves as somehow ill. The social consequences that arise from new disease labels and there legitimization would obviously involve interpersonal stigmatization or identity issues. (1)

The concept of penetrance also has important consequences for stratification because the trial medication is only given to the subject who are suitable as per given polymorphism, though individuals in the larger population might present with variable degree of penetrance. 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. 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.

The 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. The inherent variability also has serious consequences in case of multicentre and multinational trial sites data pooling. It is important, therefore, for clinical researchers to take concerns about inherent variability in the design of pharmacogenomics-based drug development research.

In general, there are two types of experimental strategy that underlie pharmacogenomics protocols: the candidate-gene approach and genomic-association studies. Practical considerations regarding the large sample size of these trials, the cost of genotyping SNPs and data interpretation, have been highlighted. It has been estimated that genome-wide association trials would require at least a threefold increase in sample size compared with the candidate-gene approach. At present, there is no clear consensus on the ideal experimental design or statistical tools that are needed to arrive at valid conclusions. (3)

Informed consent (IC) is a crucial issue in pharmacogenomics. The practice of informed consent is the main vehicle through which the patient is empowered in relation to the health care system. The availability of properly consented samples is a limiting factor for progress in many areas of pharmacogenomics research⁹. Some important or unique considerations for pharmacogenetic trials include: unfamiliar terminology; study purpose that may be difficult for subjects to understand; perceived informational risks that may result in discrimination or psychological distress; potential societal benefits such as a better understanding of the underlying causes of variable drug response and discoveries of safer and more effective drugs;

possible extended durations of genetic studies that far exceed the subject's participation (and that genetic research can continue indefinitely); potential commercial benefit that the sponsor may derive; and the issue of compensating study subjects. Researchers and sponsors must independently consider in each case what is appropriate to ensure both valuable research and adequately informed subjects. Creating an understandable IC form and an effective process to obtain consent for pharmacogenetic research is challenging. (10)

Tests are another important issue in research. To develop a drug that is effective for a particular sub-group of patients, genetic tests will be necessary for the identification of a specific population. Genetic testing involves very sensitive and intimate items of information as it can reveal personal information about blood relatives and indicate some medical trends encountered in a particular population. Unlike most general medical information, it possesses an individual, a familial and a collective dimension. To date, no regulatory authority has specifically addressed the management of pharmacogenetic tests in the research, development and licensing of medicines. We need to address the issue of the level of anonymity that should be accorded to this genetic information. (11)

Clinical Practice

The promise of pharmacogenomics in reconfiguring approaches to drug use has considerable currency. Pharmacogenomics is expected to improve, even to overturn, current approaches to drug treatment by reducing adverse reactions, increasing drug efficacy and refining prescribing practices. Indeed drugs are designed and prescribed on a population basis, but each patient is an individual. In the future by understanding of pharmacogenomics principle, doctors will be able to analyse a patient's genetic profile, define his/her appropriate patient group for a particular medicine and prescribe the best available drug therapy from the beginning. This will maximize therapeutic value and decrease the likelihood of adverse drug reaction. (12)

Yet, in spite of this positive scenario, some hurdles remain. First of all, some scientific questions need to be asked about the effectiveness of the application of pharmacogenetics in therapy. The clinical applicability of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. As well as having genetic variations, individuals are in different states of health, eat different diets; take different drugs—all of which may affect responses to drugs.

Doctors need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability without taking it for granted that genetics play the main role in determining a patient's response to treatment. (1)

The clinical application of pharmacogenetics is likely to have a significant impact on the professional requirements of primary health care providers. Currently most physicians and pharmacists receive little training in genetics or genetic counselling. (13) They might be subject to liability if they lack sufficient knowledge of genetics to adequately interpret diagnostic tests, prescribe appropriate pharmacogenomic-based drug therapy in proper dosages, consider pharmacogenomic-based drug interactions, or properly dispense pharmacogenomic-based prescriptions and maintain privacy and confidentiality of genetic information. With greater knowledge comes greater responsibility⁵. While both physicians and pharmacists play important roles in enabling patients to access to this technology, they alone are unlikely to be able to cope with the volume of knowledge with which they will need to be familiar. A practical solution may require an expansion of the role of clinical genetics services instead of educating primary health care providers about clinical application of pharmacogenomics. Morley and Hall (13) have also suggested that while physicians and pharmacists will still need to be educated about these treatments, the development of independent specialists may be a useful way to ease the burden. Clinical geneticists have the background to understand and interpret genetic tests, and genetic counsellors have the requisite knowledge and training to advise patients of genetic tests available to them, obtain informed consent and counsel individuals both before and after testing. Considering the complex nature of genetic information relating to disease development and drug metabolism, the creation of genetic information specialists is probably the best method for ensuring that pharmacogenomics and pharmacogenetics can be applied to clinical medicine without compromising the autonomy and health care of patients.

The clinical application of genomics will require new labelling and prescription guidelines. In pharmacogenomic era of clinical practice drug regimen will be based on the genotype, which is going to be decided by pretherapeutic pharmacogenetic test. This will require formulation of new prescription guidelines. Even if the results of pharmacogenetic tests suggest that an individual may respond adversely to, or derive no therapeutic benefit from, a drug, the physician and/or patient may still wish to use the drug 'off label'. Regulations may therefore need to cover the permissibility of 'off label' uses. Pharmaceutical companies are required to

consider the new labelling requirement for consumer about the risk and limitation of pharmacogenomic drugs. (13)

The question is how to allocate responsibility for taking the greatest advantage of drugs specialized to suit relatively smaller segments of the population. Put simply, pharmacogenomics will raise the legal stakes for all involved whenever a patient suffers adverse reactions from the use of a drug that might have been contraindicated based on his or her genotype. (5)

Conclusion

The perspective behind integrating pharmacogenomics with clinical research and practice is to speed-up the process of drug development with reduced failure, more safety and therapeutic values. Pharmacogenomics is still in immature state for scientific community and a lot has to be achieved in this field. Though, the inclusion of pharmacogenomics will be determined to a large extent by their scientific values and validity with respect to human ethics values. However, as discussed above, the ethical issues associated with its application are still required to be considered and should keep on developing along with scientific advances.

Therefore it is an urgent need for researchers, health care provider, government and pharmaceutical organizations to work together to formulate an international guideline/regulation on use of pharmacogenomics in clinical research and practice.

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