

# Ethical and legal implications of pharmacogenomics

Mark A. Rothstein and Phyllis Griffin Epps

Pharmacogenomics is the application of genomics technology to the discovery and development of drugs. A greater understanding of the way in which individuals with a particular genotype respond to a drug allows manufacturers to identify population subgroups that will benefit most from a particular drug. The increasing emphasis on pharmacogenomics is likely to raise ethical and legal questions regarding, among other things, the design of research studies, the construction of clinical trials and the pricing of drugs.

Pharmacogenomics is changing the way that drugs are developed, approved, marketed and prescribed. The objective of pharmacogenomics is to define the pharmacological significance of genetic variation among individuals and to use this information in drug discovery, thereby decreasing the number of adverse drug responses that injure and kill thousands each year<sup>1</sup>. By determining which genetic variations are likely to affect a person's ability to metabolize a drug, drug manufacturers intend to develop more predictable and effective therapeutic agents. Towards this end, pharmaceutical companies are investing huge amounts of capital in the technologies that will revolutionize both how researchers identify drug targets and the amount of time needed to move a drug through development and approval<sup>2,3</sup>. Pharmacogenomics promises to streamline the clinical trial phase of drug development. Researchers hope to use knowledge gained from high-throughput screening

and other technologies to construct clinical trial groups that are composed of people most likely to benefit from a particular drug. 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. In other words, drugs that were previously rejected after giving unacceptable rates of adverse responses in traditionally constructed trials will yield lower adverse-response rates after testing under the new model, thereby becoming acceptable candidates for approval. Pharmacogenomics will not only produce better drugs but also yield greater efficiency in the allocation of resources in drug development.

Other changes attributable to pharmacogenomics will be less welcome. Notwithstanding the increasingly efficient research and development process, pharmacogenomic-based drugs will be expensive, because of, for example, the need to recoup the cost of investment in new technologies. The ability to develop specialized drugs that are ultimately approved for smaller populations rather than for general use will fragment the market for pharmaceuticals. Will a pharmaceutical manufacturer react to this economic reality in a way that better suits profit margins than health, and is that socially acceptable? The use of groups in clinical trials that are increasingly similar genotypically raises several important ethical issues regarding social inclusion and the adequacy of current regulatory frameworks. Because polymorphisms of pharmacological interest

might vary in frequency among different population subgroups, important social issues arise in multi-ethnic countries, such as the United States. Finally, pharmacogenomics will change the standard of care for pharmaceutical companies and health professionals, including physicians and pharmacists.

This article provides an overview of some ethical and social concerns that arise with the integration of pharmacogenomics into the discovery of drugs and the practice of preventive and therapeutic medicine. Specifically, the article addresses issues associated with the design of clinical trials, the relatively higher cost of pharmaceuticals developed using pharmacogenomics, and the allocation of ethical and legal responsibility. The objective is to highlight a few of the questions and challenges that will require further attention in the near future.

A new model of clinical trials  
Pharmacogenomics promises to reduce the time and money required to develop a drug. The ability to predict drug efficacy by genotyping participants during the early stages of clinical trials for a drug would enable researchers to recruit for later trials only those patients who, according to their genotype, are likely to benefit from the drug<sup>4</sup>. As a result, clinical trials could become smaller, cheaper and faster to run.

The prospect of clinical trials that are composed of smaller groups with the same polymorphisms at one or more loci of interest poses some risks, however. A group that reflects the diversity of the population yields information on how a drug will behave in a greater number of people. If the clinical trial group is smaller, or is less genotypically diverse, there is a greater risk that some side effects will go undetected. So, the trials will yield a greater quantity and quality of information, but on a smaller segment of the population. Whereas the conventional model yielded information about harmful side effects in a greater proportion of the population, the concentration of individuals pre-selected for a favourable response under the newer model might not produce the same information. Compared with traditionally designed human clinical trials, genotype-specific human clinical studies might be subject to equal or greater limitations in that the relatively short duration of the study, combined with the narrower subject population and smaller size, would hinder the ability of the studies to identify rare or delayed adverse reactions or drug interactions<sup>5</sup>. A drug could reach the market with less information about the side effects or risk of harm from its non-prescribed uses. An

## Box 1 | Ethical principles of human subject research

In the United States, federal regulations that govern human subject research stem from three ethical principles that were identified in the **Belmont Report**: respect for persons, beneficence and justice<sup>26</sup>. As a principle, respect for persons includes two moral requirements: acknowledgement of personal autonomy and protection of individuals with diminished autonomy. In research that involves human subjects, the proper exercise of autonomy demands that research participants agree to enter into research voluntarily and with adequate information. The participant's informed consent is essential. Beneficence also entails two requirements: do no harm and maximize the possible benefits, while minimizing the possible harms. Justice looks at how to fairly distribute the benefits and burdens of research. In the context of research on human subjects, questions regarding how and why research participants are selected are important in satisfying the principle of justice<sup>27</sup>.

## Box 2 | Post-approval monitoring of pharmaceuticals

Despite continuing efforts to harmonize pharmaceutical regulations worldwide, the protection afforded to populations from the risks attendant to drugs that have been approved, after testing in smaller, less genotypically diverse clinical trial groups, depends on the market, member state or country at issue.

**United States:** In addition to clinical trials, the **Food and Drug Administration** requires manufacturers to maintain records of clinical experience that would be relevant to determining whether approval of a drug should be withdrawn, and to submit adverse drug reports.

**European Union (EU):** For pharmaceuticals that have been approved according to the centralized approval process administered by the EU, the **European Agency for the Evaluation of Medicinal Products** and the Commission on Proposed Medicinal Products require that reports on adverse reactions be submitted every six months for the first two years after approval. Individual member states may have different guidelines in effect that override the guidelines of the European Agency.

**Japan:** Through the **Pharmaceuticals Affairs Bureau**, the Ministry of Health and Welfare requires the manufacturer to collect data on adverse drug reactions and to submit products for re-examination and re-evaluation.

unresolved issue is whether the ethical principles of beneficence (BOX 1) and non-maleficence (that is, not causing harm to others) would preclude the deliberate inclusion of anyone who is not likely to respond favourably to treatment. With the advent of genotype-specific clinical trials, manufacturers and regulators must be ready to carefully evaluate post-market data by strengthening the existing guidelines for phase IV, or post-approval, clinical trials<sup>2,3,5,6-8</sup> (BOX 2).

As in other areas of genetic research that involve human subjects, the likely effect of pharmacogenomics on clinical trials raises important questions regarding informed consent, which might include considerations of privacy and confidentiality<sup>9</sup>. Current ideas regarding patient autonomy and informed consent require that patients agree to enter into research on the basis of adequate information regarding the risks and consequences of participation. Genotyping that is appropriate to pharmacogenomic research might not produce information regarding susceptibility to disease or early death, but it might reveal evidence of genetic variation that could lead to individuals being classified as 'difficult to treat', 'less profitable to treat', or 'more expensive to treat'. The fear of being so classified could act as a barrier to the recruitment of research participants.

Fear of stigmatization might prove to be a significant barrier to participation in clinical trials among members of population subgroups. Genetic variations of pharmacological significance are known to occur in varying frequency in groups categorized by their ethnicity<sup>10,11</sup>. For example, different variants of glucose-6-phosphate dehydrogenase (**G6PD** — an enzyme critical for NADPH (nicotinamide-adenine dinucleotide phosphate reduced) generation in mature red blood cells) are found at a high frequency in African,

Mediterranean and Asiatic populations<sup>12</sup>, some of which disrupt the function of the enzyme. A deficiency of G6PD can predispose individuals from these populations to **haemolytic anaemia**, both in individuals with loss-of-function *G6PD* mutations and in

### The ability to develop specialized drugs ... for smaller populations rather than for general use will fragment the market for pharmaceuticals. Will a pharmaceutical manufacturer react to this economic reality in a way that better suits profit margins than health ...?

response to some drugs, such as the malarial drug primaquine<sup>13</sup>. Isoniazid is an anti-tuberculosis drug that is inactivated by acetylation; its impaired metabolism by slow acetylation causes it to accumulate to toxic levels. Variation in the *N*-acetyl transferase 2 (**NAT2**) gene accounts for whether individuals are rapid or slow acetylators of isoniazid, as well as of other therapeutic and carcinogenic compounds<sup>14</sup>. About 50% of individuals in many Caucasian populations are genotypically slow acetylators of isoniazid, but more than 80% of individuals in certain Middle Eastern populations and fewer than 20% in the Japanese population have the slow acetylator phenotype<sup>13</sup>.

The significance of data that imply a role for ethnicity in research has been a source of considerable debate among the research ethics community<sup>15</sup>. One issue is how to advise potential research participants about the possibility of social harms from group-based findings even where the research is conducted without using the names of participants. Another matter of considerable debate in the literature is whether it is necessary or feasible to engage in community consultation when genetic research focuses on socially or politically distinct population subgroups<sup>15,16</sup>.

Cost as a barrier to access Pharmacogenomic drugs will be expensive, cheaper clinical trials notwithstanding<sup>17</sup>. Collectively, the pharmaceutical industry is investing huge amounts of time and money in the development of new technologies that will yield drugs that are more effective than those already available<sup>2</sup>. Without the opportunity to recoup their investment, drug companies will not continue their efforts. At the same time, insurance systems and consumers are struggling to absorb the rising costs of pharmaceutical products<sup>18,19</sup>.

Pharmacogenomics is based on the idea that pharmaceutical consumers will be better served by drug therapy once they have been subdivided by genotype and matched with the most suitable drug. From the industry perspective, the subdivision of a market into smaller markets is hardly ideal<sup>7</sup>. Incentives for pharmaceutical companies to invest time, effort and resources into the development of drugs to treat limited populations are few compared with the development of drugs to treat more prevalent genotypes in the context of pharmacogenomics. Most drug companies might be expected to direct their resources towards the development of drugs to treat the more prevalent genotypes.

Those groups characterized by less-profitable genotypes are at risk of becoming therapeutic 'orphans'. At present, pharmaceuticals for rare diseases are termed 'orphan drugs'<sup>20</sup>. The United States and Japan have enacted legislation to stimulate research and the development of orphan drugs through market mechanisms, such as tax-based cost incentives and time-limited monopolies<sup>20</sup>, with varying degrees of governmental intervention. Canada, Sweden, France, the United Kingdom and other countries rely on broader national drug policies based on more substantial governmental intervention. The European Union has entertained initiatives to stimulate legislative action on orphan drugs, and the **European Agency for the Evaluation of Medicinal Products** has a provision that exempts drug

companies from having to pay application fees to develop a drug if it is an orphan drug (see link to [The European Commission's report on orphan medicinal products](#)). Despite allegations of overpricing of orphan drugs under the American model<sup>19</sup>, nearly all efforts have been followed by a measurable increase in the number of drugs that have been developed and approved for the treatment of rare diseases<sup>21</sup>. As clinical trials increasingly consist of genetically non-diverse groups, policy makers will need to consider whether to expand the concepts underlying orphan drug policies to stimulate research into and the development of drugs for populations who, by virtue of their genetic make-up, face inequities in drug development efforts.

Cost might act as a barrier to access to pharmacogenomics in that the cost of participating in clinical trials or of the resulting drug therapy might be excluded from insurance coverage. Particularly in the United States, where managed care systems attempt to contain costs by rationing medical services, public and private third-party payers have refused or been reluctant to pay for treatments that they deem 'experimental' or not 'medically necessary'<sup>22,23</sup>. Increasingly, these terms have more political than legal or medical significance. There is some evidence that the insurers' disinclination to cover expenses that are associated with new drug therapies can be countered by high physician or consumer demand for the new drug<sup>21</sup>. If consumers must absorb rising pharmaceutical costs, pharmacogenomics will not introduce new questions so much as it will intensify existing ones about equitable access to medical care.

#### Professional standards of care

As pharmacogenomic-based drugs enter into the marketplace, physicians will encounter alternatives to conventional drug therapy and prescription practices. Although the evaluation of genetic variation among patients to determine proper medication and dosage during the course of treatment is not the standard of care at present, ethical concerns, economic considerations and the threat of malpractice liability are likely to encourage physicians to begin testing for and prescribing medications designed for use by specific, smaller groups of individuals. Moral and ethical proscriptions against causing harm might require a physician to integrate pharmacogenetics into clinical practice where necessary to minimize risk to a patient. By contrast, budgetary constraints imposed by insurers could slow the acceptance of drugs developed through pharmacogenomics by limiting their use by physicians and their

availability to patients. The issues raised are not unique to pharmacogenomics but do require new applications of ethical principles and legal doctrine.

In countries where the legal systems are based on common law (that is, the English tradition of law-making based on the court decisions of judges), physicians and pharmacists are subject to liability under theories of negligence, which involve the violation of a duty based on a 'reasonableness' standard or a standard of reasonable care. The standard of care is defined by how a similarly qualified practitioner would act in treating a patient under the same or similar circumstances. The literature, which includes professional scholarship and guidelines published by professional societies, and clinical experience establish the standard of care. In cases based on negligence in the form of medical malpractice, the standard of care is defined through the testimony of witnesses regarding what constitutes conventional practice within the medical community.

### Genotyping appropriate to pharmacogenomic research may not produce information regarding susceptibility to disease or early death, but it may reveal evidence of genetic variation that could lead to individuals being classified as ... less profitable ... or 'more expensive to treat'.

As pharmacogenomic-based drugs increase in prevalence over the next several years, the use of genotyping or genetic testing as a diagnostic tool and the prescription of medications based on genotypic information will become the standard of care for physicians. Physicians and pharmacists 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. With greater knowledge comes greater responsibility. Pharmacogenomics might provide greater information about the likelihood

of a drug being effective or causing adverse reactions in persons possessing a particular genetic characteristic, and will certainly yield drugs that are more likely to be suitable for smaller, specific groups of individuals. By increasing the information available for consideration in drug therapy and the importance of matching the right drug to the right person, pharmacogenomics will raise the standard of care applicable to all involved in the safe prescription and distribution of pharmaceuticals.

Pharmacists are primarily charged with the dispensation of prescriptions as administered by physicians, but the scope of their responsibilities has expanded over time to include ensuring that prescriptions and patient directions are correct and appropriate. Pharmacists also have a duty to warn their customers of the potential adverse effects or other problems associated with a prescribed drug therapy. Even if a pharmacist has dispensed a prescription according to a physician's instructions, some jurisdictions have imposed liability on pharmacists for the harm that resulted from a drug that was properly dispensed in accordance with an improper or harmful prescription<sup>24</sup>. As information regarding the genotype of an individual becomes increasingly important to safe prescription and dosage, pharmacists might be charged with greater knowledge of their customers' genetic information than they now require. The increased amount of genetic information in pharmacies raises privacy and confidentiality concerns, especially where pharmacists belong to large pharmacy chains or corporations with widely accessible, centralized records. For physicians and pharmacists, the issue of continuing professional education and record maintenance will become more important, not only for improving competence but also for preventing liability.

Pharmacogenomics is likely to increase the burden shared by the pharmaceutical industry to provide adequate warnings of the limitations and dangers of their products. In the United States, for example, pharmaceutical manufacturers have a duty to warn physicians about any known or knowable risks, or dangers, of the use of a manufactured drug. Many states in the US will impose strict liability on a drug company for harm caused by the failure to adequately warn against the dangerous propensities of a drug that it has manufactured. Unlike negligence theory, the rules of strict liability are not concerned with the standard of care nor the reasonableness of the manufacturer's conduct; and an aggrieved party need only prove that the manufacturer did not adequately warn of a particular risk

Physicians and pharmacists might be subject to liability if they lack sufficient knowledge of genetics to adequately interpret diagnostic tests, . . . , or properly dispense pharmacogenomic-based prescriptions. With greater knowledge comes greater responsibility.

that was knowable in the light of generally recognized and prevailing best scientific and medical knowledge available at the time of manufacture and distribution. Pharmaceutical companies must consider the potential for liability if patients are harmed because they were excluded from the subgroup for which a pharmacogenomic-based drug is deemed safe and efficacious, particularly if the exclusion leads to a failure to yield information on possible side effects or alternative therapies. Not all adverse side effects are predictable, owing to the number of genes relevant to drug responsiveness, as well as environmental factors<sup>8</sup>. The question is how to allocate responsibility for taking the greatest advantage of drugs specialized to suit relatively smaller segments of the population.

In June 2000, four individuals filed a class action lawsuit against SmithKline Beecham, alleging that the manufacturer of a vaccine for **Lyme disease** knew that some individuals would be susceptible to arthritis on exposure to the vaccine because of their genotype, but failed to warn about this by labelling<sup>25</sup>. The case is still pending. Similar cases involve malpractice actions by the patient against the prescribing physician, who in turn seeks to recover against the manufacturer for failure to provide adequate information. 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.

#### Conclusion

By lessening the uncertainty associated with the selection of drug targets and the design of human clinical studies in the development of new drugs, pharmacogenomics will result in the production of safer, more effective drugs

for use in therapeutic medicine. The integration of pharmacogenomic technology into the drug development process and the practice of medicine will require consideration of ethical, social and legal questions. Answers to these questions might well determine the level of social acceptance and realization of the benefits of pharmacogenomic technology.

*Mark A. Rothstein is at the Institute for Bioethics, Health Policy and Law, University of Louisville School of Medicine, 101 West Chestnut, Louisville, Kentucky 40202, USA. Phyllis Griffin Epps is at the Health Law and Policy Institute, University of Houston Law Centre, Houston, Texas 77204 - 6391, USA. Correspondence to: maroth01@gwise.louisville.edu*

#### Links

DATABASE LINKS **G6PD** | **haemolytic anaemia** | **NAT2** | **Lyme disease**

FURTHER INFORMATION **European Agency for the Evaluation of Medicinal Products** | **The European Commission's report on orphan medicinal products** | **Belmont Report** | **Food and Drug Administration** | **European Agency for the Evaluation of Medicinal Products** | **Pharmaceuticals Affairs Bureau** | **Journal of Health Politics, Policy and Law** | **Journal of International Law and Practice** | **Santa Clara Computer & High Technology Law Journal** | **Genetic Engineering News**

1. Lazarou, J., Pomeranz, B. H. & Corey, P. N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *J. Am. Med. Assoc.* **279**, 1200–1205 (1998).
2. Flanagan, A. Screening technologies evolve: innovations spurred by race to profit from genetic data. *Genet. Eng. News* **20**, 1, 19–20, 71 (September 1, 2000).
3. Barrett, A. The pharma frenzy: in the race for gene-based therapies, big drugmakers join forces with startups. *Business Week* 160–161 (June 2000).
4. Roses, A. D. Pharmacogenetics and the practice of medicine. *Nature* **405**, 857–865 (2000).
5. Noah, B. A. Adverse drug reactions: harnessing experiential data to promote patient welfare. *Catholic U. Law Rev.* **49**, 449–504 (2000).
6. Roses, A. D. Pharmacogenetics and future drug development and delivery. *Lancet* **355**, 1358–1361 (2000).

7. Richmond, M. H. *et al.* *Human Genomics: Prospects for Health Care and Public Policy* (Pharmaceutical Partners for Better Healthcare, England, 1999).
8. Wood, A. J. J. & Woosley, R. Making medicines safer — the need for an independent drug safety board. *N. Engl. J. Med.* **339**, 1851–1853 (1998).
9. Rothstein, M. A. Genetic privacy and confidentiality: why they are so hard to protect. *J. Law Med. Ethics* **26**, 198–204 (1998).
10. Meyer, U. A. Pharmacogenetics and adverse drug reactions. *Lancet* **356**, 1667–1671 (2000).
11. Evans, W. E. & Relling, M. V. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* **286**, 487–491 (1999).
12. Beutler, E. G6PD: population genetics and clinical manifestations. *Blood Rev.* **10**, 45–52 (1996).
13. Weber, W. W. *Pharmacogenetics* Vol. 15 (Oxford Univ. Press, New York, 1997).
14. Grant, D. M. *et al.* Human acetyltransferase polymorphisms. *Mutat Res.* **376**, 61–70 (1997).
15. Sharp, R. S. & Foster, M. W. Involving study populations in the review of genetic research. *J. Law Med. Ethics* **28**, 41–50 (2000).
16. Juengst, E. T. Commentary: what 'community review' can and cannot do. *J. Law Med. Ethics* **28**, 52–54 (2000).
17. Holmer, A. F. Correspondence: the pharmaceutical industry — to whom is it accountable? *N. Engl. J. Med.* **343**, 1415 (2000).
18. Mrazek, M. F. & Mossialos, E. Increasing demand while decreasing costs of generic medicines. *Lancet* **356**, 1784–1785 (2000).
19. Angell, M. The pharmaceutical industry — to whom is it accountable? *N. Engl. J. Med.* **342**, 1902–1904 (2000).
20. Thamer, M. *et al.* A cross-national comparison of orphan drug policies: implications for the U. S. Orphan Drug Act. *J. Hlth Politics Policy Law* **23**, 265–290 (1998).
21. Pulsinelli, G. A. The orphan drug act: what's right with it. *Santa Clara Computer & High Technology Law J.* **15**, 299–345 (1999).
22. Kuszler, P. C. Financing clinical research and experimental therapies: payment due, but from whom? *DePaul J. Hlth Care Law* **3**, 441–494 (2000).
23. Schoonmaker, M. M. *et al.* Factors influencing health insurers' decisions to cover new genetic technologies. *Intl J. Technol. Assess. Hlth Care* **16**, 178–189 (2000).
24. *Horner v. Spallito*, 1 S. W. 3d 519 (Mo. Ct. App. 1999) (reversing grant of summary judgement in favor of customer who died from overdose following accurate filling of incorrectly prescribed drug by pharmacist). Available at <http://www.mobar.org/bulletin/nov99/bul-bod.htm>
25. *Cassidy v. Smithkline Beecham*, No. 99-10423 (Pa. Chester County Dec. 14, 1999).
26. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report* (April 18, 1979).
27. Emanuel, E. J., Wendler, D. & Grady, C. What makes clinical research ethical? *J. Am. Med. Assoc.* **283**, 2701–2711 (2000).

#### Acknowledgements

This work was supported by the National Institutes of Health. The authors are grateful to Joseph Wang for his research assistance.

#### We welcome correspondence

Has something in the journal caught your attention?

If so, please write to us about it by sending an email to: [naturereviews@nature.com](mailto:naturereviews@nature.com) and flag it for the attention of the *Nature Reviews Genetics* editors.

Correspondence to the journal will be selected by the editors for publication on the *Nature Reviews Genetics* website at <http://www.nature.com/reviews/genetics/> where it will be linked to the relevant article.