

Ethical considerations in clinical pharmacogenomics research

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In recent years there have been unprecedented advances in our understanding of the involvement of genetic polymorphisms in the response to drug therapies. Polymorphisms have been identified that lead to variable patient responses to several medications including cardiovascular, psychiatric, anti-infective and analgesic therapies. The potential for the development of customized, genotype-based therapies is scientifically and clinically attractive. However, these developments, although bearing scientific promise, raise ethical concerns for the conduct of research with human subjects, particularly with respect to confidentiality, risk–benefit analysis, DNA-banking and pharmacoeconomic issues. This article discusses some of the ethical considerations that are related to the use of pharmacogenomics in clinical research protocols.

Individual variability in both the response to therapeutic drugs and drug toxicity is common in the clinical setting as well as in the development of a new drug. A major reason for this inter- and intra-individual variability relates to pharmacokinetic and pharmacodynamic differences that are influenced by genetic polymorphisms (variations in DNA sequence among individuals). Although the terms pharmacogenetics and pharmacogenomics are often used interchangeably, classical pharmacogenetics refers to the investigation of variations in candidate genes relevant to drug metabolism and is based on the observation of phenotypes. Pharmacogenomics has emerged as a relatively new sub-discipline as a result of the availability of molecular genomic technologies, and encompasses the study of polymorphisms in relation to individual variations in therapeutic drug response and in the occurrence of adverse drug reactions. The prediction and identification of polymorphisms are of particular interest to clinical pharmacologists and researchers involved in drug development and should lead to a better understanding of pharmacokinetics and pharmacodynamics, a reduction in adverse events, and an improvement in the design of rational drug regimens.

Over the past decade there have been unprecedented advances in our understanding of the role of genetic polymorphisms in the inter- and intra-individual variability in the response to therapeutic drugs^{1–3}, as a result of information derived from the Human Genome Project. 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 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. However, the ethical issues related to the use of genotyping in clinical research have not yet received extensive consideration. Not all of the ethical concerns discussed below are unique to pharmacogenomics research and practice. However, some characteristics of the use of pharmaco-

genomics in drug development research, such as the uncertainty about the valid phenotypic identification of drug responses in patients, do increase the complexity of the ethical concerns and present novel challenges for public policy. The following discussion explores some of the pertinent ethical concerns that surrounds the use of genotyping in clinical pharmacogenetics research and highlights issues that merit serious attention by clinical pharmacologists.

Recruitment and selection of research subjects

The selection of human research subjects for clinical trials is of increasing concern to ethicists and research ethics committees, and recent attention has focused on eligibility criteria for such trials⁵. One crucial question raised by the current and possible future uses of genotyping in clinical trials is whether it is justifiable to select a specific group of individuals for a research protocol based on their genotype. The argument could be made that genotyping to assign individuals to particular treatment groups or select them for a specific trial is simply another criterion for eligibility. However, given the current level of knowledge, genotype-based stratification or classification of research subjects might lead to unfair representation in trials and possibly to loss of the benefits of participation in a trial that might otherwise accrue to subjects.

Furthermore, genotyping for a drug response in a trial could cause a reduction in the number of subjects that enrolled, which might affect the external validity of the study and its applicability to the clinical setting. Thus, the potential use of genotyping to stratify subjects in a clinical trial poses a challenge to our current understanding of clinical research design.

Pharmacogenomics research on families and populations

The potential for the usefulness of clinical pharmacogenomics is based on the fact that researchers are able to collect genetic data from a large number of participants in large-scale trials. This notion is currently advanced by certain authors and biotechnology companies^{6,7}. No doubt some benefits can accrue from proposed clinical pharmacogenomic

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studies, such as an increased understanding of population-based drug reactions and improved therapeutic efficacy. One argument in favour of the ethical justification of population-based pharmacogenomics research is the adoption of public health screening programs such as that for neonatal phenylketonuria⁸.

However, although genetic information is, by its nature, inherently personal, it is at the same time familial and also communal. Therefore, there are serious potential risks for discrimination and loss-of-privacy, which need to be addressed to formulate a policy to prevent such possible harm. Thus, despite the obvious scientific value of using families in pharmacogenomic trials, such studies raise serious ethical concerns⁹ that ensue from the dynamics and social significance of the family. Recruiting and enrolling families into pharmacogenomic studies also pose novel challenges to the traditional relationship between health care providers and patients. Traditionally, the hallmark of this relationship has been one of privacy, confidentiality and beneficence¹⁰. The shift in attention of the clinical investigator towards the family or community in efforts to recruit members to pharmacogenomic studies threatens this triune pillar.

Using pharmacogenomics to understand the genetic basis of the response to a drug also affects individuals from particular ethnic communities, as exemplified recently by genetic research on Ashkenazi Jews¹¹ or the association of apolipoprotein E genotypes with Alzheimer's disease¹². It is important, therefore, for scientists, ethicists, lawyers and policy makers to collaborate closely with members of ethnic communities to develop mechanisms to protect against discrimination or stigmatization. In this regard, it has been argued recently that a new principle for research ethics, 'the principle of respect for communities', should be added to the currently accepted working principles of bioethics¹³.

Risk-benefit assessment

To be justifiable ethically, clinical research must produce benefits and either prevent or minimize possible risks¹⁰. Risk-benefit assessment is a necessary standard component of protocol review. Pharmacogenomics poses novel questions for the ethical analysis of risks and benefits. The possible long-term benefits include the potential for customizing drugs for defined sub-populations of patients, improving therapeutic efficacy, minimizing adverse events, increasing safety and drug-tolerance during clinical trials, and reducing the overall cost of disease management^{2,4}. In addition to the potential risks to privacy and confidentiality discussed above, other risks are complex and include (but are not limited to) issues surrounding insurance and employment, pleiotropy or polygenics, storage of DNA samples and access to the information generated.

The storage of DNA in a 'DNA bank' for the future analysis of samples is an important feature of any protocol involving pharmacogenomics. Serious ethical questions are raised by the increasingly routine storage of DNA samples and the prospect that genetic information might be entered into computerized databases. Such storage presents novel issues related to autonomy, privacy and informed consent

that warrant clarification, discussion and immediate action. It has been argued that genetic information is more vulnerable to violation of privacy because it contains an 'individual's probabilistic "future diary"'¹⁴. Indeed, the possible social ramifications for individuals, families, familial relationships and possibly entire communities are enormous.

Genotyping and storage of DNA also creates the potential for discrimination by employers and the insurance industry^{15,16}. The possibility that employers and insurers could have access to an individual's genetic information through medical records of family members might also affect future employment or insurability of their offspring.

Further issues raised by the use of pharmacogenomics in clinical trials involve the risks of discrimination, privacy and confidentiality, and other psychosocial concerns generated by pleiotropy or polygenics, whereby sampling for a single gene might reveal information about more than one condition¹⁷. The differing social consequences and availability of treatment between the different conditions contribute to the ethical complexity.

The development of guidelines, policies and legal standards have not kept pace with the rapid scientific progress. Clinical pharmacologists need to be aware of the pertinent legislation and legislative channels in their jurisdiction, and become more vigilant in encouraging the development of ethical and legal policy.

Pharmacoeconomic considerations and equity

The increasing socioeconomic costs of treatment for adverse drug reactions¹⁸ coupled with market pressures and potential benefits are likely to increase the demand for the development and use of genotype-based pharmacotherapies. Pharmacoeconomics, the study of costs and benefits of various therapies and technologies, addresses issues of drug availability, cost and outcome of medical care, and is increasingly important in an era of global economic pressures¹⁹.

With the development of more efficient and less expensive methods for genotyping, the pharmaceutical industry is directing more of its research and development (R&D) efforts towards clinical pharmacogenomics²⁰, which is likely to have significant effects on the economic structure of the whole R&D process itself. On the one hand, pharmacogenomics will generate opportunities for the development and use of customized drugs, and will allow the re-introduction of older drugs that are effective in some individuals but have been discarded because of serious adverse events in a few people. On the other hand, a genomics-based approach to drug discovery and development has the potential to identify precisely the patients that will benefit from any one drug and so reduce the number of patients from whom the industry can regain its investment in that particular treatment.

This latter point identifies a further ethical concern for policy makers and government regulators when considering the availability of individualized genomics-based therapeutic prescriptions: should pharmaceutical companies conducting a clinical trial or marketing a particular drug be obliged to offer genotyping to patients given that doing so might lead to reductions in their potential market?

Concluding remarks

The potential for optimizing therapy based on a pharmacogenomics approach is scientifically and clinically attractive. However, as highlighted above, it is important to anticipate and consider the social, legal and ethical consequences of this technology and develop appropriate guidelines and policies for its use.

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Acknowledgement
The author is supported by a fellowship from the Fonds de la recherche en santé du Québec.

The dual personality of NO

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In the body, nitric oxide (NO) is an important physiological regulator of functions such as vasodilatation and neurotransmission. Under pathological conditions, high concentrations of NO can either be beneficial (e.g. anti-bacterial, anti-parasitic and anti-viral) or detrimental; NO can therefore be considered a double-edged sword. When manipulating NO levels clinically, attention should be paid to minimize the negative effects and maximize the beneficial effects of NO. This article highlights recent evidence that supports the complexity of the regulatory mechanisms that lead to sophisticated endogenous NO production.

Initially, nitric oxide (NO) was discovered to be a potent vasodilator as well as a novel type of retrograde neurotransmitter; however, in the past few years physio-pathological events in which NO has been shown to exert an effect have grown exponentially. Such effects include modification of skeletal muscle contractile force and development, the control of total body Na⁺ content and body fluid homeostasis, male sexual function, and the development of the gastric pyloric sphincter. Under physiological conditions, in all parts of the body, the concentrations of NO are believed to be fluctuating continuously at rather low levels. These levels are controlled by constitutively expressed neuronal and endothelial types of NO synthase [nNOS (NOS-I) and eNOS (NOS-III), respectively], which are present widely in the body. However, the concentration of NO can rapidly increase by hyper-activation of nNOS in disorders such as ischaemia-reperfusion injury and glutamate-mediated neurodegenerative processes in the CNS.

Under pathological conditions (e.g. during inflammation), temporal high levels of NO are produced in the body after induction of the expression of an inducible type of NO synthase [iNOS (NOS-II)]. In this context, NO can be considered a double-edged sword. On the one hand, it can exert beneficial effects on the body, by acting as an anti-bacterial, anti-parasitic, anti-viral agent or as a tumoricidal agent; on the other hand, high levels of NO, if uncontrolled, can be detrimental. Such detrimental effects are produced because persistent high amounts of NO can react with concomitantly produced superoxide anions, which thereby generates highly toxic compounds, such as peroxynitrite and hydroxyl radicals. Fortunately, the body is equipped with a machinery that is capable of carefully controlling iNOS expression via several endogenous and exogenous molecules. The latter can act either as inducers of this expression [e.g. bacterial lipopolysaccharides (LPS) and immune

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