The Consortium was created to promote a balanced and informed approach to ethical and regulatory issues in the rapidly developing field of pharmacogenetics. The guiding idea of the Consortium was to create a venue in which academic bioethicists from Law and Philosophy with scholarly and public policy expertise and scientists and policy experts from the pharmaceutical and biotechnology industries could work together proactively and constructively. Too often public commissions on bioethical topics fail to utilize as well as they might the essential expertise of the best minds from industry, and too often representatives from industry find themselves in the role of reacting defensively to policy proposals that were developed largely without the benefit of their input.
The initial proposal for forming the Consortium came from discussions between Dr. Allen Roses, Dr. Penelope Manasco, and Elizabeth McPherson, all of GlaxoSmithKline, and Allen Buchanan. GlaxoSmithKline, IBM, and First Genetic Trust provided financial support for the Consortium through an unrestricted grant administered by the University of Arizona. The three industry sponsors of the project also generously provided scientific and policy experts to advise the core research team, which consisted of Baruch A. Brody, Director, Center for Ethics, Baylor College of Medicine; Allen Buchanan (Consortium Director), Professor of Law and Philosophy, University of Arizona; Andrea Califano, Chief Technology Officer, First Genetic Trust, Inc.; Jeffrey Kahn, Director, Center for Bioethics and Professor of Medicine, University of Minnesota; Ned McCulloch, Governmental Programs, IBM Corporation; Elizabeth McPherson, Genetics Ethics Advisor, GlaxoSmithKline; and John A. Robertson, University of Texas-Austin Law School. The core research team convened for a total of seven meetings between November, 2000 and October, 2001.

The Consortium completed three written products: this Report, an article entitled “Pharmacogenetics: Ethical Issues and Policy Options,” forthcoming in the May 2002 issue of The Kennedy Institute of Ethics Journal, and an article entitled “Pharmacogenetic Challenges for the Health Care System,” forthcoming in the July 2002 issue of Health Affairs. The three industry sponsors provided experts who supplied valuable comments on drafts of all three written products, but the core research team exercised full control over the content.

The development of this Report also benefited greatly from the generous comments of the following persons on the penultimate draft: Kathy Hudson, Director of Policy and Public Affairs, DHHS/NIH, Washington, D.C.; Laura Beskow, Doctoral Candidate, Department of Health Policy and Administration, School of Public Health, University of North Carolina-Chapel Hill; Bert Spilker, Senior Vice President of Scientific & Regulatory Affairs of the Pharmaceutical Research and Manufacturers of America; Bartha Knoppers, Law Professor and Senior Researcher at the Centre for Public Law Research, University of Montreal; Susannah Baruch, Director, Legal and Public Policy of the National Partnership for Women & Families; David Beier of the law firm of Hogan and Hartson, and former Vice President of Government Affairs for Genentech; and David Flockhart, Medicine Department, Indiana University. The Consortium endeavored to take these comments to heart and we are convinced that in doing so the Report was greatly improved. However, the responsibility for the content of the Report rests solely with the Consortium, and nothing contained in the Report should be seen as being endorsed by the reviewers.

The authors of this Report believe that the Consortium on Pharmacogenetics can provide a model for extensive, sustained collaborative efforts between industry and academia on a wide range of public policy issues in the pharmaceutical and biotechnology industries. It is also our hope that the work of the Consortium will contribute to an environment in which public policy bodies addressing bioethical issues will engage more proactively with experts not only from academia but from industry as well.
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PHARMACOGENETICS: ETHICAL AND REGULATORY ISSUES IN RESEARCH AND CLINICAL PRACTICE

I. INTRODUCTION

For as long as physicians have administered drugs, they have known that individuals can respond differently to the same drug and surmised that this was at least sometimes due to in-born differences among individuals. But only with the recent rapid increase in scientific understanding of the human genome is it becoming possible to identify the extent to which genetic variations influence drug response. The emergence of pharmacogenetics (PGx) heralds a new era in which drug therapies will be selected in the light of differences in individuals’ genotypes, enhancing drug safety and efficacy.

A. Definitions

The terms pharmacogenetics and pharmacogenomics have yet to achieve a fixed standard usage. For purposes of this report, we define pharmacogenetics as the study of the effects of genetic variations in the individual on drug response, including safety and efficacy, and drug-drug interaction. These genetic variations are not tissue-specific and constitute a static, global characteristic of the individual.

The second type of variation that influences drug response lies in the expression of genes in the cells of particular tissues. This factor is dynamic, changing in response to endogenous and exogenous stimuli. The study of this second source of variations in drug response is pharmacogenomics. The major focus of this Report is pharmacogenetics, primarily because this methodology employs knowledge of an individual’s stable genotype and therefore generally may raise more significant ethical issues concerning privacy and confidentiality, including the implications of pharmacogenetic test results for biological relatives of the person tested.

Both types of variations in individuals have been shown to be strongly correlated with drug response. Once such correlations are established, a pharmacogenetic or pharmacogenomic test can be devised. Such a test reveals the likelihood of an individual’s response (regarding safety or efficacy) to a particular drug or class of drugs.

PGx research focuses either on establishing correlations between particular genotypes of individuals and responses to particular drugs (or related groups of drugs) or upon general mechanisms of drug response, as these are affected by genetic variations. As PGx advances, the latter, potentially much more efficient approach, is likely to become dominant.

B. The need for—and risks of—prospective analysis

PGx has the potential to become a large-scale methodology with profound effects both on drug development and on clinical medicine. As with other major biomedical advances, PGx raises ethical, regulatory, and policy issues. This Report provides a systematic prospective analysis of these issues.

PGx research and the development of PGx testing are taking place in an era of globalization. As we argue below, harmonization, both at the national and international levels, is required in the development of appropriate guidelines and protections. While there is a recognized need for oversight of genetic research and genetic testing, there has been insufficient appreciation of the particularities of PGx. Appropriate protections and guidelines that take into account the particularities of PGx should be integrated into a comprehensive framework for the development of this methodology that includes provisions for approval of and reimbursement for PGx tests and of drugs for which there are PGx tests.

The Consortium believes that at the present time pharmacogenetics represents a rare opportunity to explore the ethical, regulatory, and policy issues of an important new advance in biomedical science while it is still under development and before it has come to shape and be shaped by existing institutions and social practices. This prospective analysis should continue the focus on ethical, legal and social
implications (ELSI) that has distinguished the Human Genome Project from its very beginning, along with other efforts such as those of the National Institute of General Medical Sciences (NIGMS) Pharmacogenetics Research Network. The Consortium has taken a first step toward a comprehensive prospective analysis by focusing primarily on PGx in the United States.

Too often, serious analysis only occurs after the fact, as a reaction to ethical problems that are recognized only after a new biomedical advance has already become so thoroughly entrenched in concrete social practices and institutions that efforts to solve them are futile or at least extremely difficult. Although it would be naive to think that all the issues raised by PGx can be foreseen in advance, now is the time to attempt to identify the most important questions and to articulate a range of reasonable responses. The advantage of prospective analysis is that it may succeed in identifying potential problems early, when less costly and more effective responses to them are possible.

Prospective normative analysis is not a risk-free enterprise. One danger is that some of the potential issues may not be identifiable prospectively. Alternatively, some potential issues that are identified may never arise. All biomedical advances carry risks. Although we attempt to fully identify the issues that may arise from PGx, nothing said in what follows should be understood as implying that PGx presents risks that are disproportionate to its potential benefits.

One final limitation on prospective analysis should be noted. Which ethical, regulatory, and policy issues turn out to be most significant will depend upon the broader social context in which PGx develops (insurance discrimination, reimbursement decisions, etc.), and this is notoriously difficult to predict. Nevertheless, we believe that the risks of prospective analysis are worth taking and that much is to be gained from an attempt to anticipate the most significant social issues that PGx is likely to raise.

Before the ethical, regulatory, and policy issues can be usefully addressed, it is necessary to articulate the potential benefits and risks of this new methodology, and to understand the conditions under which these potential benefits and risks may or may not be realized.

C. Potential benefits of PGx

These fall under six main headings.

(1) Understanding the genetic bases of drug response mechanisms. Discovering links between drug response phenotypes and genotypic variations can contribute to a better understanding of how genes affect drug metabolism, transport, distribution, excretion, and absorption. For example, it has long been known that individuals with one or more specific mutations in the cytochrome P450 family of enzymes tend to be poor or rapid drug metabolizers over a wide range of drugs. This PGx information could be valuable, not only for physicians and patients, but also for drug developers. It is also information that health care payers may find valuable for the design of more rational drug use policies.

(2) More efficient, safer, and quicker drug development, through smaller-scale clinical trials. PGx testing could allow individuals who are not likely to respond to a candidate drug or who are likely to experience adverse reactions to it to be identified and excluded from participation in phase III (or possibly phase II) clinical trials. Exclusion on the basis of genotype from the participant pool would have three advantages: (a) a reduced risk that some participants will suffer adverse reactions in the trial, (b) an increased probability of success in developing a drug that will be approved and made available, by reducing the percentage of adverse reactions and low- or non-responders, and (c) savings in time and money by facilitating trials with fewer participants.

(3) Safer drug use. If reliable correlations between specific genotypes and adverse reactions to drugs can be identified, existing drugs can be used more safely. In some cases this will be a
matter of using knowledge of genotype to choose a different drug with a lower-risk of adverse reactions; in other cases, genotypic information will indicate the need to adjust the dosage of a drug.

(4) Increased drug efficacy. PGx tests can be used to distinguish responders from non-responders or high- from low-responders to a particular drug or group of drugs. More effective treatment in a shorter time frame can then be achieved, by avoiding fruitless or less productive treatments, by avoiding a trial and error process of modifying dosages, or by selecting alternative drug therapies.7 8 9 10

(5) Improved post-market surveillance of approved drugs. Regrettably, a serious frequency of adverse reactions sometimes appears after a drug has been approved by FDA and used for some considerable period of time. If the genotypes of those individuals who have adverse reactions can be ascertained, it may be possible to identify correlations between specific genotypes and the risk of adverse reaction. It may then be possible to identify an adverse reaction problem earlier and to predict more accurately how widespread the problem is likely to be.11

(6) Salvaging beneficial drugs. Drugs that are highly beneficial for many individuals may not be approved or may be withdrawn from the market after approval because a minority of users experience serious adverse reactions. If a PGx test can identify those who are likely to experience adverse reactions, the drug could be salvaged for the many individuals who can benefit from it, with appropriate labeling regulations.

D. Risks of PGx

Bearing in mind the impossibility of definitively identifying in advance the risks of new biomedical advances, we nevertheless believe that the following are risks worth considering. Most of the remainder of this Report elaborates upon these risks and possible strategies for addressing them. We also address the questions as to whether these risks and strategies for addressing them are unique to PGx.

In the research area, risks include: use of biological samples and health information without appropriate consent; harms to families or groups from stigmatizing information; inappropriate disclosure of information from PGx tests; failure to disclose clinically relevant research results; failure to include diverse groups in research; and narrowing of the research agenda in ways that may create orphan drug groups (populations for whom it is not sufficiently profitable to develop special drugs).

In the clinical area, risks include: introduction of PGx testing without adequate validation; suboptimal access to and use of PGx testing; testing without adequate consent; inappropriate uses of PGx testing as a result of direct marketing; discriminatory uses of PGx information by third parties; and secondary information conveyed by PGx results that may produce psychosocial harms.

E. Scientific and social factors that may affect the development of PGx

The extent to which the benefits and risks of PGx will be realized will depend on both scientific and social factors.

Scientific factors. The range of genotypic variability regarding drug response is perhaps the single most important scientific factor. Whether or not PGx becomes a large-scale methodology that plays a prominent role in clinical medicine will depend upon whether there is genetic variation sufficiently associated with differences in drug response to make pharmacogenetic testing worthwhile, yet not so much variation that an impractically large number of PGx tests—and a correspondingly large number of genotype-tailored drugs—would be necessary.

Two other important scientific factors concern the complexity and significance of PGx tests. First, in many cases, more than one gene influences drug response. Several genes may be needed to produce the set of proteins that are responsible for the drug response effect (e.g., how the drug is distributed or absorbed) or there may be counter-acting genes that affect drug response.
Where several genes are involved, PGx testing may be both more complex and less definitive as a predictor of drug response. Second, drug response is influenced not only by stable genotype and gene expression, but also by a number of other factors, including the individual’s state of health (especially liver, kidney, and endocrine functions, and the immune system), environment (including workplace chemical exposure, food, alcohol, and tobacco intake, etc.), compliance with drug treatment, and drug interaction. Consequently, PGx tests will not by themselves provide definitive guides to treatment. Complex clinical judgment will be required to determine (a) whether to administer a PGx test rather than relying on phenotypic tests, drug dose adjustment based on clinical studies or on trial and error with a particular patient, and (b) if the PGx test is used, how much weight to give its results in relation to other factors in making a therapeutic decision.

**Social factors.** Among the most significant social factors that will influence the direction, pace, and scale of PGx research and clinical application are the following: (i) the willingness of pharmaceutical and biotechnology companies to invest in the technologies needed to develop and deploy the methodology, (ii) the character of regulation and oversight practices regarding PGx research and clinical use, (iii) the extent, quality, and distribution of knowledge about the potential benefits, costs, and risks of PGx among payers, health care administrators, providers, and consumers, (iv) public attitudes toward genetic research and testing in general, including the ability (or lack thereof) to distinguish between PGx tests and other genetic tests that may carry higher psychosocial risks, and (v) the nature of the existing health care insurance and delivery systems, and in particular the sorts of reimbursement policies and cost-containment strategies that are pursued in drug use policies.

These social factors, which impact society as a whole or particular stakeholders, may interact in complex ways. Whether pharmaceutical and biotechnology companies will be willing to invest sufficient resources in PGx research and test development will depend in part upon their predictions of how likely it is that cost-conscious private insurers and government payers will view PGx testing as a significant cost-saver rather than as yet another costly procedure of uncertain benefit. Insurers’ and payers’ initial resistance to adopting PGx tests might be overcome if direct marketing of tests and the availability of information about their potential benefits on the internet serve to stimulate strong consumer demand.

Public perception—or misperception—can also shape regulation and oversight, which may in turn either facilitate or inhibit PGx research or the integration of PGx into clinical medicine. Negative attitudes toward anything regarded as a genetic test, and hence as a possible source of stigmatization or insurance or employment discrimination, might prompt regulators to impose overly-stringent protections of confidentiality that will inhibit the development of this methodology and reduce the benefits it could yield.

**Incentives to develop PGx tests.** In the not-too-distant future the health interests of patients may generally be served by PGx testing prior to prescription of a drug. However, the incentives to develop such tests may vary across different parties.

Generally speaking, pharmaceutical companies will have strong incentives to develop PGx tests for *safety* for their own drugs, both to reduce liability and to avoid having approved drugs taken off the market due to adverse reactions. The same may not hold, however, for PGx tests for the *efficacy* of their own drugs. Pharmaceutical companies traditionally attempt to develop “blockbuster” drugs that bring large revenues annually throughout the life of the patent. A pharmaceutical company’s financial interest in sustaining sales of drugs may conflict with patient, provider, insurer, and payer interests in having PGx tests for efficacy performed on their drug. Some pharmaceutical companies might therefore be unwilling to develop—and might even seek to prevent others from developing—PGX tests that would determine that their drugs are not appropriate for substantial numbers of the individuals who are now taking...
The counter-argument is that it is difficult to imagine a blockbuster that lacks substantial efficacy in a significant segment of the patient population. A drug that has marginal efficacy in a narrow segment of the patient population will not bring large revenues annually throughout the life of the patent and hence would not qualify as a blockbuster. An efficacy PGx test would merely identify the suboptimal efficacy of a drug earlier in the product’s life cycle.

Probably the bigger concern for a pharmaceutical company with efficacy PGx is that it may result in very narrow labeling indications. This in turn has the potential to reduce off-label use, which for many drugs represents a substantial component of product revenue. However, a pharmaceutical company might have a legitimate interest in preventing the use of a PGx test for efficacy that it reasonably believed to be unreliable.

There may be a difference in incentives, so far as pharmaceutical companies are concerned, between established drugs and new drugs. If a drug can be initially marketed with a PGx test that reliably predicts its safety and efficacy for a significant population of patients, drug makers may see this as a competitive advantage that makes the drug more attractive to providers and payers. In addition, a pharmaceutical company might see a PGx test for efficacy of one of their drugs in a more favorable light if it believed that the test would reveal that drug to be more efficacious for a larger number of patients than a competitor’s drug. As a broad generalization, it may be the case that pharmaceutical companies will have stronger incentives for using PGx in the drug development process and for developing PGx tests for safety than for encouraging PGx tests for efficacy of their own drugs that have already been approved and have proved successful in the market.

**Intellectual property.** A detailed examination of the complex and changing landscape of intellectual property is not within the purview of this Report. However, it is worth pointing out that there are two ways in which intellectual property rights can affect the development of PGx. First, the possibility of obtaining intellectual property rights and the financial rewards that flow from them can motivate the development of PGx tests and the search for genetic markers that can be used in them. Without an appropriate regime of intellectual property rights, individuals and organizations will be reluctant to incur the risks and costs of discovery and development because whatever they create or discover can simply be used by others, without financial benefit to them. Second, intellectual property rights can in some cases pose an impediment to development of a technology. In the case of PGx the worry is that if a number of different entities hold patents on the various genetic markers and other inputs needed for PGx tests, then the costs of getting licenses for the use of these components, and hence the costs of the tests themselves, will be prohibitive. This is the concern about “patent bottlenecks.”

**F. The possible expansion of the methodology beyond medicine**

The basic methodology of PGx is not confined to the discovery of correlations between medical drugs and the body’s responses to them. Any substance which when ingested affects the body, including not only workplace or environmental chemicals, but also vitamin supplements, various “botanicals,” foods, and even biological warfare agents, may differ in its effects depending upon variations in genotype. Given the size of the market for special diet foods, botanicals, and vitamin supplements, it would not be surprising if tests are eventually marketed that purport to help an individual determine which combination of supplements and diet, and even which regimens of exercise, are optimal for his or her health.

The methodology is also applicable to determining the influence of genotype on responses to alcohol and tobacco or to illicit drugs such as cocaine. Researchers have recently reported success in developing an immunization against certain addictive substances. In the future tests might be used to determine which individuals are genetically predisposed to
addiction, in order to identify those who could most benefit from immunization.

What begins as a biomedical advance may, under the influence of demand stimulated by vigorous marketing, come to have quite different applications, some of which raise their own distinctive ethical and regulatory issues. While noting that it may be naive to assume that PGx will remain a medical methodology largely within the control of medical professionals, this Report will address primarily the medical applications.

**G. Clearing the way for productive ethical analysis**

**Ethics, risks, and benefits.** For society the objective is to realize the great potential benefits of PGx to the fullest extent possible, consistent with adherence to sound ethical principles. But adherence to ethical principles is not costless. It can entail not only financial costs, but the forgoing of important benefits as well. For example, respect for the dignity of the individual requires informed consent for participation in research, yet having to obtain informed consent may make it more difficult for researchers to pursue the morally worthy goal of curing disease. So in determining how robust the requirement of informed consent should be—how much information about what magnitudes of risk, etc., must be disclosed—it is important to keep in mind the costs in terms of foregone potential benefits.

Similarly, sound ethical principles require protections against breaches of confidentiality concerning access to stored biological samples used in PGx and other research. However, requiring the most extensive protections possible, including permanent anonymizing of samples, would not only cripple the research endeavor, but also preclude participants from being notified about research findings from which they could greatly benefit.

In other words, efforts to maximize protections of confidentiality, like other efforts to reduce risks to zero, are virtually always inappropriate because they sacrifice other important values. The goal is not the reduction of all risks to zero, not only because this is generally impossible, but because even to attempt to do so would deprive us all of benefits we have moral reasons for seeking.

Unless the potential benefits are adequately appreciated, it is impossible to evaluate accurately the various options for reducing risks. Yet too often ethical analyses of biomedical technologies or methodologies (e.g., xenotransplantation) look only to risks and then propose policies to reduce risk, but fail to take seriously the ethical costs of their risk-reduction proposals. To avoid this all too common error, we have prefaced our consideration of the risks that may be associated with PGx with a discussion of the methodology’s potential benefits. What is needed is a sensitive balancing of risks and benefits, not an exclusive attention to either.

**Avoiding three fallacies regarding things genetic.** In addition to the incorrect assumption that risk-reduction is ethically costless, there are several other misapprehensions that may result in constraints that would unnecessarily limit the benefits pharmacogenetics could deliver. These include (1) genetic exceptionalism, the assumption that all things genetic involve especially serious or unique ethical risk and therefore require novel ethical principles and/or special regulatory responses, (2) genetic determinism, the assumption that genes are autonomous, self-sufficient causes, which overlooks the importance of environment broadly understood and consequently over-estimates the risks posed by information about genes, and (3) genetic overgeneralization, the failure to appreciate the heterogeneity of “genetic tests” and their results, so far as psychosocial risk is concerned (for example, lumping together tests for fatal single gene dominant disorders such as Huntington’s chorea with tests for drug efficacy).15 16 17 18 19

Genetic exceptionalism appears to be widespread. Consider, for example, the fact that legislation is being adopted in many states to prohibit “genetic discrimination” by insurers, while at the same time little is said about the fact...
that insurance companies in some markets routinely refuse coverage or charge higher premiums for those deemed to be at higher-risk due to non-genetic factors beyond their control.

Genetic determinist thinking fuels genetic exceptionalism by portraying genes as all-powerful—as fate—but it can also lead to unrealistic expectations about the fruits of genetic science, including PGx. Genetic determinist thinking may result in a PGx test being regarded as definitive, rather than as probabilistic information to be balanced against other factors. And this exaggeration of the significance of a PGx test may in turn encourage an over-estimation of the psychosocial risks associated with testing.

Finally, it may be misleading to apply the rather uninformative term ‘genetic test’ to the many different types of DNA tests without explaining their differences, since doing so may encourage one to make assumptions about psychosocial risk that apply to some tests but not others. For example, a test for the “Alzheimer’s susceptibility gene” (APOE4) may carry a much higher-risk of stigma, discrimination, and psychological distress, than one for the mutations associated with hereditary hemochromatosis (a condition that can be effectively treated) or a PGx test to determine whether one is likely to be a low-responder to one particular drug among several that can be used to treat one’s condition.

II. RESEARCH

A. The need to integrate clinical, epidemiological, and research data

Multiple sources of information. Research to determine the influence of variations in genotype on drug response requires not only the collection, storage, and analysis of DNA samples, but also the ability to integrate this genetic information with information from the individual’s medical record on a wide range of factors from general health status to current medications, other interventions, family history, and behavioral and environmental factors. To determine the extent and nature of genetic variations, in order to ascertain which variations affect drug response, many studies will be needed with proper sampling techniques to ensure the inclusion of the full range of genetic variation.

The flow of information. One of the most important ethical challenges of PGx research is to devise structures and procedures that facilitate and at the same time properly control the flow of information. The researcher needs access to DNA samples and medical records, as well as epidemiological studies of genetic variations across large populations. The individual who participates in PGx research has a legitimate interest in having access to information that is beneficial to him, but at the same time needs assurance that confidentiality and privacy will be maintained. Thus it is necessary to consider both the flow of information to the researcher and to the research subject. These issues are not unique to PGx research, but the potential scale of the flow of information makes them particularly salient.

B. Informed consent

Before information can begin to flow to the researcher, the individuals to be included in the study must give informed consent. As in all human subjects research, informed consent is required for the collection of DNA samples for PGx research. The ethical basis of informed consent in research. Seeking informed consent shows respect for the dignity of the individual, but it also provides a protection against exploitation of the subject under conditions in which the interests of the researcher and that of the subject may be in conflict. In the clinical context the presumption is that the physician is a fiduciary whose primary commitment is to the patient’s well-being. In the research context this presumption does not hold, and the researcher may have academic and/or commercial interests that can conflict with what is in the best interest of the subject. For this reason, as we shall see, the requirement of informed consent is both clearer and more demanding in PGx research than in the clinical application of the methodology. The same respect
for individual dignity and well-being also requires the participant’s consent to the researcher’s access to medical records.

The ethical issues of informed consent in PGx research can be analyzed under four headings: (1) the scope of informed consent, (2) the content of informed consent, (3) the proper terminology for the informed consent process, and (4) whether the informed consent process involves only the individual research subject or also a group or community of which the individual is a member.

Scope. The scope of consent includes both the period of time during which the researcher is to be allowed to store and have access to biological samples and other information and the uses to which the samples and information may be put, either by the current researcher or other researchers. At one extreme, the subject might give a blanket, time-unlimited consent for the use of his DNA sample and/or medical records for any research project the researcher or any other researcher chooses. At the other extreme, the subject might give a very narrowly focused consent only for the use of the DNA sample and certain specified information from the medical record, only for a limited period of time, with restricted genotyping, and only for this researcher.

Between these extremes there are many variations on the scope of consent. For example, a subject might consent to access to his DNA sample and all medical records for a specified research protocol studying response to a particular cancer drug and only for other, currently unspecified protocols for research of the same type, to allow participation in future research on other cancer drugs. This consent might or might not include a stipulation that after a period of time the DNA sample is to be destroyed or “permanently anonymized,” that is made unlinkable to the subject by anyone.

Informed consent of relatively broad scope has two apparent advantages. First it provides valuable flexibility in an area where knowledge and research capability is changing rapidly and in sometimes unanticipated ways. This flexibility can avoid substantial losses of research subjects, as well as intrusions into the subject’s life entailed by “re-consenting.” Moreover, during drug development, significant attrition of subjects, loss of time and additional cost could put an entire study on hold or even cause it to be terminated. Second, allowing the subject to give broad-scope consent might also be seen as more respectful of individual autonomy, whereas restricting his right to grant access to the information by reducing the scope of consent might be viewed as paternalistic.

The disadvantage of such broad-scoped consent is that it may not achieve the chief purposes of the requirement of informed consent. In addition to showing respect for the dignity of the individual, the requirement of informed consent to research places the individual in a position to understand and weigh the more significant costs and benefits of participation, on the assumption that he is generally the best judge of what is in his interest. But it is difficult to see how one could in any meaningful fashion weigh the costs and benefits of participation in a wholly unspecified, indefinitely large range of possible future uses of one’s DNA and medical records. It is therefore implausible to argue that respect for the individual’s autonomy requires the option of consent of extremely broad scope. It is not paternalism to refrain from facilitating extremely uninformed choices.

Nor is the other extreme regarding the scope of consent an attractive option. Requiring specific consent for every distinct protocol would be contrary to the interest not only of society at large in medical progress but also to the interest of the individual research subject as well.

A reasonable policy is to secure a degree of flexibility by allowing the subject to consent to a range of related studies over time, at least if there is a provision for specific consent to studies that may be especially problematic. For example, a subject might give blanket consent to use of his sample for any cancer drug studies conducted by the investigator of the cancer drug study in which he is presently enrolled, but require special consent to any use of his DNA for other purposes.
in general or, say, for studies involving sensitive issues. For instance, a subject might reasonably wish to be offered the opportunity for special consent to a protocol using his DNA for a study of the relationship between race and susceptibility to certain mental illness or to violent behavior or poor impulse-control.

**Content.** The content of informed consent for PGx research should include at least five elements.  
(1) The risks and benefits of participation must be impartially and accurately explained in terms that are accessible to the individual. Risks here include the possibility of deleterious effects of breaches of confidentiality regarding sensitive information and the minimal risks of the various techniques for collecting biological samples.  
(2) The individual should be informed of the provisions for safe-guarding the confidentiality of the sample and medical records (who will have access, for what purposes, what coding or anonymizing provisions will be employed, if the sample or other information will be destroyed after what period of time, and who is ultimately responsible for preserving confidentiality and privacy).  
(3) The sponsor of the research should be disclosed, as well as the possibility that the sample and/or products of the study will be used for commercial purposes and will generate revenue.  
(4) The informed consent process should include a discussion of the possibility that information that is reliable and potentially beneficial to the individual subject will be discovered in the course of the study. That discussion should make clear who is responsible for this determination and what standards they will use, and who is responsible for disclosing such information to the subject and how it will be provided. The subject should be able to opt to have such information provided, with suitable provisions for protecting the confidentiality of other subjects where appropriate.  
(5) The individual should be informed of his right to withdraw from the study at any time without penalty and without compromising his access to medical care provided independently of the study.

**The terminology of informed consent.** The need to avoid genetic exceptionalism raises a question about the precise terminology by which the nature of the research is to be described in the informed consent process. In particular, is it necessary for the informed consent process to employ the vague but perhaps emotionally-charged term “genetic test” in the case of research designed to discover links between genotype (or gene expression) and drug response, or to ascertain the sensitivity, reliability, and specificity of an experimental PGx (or pharmacogenomic) test?

Collection and use of DNA samples should of course be described as such in the informed consent process. However, given the great heterogeneity of “genetic tests” and the quite different psychosocial implications of tests for single gene disorders or susceptibility to disease, on the one hand, and tests for likely responses to drugs, on the other, it may be unnecessary and in some instances even misleading to require that the individual be informed that “genetic tests” will be performed on his DNA sample. Instead, a more accurate statement would be that DNA extracted from the sample will be used to study the relationship between genetic variations among individuals and how they respond to drugs.

The fundamental issue here is what a reasonable person would want to know in order to evaluate the risks and benefits of participation in research. An accurate description of the use to which the sample will be put (namely, an attempt to correlate genetic variation and drug response) seems more apt than the vague label “genetic test,” especially since, due to the pervasiveness of genetic determinism and genetic exceptionalism, the latter might encourage the individual to over-estimate risks.

**Group-based harms and the limitations of individual consent.** There is a growing recognition that in some cases genetic information may contribute to “group-based harms.” These are harms that individuals suffer as a result of being perceived to be members of ethnic or racial groups (or other groups ranging from families to larger groups such as “the disabled.”) For
example, if PGx research were to reveal that African-Americans, Azkenazi Jews or certain Native American groups have a lower response rate to certain treatments, this might result in stigmatization or discrimination to which all members of the group would be vulnerable. It has been argued, therefore, that because genetic research on some member of a group may have harmful effects on all or many members of the group, the informed consent process should not be exclusively individualistic, but rather should include some input and/or oversight from the group or its putative representatives.32

The first point to note is that presented in this way, the case for group participation in the informed consent process for PGx testing appears to be an instance of genetic exceptionalism. Many types of research, including nongenetic and even nonmedical research have the potential for group-based harms. For example, studies that purport to show that a particular racial or ethnic group incurs higher medical costs have the potential to reinforce negative stereotypes and to perpetuate patterns of discrimination.

The most extreme form of the view that the potential for group-based harms requires a departure from the traditional individualistic paradigm of informed consent would confer a right on the group or its putative representatives to veto an individual member’s consent to participation in research.33 This view seems unacceptable, because it wholly subordinates individual autonomy to group preference.

A less extreme and more plausible response to the problem of group-based harms would be to allow group or community consultation at the earliest stages of enrolling individuals in cases in which there is a significant risk of group-based harms—in particular where there is evidence that a group is at risk for negative stereotyping or discrimination. The intuitively plausible idea here is that consultation would allow concerns about group-based harms to be voiced and properly addressed in the research design, including plans for disseminating the results of the study.34

The notion of group consultation is problematic, however. Two difficulties in particular are worth noting. First, there is the issue of authentic representation.35 Conferring with all members of the group will generally be impossible or at least impractical. But it may not be clear who, if anyone, may serve as an authentic representative of the group’s interests. This problem is especially obvious in the case of groups (such as Azkenazi Jews) that are not politically organized and hence do not have official representatives authorized to make important decisions on behalf of the group. But even in cases in which certain individuals are duly authorized to speak for the group, questions remain about whether they do in fact represent the interests of all their constituents and about which types of issues they are authorized to make definitive pronouncements. For example, tribal leaders may have the authority to make a wide range of decisions, but it does not follow that they have the authority to prohibit members of their tribes from participating in genetic research.

In spite of these difficulties, group consultation may achieve two worthy goals.36 First it can show respect for members of the group and concern for their well-being, by allowing the issue of group-based harms to be addressed by those who might suffer them. This may be especially salutary in the case of groups, such as African Americans, who have been subject to discrimination or exploitation in the past, sometimes at the hands of medical researchers.37 Second, group consultation may encourage the cooperation of group members in the research.

To summarize: it is one thing to say that
both researchers and individuals deciding whether to participate in PGx research ought to take the risk of group-based harm into account and that consultation with other members of the group may facilitate this. It is quite another to assert that the potential for group-based harm—which may be highly speculative—trumps the individual’s right to participate in research that he believes will be valuable to himself or to others, including members of the group; moreover, additional research is needed concerning whether group-based harms are likely to occur. From the standpoint of public policy and regulation, it would be inappropriate to mandate group consultation, much less group consent, as a general requirement for genetic research, including PGx research. However, in particular circumstances, for especially sensitive research with historically vulnerable groups, responsible researchers will seek to incorporate group input into the research design and informed consent process.

C. The problem of secondary information

In some cases PGx test results, whether in the research or clinical context, might convey any of several types of secondary information that might, under certain circumstances, represent a risk of psychosocial harm, either to the person tested or to relatives. These risks must be discussed in the informed consent process.

Types of secondary information. (1) A PGx test result might be linkable to genetic disease or, more likely, to a genetic predisposition to disease, either because the genotype that influences drug response also plays a role in the disease process or because it is correlated with one that does. Whether such an eventuality poses a significant risk will depend upon several factors, including: how probable it is that the individual will get the disease, how serious the disease is, whether it is treatable, and whether the knowledge that a person has the disease is stigmatizing.

It is also important to emphasize that the perception that an individual has a genetic susceptibility to a disease is only potentially a source of insurance or employment discrimination in a society in which insurers and employers are allowed to take genetic risk into account. The trend in the U.S. is to prohibit such genetic risk-rating by insurers, as well as genetic discrimination in employment.38

(2) Under certain conditions the information that an individual is likely to be a non-responder or an unsafe-responder to a particular drug or class of drugs might itself have adverse insurance and/or employment implications. For example, if an individual has a genotype which indicates that the only effective drug (or group of drugs) for his serious condition will not be efficacious for him, or cannot safely be taken by him, he might be classified by insurers or employers as having an untreatable serious illness. This risk would only arise in cases in which (a) there is no alternative effective treatment for the condition in question, or the alternative treatment is much more expensive, or (b) the condition is serious enough to be of concern to insurers or employers, and insurers and/or employers are able to take this sort of information into account in making decisions.

(3) Studies indicate that some individuals may have genotypes that confer susceptibility to addiction to certain substances. If that genotype is linked to a marker that is associated with a particular drug response, then a test for the latter would indicate susceptibility to addiction. Information that an individual is susceptible to addiction may pose a risk of stigma and discrimination, depending upon social circumstances, including the effectiveness and availability of drug abuse treatments and the ability of insurers and employers to act on the information that an individual has a predisposition to addiction.

(4) Information about genetic factors in drug response, like all genetic information, can have implications for relatives, not just for the individual tested, for example, that they have a higher than average risk of adverse reaction to a particular drug or have a susceptibility to disease that is linked to the marker detected in the PGx test. In some cases, PGx test results, in the context
of other information, might convey information regarding nonpaternity. For instance, if a PGx test reveals that the child is a “slow-acetylator” but it is also known that the presumed father does not carry either of the alleles (gene-variations) responsible for this recessive trait, this could indicate nonpaternity.

(5) If a particular drug is only prescribed for individuals who have a particular genotype, then simply knowing that the individual takes that drug can convey the information that he has that genotype. Whether or not the latter knowledge would carry any risk of psychosocial harm would depend upon whether the genotype in question is associated with a susceptibility to disease or with some other negatively valued characteristic, whether physical or behavioral.

The speculative nature of risks associated with secondary information. It should be emphasized that these concerns about secondary information are rather speculative and arise only under certain highly specific circumstances that may not occur with much frequency. Moreover, none of them is peculiar to PGx. Secondary information that may pose a risk of psychosocial harm is revealed by other, more established forms of research and other medical tests. For example, tests for blood type have the potential to convey information about genetic risk and about nonpaternity. Yet for these there is often no informed consent or at least none that addresses the risks associated with secondary information. Similarly, home pregnancy tests and HIV tests (both of which are self-administered, without benefit of counseling or medical supervision) have the potential for psychosocial harm to the individual tested as well as implications for other persons.

There is another important qualification concerning potential problems of secondary information in drug response testing that seems to have gone unnoticed in the literature to date. The potential for sensitive secondary information about others than the person tested may be limited for the most part to PGx tests, that is, DNA assays that correlate drug response with stable genotype, not pharmacogenomic tests, which correlate drug response and gene expression. For as was noted in the Introduction, information about gene expression less frequently has implications regarding the genetic risks of relatives or nonpaternity.

Finally, how much secondary information is conveyed by a PGx test result will partially be a function of the technology employed. In particular, some genetic markers correlated with drug response may be relatively “clean,” carrying little or no secondary information about genetic predisposition to disease, disease progression, etc. If it turns out that more than one marker can be reliably correlated with drug response, it may be possible to select a “clean” one for use in a PGx test.

D. Reducing the risks of secondary information

Fire-walls versus prohibitions on uses of information. Policy designed to reduce the risk of psychosocial harms from secondary information should distinguish between (1) the role of “fire-walls”—barriers to the dissemination of sensitive information—and (2) the role of regulation to prevent certain damaging uses of information the dissemination of which may be impossible or too costly to prevent. Coding technologies that create a barrier between medical or research information and the identity of the individual patient or subject are one instance of the fire-wall approach. Laws prohibiting “genetic discrimination” by employers and insurers are attempts to prevent certain uses of genetic information.

Another example of a fire-wall strategy is a policy of including only the medicine response result in a laboratory report of PGx test results, but no secondary information—including information about the genotypic features that are responsible for the drug response result. However, as noted above, in some cases the drug response result itself, apart from any information about its genetic basis, may have damaging implications. For example, where there is no other effective treatment for a serious disease, a test indicating
that the individual is a non-responder for a drug for a serious condition would imply that he has an untreatable serious condition and will therefore represent high costs.

A fire-wall strategy cannot completely protect the individual against discrimination based on an unfavorable PGx test result. First, insurers and sometimes employers have access to medical records, and these sometimes contain research results, especially when the researchers are the clinicians caring for the individual. Second, rigid fire-wall strategies may not allow for needed breaches of security mechanisms for patient care purposes. To reduce the risk of discrimination on the basis of information that cannot be contained by fire-walls, regulations prohibiting insurers (and employers) from using such information to the detriment of the individual may be an important ingredient in a sound public policy.

How such legislation should be crafted is a complex question. Among the issues to be considered are (1) whether and if so what limitations on liability for prohibited uses of information are appropriate and (2) whether employment and insurance (or health versus life insurance) should be covered by separate legislation. Here again, PGx raises no new issues, but the eventual scale of the PGx research enterprise may make old issues more acute.

**Trusted intermediary entities.** A different approach to reducing the risk of breaches of confidentiality, and one that is designed to allow for recurring access to biological samples and other relevant data, is the use of “trusted intermediaries.” Such private or public entities would serve as secure repositories for biological samples and information about the individuals from whom the samples are taken. Those seeking access to samples or information for clinical or research uses could only obtain it from the intermediary, on terms that are agreed to by the individual and which are designed to protect privacy and confidentiality.

At present there are several private intermediary entities operating in the U.S. and in some other countries large-scale public repositories for DNA samples already exist. Because this strategy concentrates a very large amount of potentially sensitive information in the hands of the intermediary, any breach of confidentiality that occurs might be quite serious. Regulation specifying standards for confidentiality and privacy and perhaps clarification of standards for liability in the case of breaches may be needed to reduce this risk.

Most states provide some degree of legal protection against unauthorized disclosure of medical information. These protections would almost certainly apply to PGx test results contained in medical records in hospitals or physicians’ offices. However, the scope of legal protection varies widely across jurisdictions and many holders of medical information may not be directly subject to legal restrictions. Recently issued federal privacy regulations under the Health Insurance Protection and Portability Act (HIPAA) of 1996 would greatly extend protection against unauthorized uses of medical and PGx information, although further measures may be required.

### E. Disclosure of information to research subjects

So far we have considered the flow of information from the subject to the researcher. But the flow of information may also go in the opposite direction. Although not likely to be common at the early stages of PGx research, there may be cases in which information of potential benefit to a research subject emerges during the course of a study. Such potentially valuable information might be either the object of the study or adventitious.

**The responsibility to inform.** Researchers have an ethical obligation to provide subjects with the option of having this potentially beneficial information disclosed to them. However, this obligation carries an important qualification: information should not be disclosed unless its reliability has been established.

As noted above in our discussion of the
content of informed consent, the possibility that information of benefit to the subject may be discovered in the course of the study ought to be broached in the informed consent process, and at that time the individual should be given the option of disclosure of reliable information that is potentially beneficial. In addition, the informed consent process should explain who has the responsibility for determining reliability and what standards will be used in its determination, and who has the responsibility for disclosure if the individual opts for it.

Generally speaking this will be the researcher, because it is with the researcher that the subject has the most contact and who is responsible for the informed consent process. The alternative of making the subject’s physician responsible for the disclosure of potentially beneficial information has at least two serious drawbacks. First, some subjects may not have a regular physician. Second, if the researcher communicates the information to the physician, there is the risk that it will be incorporated into the medical record and that a breach of confidentiality will occur. If instead the researcher discloses the information directly to the subject, the latter then can decide whether or under what conditions to convey the information to his physician if he has one, or to seek medical care in the light of the information if he does not. This conclusion, that the researcher has the primary responsibility for disclosure, must be qualified in those cases in which the researcher lacks the relevant clinical expertise or knowledge of the individual subject.

The responsibilities of sponsors. Although the researcher has the primary responsibility for disclosure, sponsors of research, whether public or private, have a responsibility for oversight of the research they fund. This responsibility extends to taking reasonable steps to require that a proper disclosure policy is followed by the researcher.

The obligation of the researcher to disclose potentially beneficial information to subjects who opt for disclosure extends only to reliable information. The information must be sufficiently accurate that, given its potential benefit, a reasonable individual would want to have it. What counts as sufficient accuracy will vary contextually; sound judgment will be required to determine how accurate the information must be before the researcher is obligated to disclose it to the subject. If, for example, an experimental PGx test indicates that the subject cannot safely take a drug that is likely to be prescribed for his condition, and the test is judged to be sufficiently reliable, then this information should be disclosed to the subject if he has opted for disclosure in the informed consent process.

How the information is disclosed also matters. In some cases the subject should be informed of the availability of counseling, and in all cases the information should be conveyed in a sensitive manner and in terms the subject can understand.

F. Alternative models for controlling the flow of information

After informed consent for PGx research is obtained, protection of the confidentiality of information going to the researcher is necessary. Three distinct models for controlling the flow of information to the researcher and for setting the conditions under which he may use the information can be distinguished for genetic research in general and PGx research in particular: identified, coded, and permanently anonymized information. This way of conceptualizing the alternatives draws upon and is consistent with the terminology used by the Pharmacogenetics Working Group (representatives of 13 pharmaceutical companies) and the European Agency for the Evaluation of Medicinal Products Evaluation of Medicine for Human Use (EMEA) Committee for Proprietary Medicinal Products (CPMP).46 47

All three models, if properly employed, presuppose that informed consent has been obtained to start the flow of information to the researcher, but propose different ways of providing additional protection to the subject. The second and third models, which rely on coding technologies, either to permanently anonymize samples or to de-link samples from subjects by
coding, provide fire-walls against breaches of confidentiality that lessen the burden of protection to be borne by the consent requirement itself.

In the first model, the flow of information begins with an identifiable DNA sample, one that the researcher knows comes from a particular subject, and the sample remains identifiable throughout the process of investigation. The advantage of this model is that it allows the researcher to know the identity of the source of the sample and therefore to be able to go back to the subject’s medical record at any time during the research process. This enables the researcher to take advantage of new opportunities for gathering data the relevance of which might not have been apparent at the beginning of the study. Another advantage of the first model is that the researcher’s ability to link the DNA sample to the subject and to his medical record may facilitate discoveries that will benefit the clinical management of the subject’s condition.

The disadvantage of the first model is that potentially harmful secondary information, if it exists, will be linkable to the subject’s full medical record, which may contain some information that the subject would not want the researcher to know and which may not even be of any significance for the research in which the subject has agreed to participate. The first model places the full responsibility—and possible legal liability—on the researcher for ensuring that sensitive information about the subject is not conveyed to other parties. (It will be impossible, however, for the researcher to prevent those who control the subject’s medical record from knowing that he is involved in a research project, because they will be authorized to release this information to the researcher).

The second, or coding model, has two variants. In a single-coding system the researcher holds the key that links the subject’s sample and data with an identifying number. The researcher assigns an identifying number to the sample taken, which is then used throughout the research process. Therefore, the researcher does not have ready access to the identity of the subject from whom a sample is taken. Although the subject’s identity could be learned by breaking the code, this approach provides a fire-wall between potentially sensitive information and parties other than the researcher.

In the second variant of the second model, double-coding, a second code or link is used and maintained in a secure database affording an additional level of protection. The researcher does not have access to the code that supplies the link between the sample and identity of the subject from whom it is taken. The researcher knows the sample and the research data only as “no. xxx,” and someone else holds a “key” linking the designation “no. xxx” to a subject’s identification number, which in turn can be linked to the subject’s medical records by those who hold the records. Double-coding provides a fire-wall between the researcher as well as others, and potentially sensitive information about the subject of research. Generally speaking, double-coding entails more costs than single-coding.

In the third model the sample is permanently anonymized: the key linking the first and/or second codes between the sample, data and the particular subject who is its source are permanently severed, so that no one can determine whose sample it is. In other words the sample and data do not carry any personal identifiers. Once the key has been deleted the subject’s research results can never be linked.

Comparing the models. The advantage of the permanent anonymization model is that it virtually eliminates the possibility of breaches of confidentiality and hence of harms associated with secondary information. In addition, under current U.S. regulations for the protection of human subjects, existing biological samples that are permanently anonymized may be used for research that meets IRB approval without informed consent.48 (In many cases, adequate informed consent was not given for the collection of existing samples).

Several policy bodies, including the National Bioethics Advisory Committee, have
recommended that for any new samples collected, informed consent is required, even if the sample is to be permanently anonymized.49 50 51 The rationale for this stringent requirement is that respect for the individual’s dignity, quite apart from the protection against more tangible harms that informed consent is designed to provide in other research contexts, mandates that DNA samples must not be collected without consent.

It is not so clear, however, that informed consent for all new uses of permanently anonymized samples is in fact ethically required strictly speaking. Much will depend upon how reliable the process of anonymization is and upon what other protections for confidentiality are in place should a sample remain linkable to a subject due to an error. However, so long as the consent process is not unnecessarily elaborate, the requirement does not seem to be unduly burdensome.

The permanent anonymization model has four disadvantages. First, the researcher cannot link the sample to the subject’s medical record once anonymization has occurred, and this greatly reduces the value of the medical record in PGx research. The difficulty is that subsequent to anonymization it is not possible to collect additional information from the medical record, and therefore not possible to determine whether drug responses observed in the course of the research are the result of genetic variations or instead are due to other factors. Second, if research conducted with the sample uncovers any information from which the subject would benefit, it will not be possible to convey it to him or his physician. Third, if the subject withdraws from the study, it will not be possible to destroy the sample and information acquired about the subject. Fourth, the audit trail needed for regulatory approval will be broken if the sample and information are permanently anonymized.

The coding model, in both its single- and double-coding variants, reduces the risk of breaches of confidentiality to which identified samples are vulnerable while at the same time avoiding the disadvantages of permanent anonymization. Though it may not be ethically required for all cases of PGx research, double-coding in particular has certain advantages. With a double-coded sample, the researcher can request the “key-holder” to provide information from the medical record as need for this arises, without ever having access to the medical record, and hence to the identity of the subject from whom the sample was taken. In addition, the third-party key-holder need not know the name of the sample source: all he needs to have in order to meet the researcher’s request for medical records is a patient identification number, supplied by the physician’s office or hospital where the subject’s medical records are stored.

Finally, the use of double-coding alleviates some of the burden placed on the informed consent process in two ways. First, the use of this particular fire-wall protection lowers the risk of breaches of confidentiality concerning secondary information, so that the subject’s weighing of costs and benefits in deciding whether to participate is simplified. Second, because the informed consent process is not bearing the whole weight of protecting the subject, there is less need for an extremely detailed and rigorous informed consent process, other things being equal.

**Single- versus double-coding.** Generally, a coding approach (in either of its variants) is superior to both the identified information model and permanent anonymization model. Using either the identified information model or the permanent anonymization model for controlling the flow of information to the researcher is problematic and would require special justification. The choice between double-coding and single-coding is perhaps somewhat less clear-cut. From the standpoint of maximizing protection of confidentiality, double-coding is superior. However, double-coding entails added expense and time. Whether these costs are worth bearing will depend upon an accurate assessment of the risks of a given research study.
G. Inclusiveness and diversity

As noted in the Introduction to this Report, one of the potential benefits of PGx is that it may expedite and reduce the costs of drug trials by enabling the researcher to exclude from the subject pool those who are likely to be poor-responders or to experience adverse reactions due to their specific genotypes. It might be objected, however, that such exclusion is inequitable, since PGx information is only probabilistic, and some members of the genotypic subgroup that are excluded might in fact benefit from the research. (A related, though distinct issue that we take up in part II is the possibility that exclusion of certain genotypic groups from drug research may result in the unavailability of drugs for those groups).

The rationale for the requirement of inclusion. The issue of inclusion has received attention prior to the emergence of PGx. Current NIH regulations concerning grants for medical and other research encourage inclusion of groups that have traditionally been underrepresented in research: women, minorities, and children.52 However, the rationale for this inclusion requirement does not apply to genotypic subgroups that might be excluded on PGx grounds from drug research.

The rationale for inclusion of women, minorities, and children is that these groups have often been excluded from research from which there is every reason to believe they would have benefited. But in the case of PGx exclusion, this is not the case. Indeed in some cases it would likely result in harm.

Exclusion of racial or ethnic groups. A more subtle form of the objection to exclusion on PGx grounds would arise if a researcher excluded certain racial or ethnic groups, rather than groups directly identified by genotype, from participation in a drug trial on the grounds that members of the group are known to not respond to the drug in question or to have adverse reactions to it. The problem is that race and ethnicity are at best very crude, approximate markers for distinct genotypes. (There may be more genetic variation within such groups than between them). Given that this is so, there is something very troubling about a researcher treating race or ethnicity as if it were a scientific classification and thereby implicitly endorsing a mistake that has played a major role in discriminatory attitudes and practices in the past.53

Because race and ethnicity are only crude markers for genotypic subgroups, a drug research protocol that excludes members of such a group on the grounds that they are likely to be poor-responders may certainly exclude some individuals who would have been good-responders and therefore deprive them of the benefits of participation. Given the historical abuses of racial and ethnic categories and the dangers of misconstruing them as scientific classifications, it can be argued, then, that equity in access to research participation requires researchers to enroll subjects on the basis of genotype without considering racial or ethnic background.

For example, suppose, as now appears to be the case, that African Americans as a group tend to be poor-responders to a particular medication m, for congestive heart failure.54 Equity would seem to require that researchers not simply exclude African Americans from clinical trials for a drug that is similar to m on the grounds that they are poor-responders. Instead, it appears that the researcher should attempt to get beyond race as a crude (and historically abused) marker and simply enroll subjects based upon their likely response. If a serious adverse reaction was associated with a particular race or ethnic group, exclusion of all members of the group would clearly be less problematic.

H. The availability of drugs

Orphan genotypes? Several commentators on PGx have noted that the integration of PGx into the drug development process may result in “orphan genotypes.”55 The concern is that PGx may reveal that an investigational drug is not likely to be safe and effective for a particular genotypic subgroup of the general population or the population of those with a particular disease.
and that if this group is small enough pharmaceutical companies may not find it worthwhile to try to develop an alternative drug for it. For such groups, safe and effective drugs will be unavailable, not because they lack insurance coverage for them, but because the drugs have not been developed.52

**PGx orphan diseases?** A related concern might be called the PGx orphan disease problem. The worry is that if it turns out that there is great genetically-based variation in drug response among those who have a particular disease, then the pharmaceutical industry might not find it financially worthwhile to try to develop drugs for this disease. In other words, PGx research might reveal that what had been thought to be a large market for a drug for all who have a particular disease is in effect a collection of very small markets composed of genotypic subgroups of those with the disease. If this occurs, pharmaceutical companies might decide to direct their research toward treatments for other diseases where drugs with larger markets are likely.

It is important not to over-estimate the probability of the orphan genotype or PGx orphan disease scenarios occurring. For either scenario to eventuate and to be of serious ethical concern, the following conditions would have to be satisfied. (1) There must be no alternative safe and effective drug or other treatment available for the disease. (2) The groups that are identified by PGx must be so small that even over the duration of the standard drug patent period there will not be sufficient market demand to make it worthwhile to produce the drug. (3) In the case of “orphan genotypes” the drug that is safe and effective for the larger group of those having the disease must provide a substantial benefit for a serious condition.

Although large pharmaceutical companies might not find it worthwhile to try to develop a drug for a PGx-identified genotypic subgroup, smaller companies, including newer biotechnology enterprises, might identify the group as a desirable market niche. What is financially attractive may vary with the scale of the enterprise.

**Identifying, not creating orphan groups.** Furthermore, it is misleading to speak of PGx (or pharmaceutical companies) “creating” new orphan groups. PGx research merely identifies individuals who are not likely to respond to a drug or are likely to suffer an adverse reaction, and this provides medically useful information about them.

Finally, the PGx orphan disease scenario may not in fact be coherent. If, as the scenario assumes, there is so much genetically-based variation in drug response among those who have the disease, then presumably any particular drug intended for all those with the disease would be ruled out in Phase II trials anyway, because it would not demonstrate sufficient efficacy to justify a Phase III trial. But if this is the case, then a drug would not have been successfully developed even in the absence of PGx information.

**A different access problem.** If, despite the above considerations, the integration of PGx into the drug development process should turn out to result in “orphan genotypes” or “PGx orphan diseases,” the problem is best conceived as one of access to medical care. This particular access problem deserves further attention.

The more familiar and discussed access problem occurs when some individuals are unable to secure medical services that are available and from which they would benefit, because they have no health care insurance. The second access problem occurs when medical services from which some individuals could benefit are simply not available at all. This would be the case with orphan genotypes or PGx orphan diseases. Because there is insufficient market demand to make it economically viable for the pharmaceutical industry to develop a special drug for a small genotypic group or because there is so much genetically-based drug response variation among those who have a certain disease, the market does not produce a treatment to meet important health care needs.

This is not a new problem, nor one that is
peculiar to PGx. It has been widely discussed in the context of the unavailability of treatments for certain diseases that are common in the poorer countries but not in the richer ones. For example, even though a very large number of individuals in the poorer countries suffer from certain parasitic diseases, they may not represent sufficient market demand (in terms of ability to pay) to make it worthwhile for pharmaceutical companies to try to develop drugs to treat these diseases.5

Access to health care in the first sense distinguished above is a matter of social justice in the most literal sense: there is a societal obligation to ensure that all have equitable access to available health care services.57 The same basic moral considerations that ground this societal obligation to ensure equitable access for all also speak in favor of an obligation to produce the drugs and other treatments required for meeting important health care needs. But this obligation, like the obligation to ensure that all have equitable access to the health care services that are available, falls first and foremost on society as a whole, not upon particular private entities such as pharmaceutical companies.

It is true that to ensure that these societal obligations are met, a social division of labor may be needed—some way of authoritatively assigning specific duties to identifiable and accountable entities within society, with the overall result that all have equitable access to health care benefits that meet the more important health care needs of all. But in our society at present, there has been no assignment of duties—that includes a clear mandate for pharmaceutical companies or other private entities to subordinate their legitimate business concerns to solving the access problem.58 Similarly, it may be the case that everyone has a moral right to decent shelter, but from this it does not follow that home-builders are in default of an obligation if decent homes are not available to some people.

It might be argued that pharmaceutical companies benefit from massive public investment in medical research and that this benefit grounds an obligation on their part to ensure that safe and effective drugs are available to meet everyone’s health care needs. There are two difficulties with this view. First, it can be argued that it is the public who is the primary beneficiary of public subsidization of medical research (as the public justifications for NIH budgets, etc. explicitly state). Second, even if it were true that public subsidies for medical research somehow create an obligation on the part of pharmaceutical companies to produce public benefits, it would not follow that this requires any particular pharmaceutical company to incur the costs of developing a particular drug for a particular genotypic or disease group. Not only is the requirement of producing public benefits too vague to entail any such specific duty, but pharmaceutical companies can argue that they are already producing important benefits.

This is not to say, of course, that pharmaceutical companies are immune to moral criticism if they choose to develop only drugs that are maximally profitable or choose not to offer discounted prices for urgently needed drugs for persons in poor countries. A higher moral standard than simply that of not violating anyone’s rights is often appropriate for corporations, as it is for individuals. The point, rather, is that it is dubious simply to assume that if some people cannot afford needed drugs or some drugs that would be beneficial for some persons are not developed, then pharmaceutical companies have violated someone’s rights or failed to fulfill a duty that society has assigned to them.

The existing orphan drug law59 and its rationale are consonant with this analysis. That law does not assign a duty to pharmaceutical companies to develop drugs that otherwise would not be developed due to lack of market demand; nor does it assert or assume that every group has a right to whatever medications it needs. Rather, the Act creates market incentives for pharmaceutical companies to develop drugs by granting a seven year period of market exclusivity, tax credits, and in some cases funds for orphan drug research and clinical trials.60 This approach makes sense on the assumption that the obligation to ensure the
availability of care that meets all important medical needs is a societal obligation, not a specific obligation of pharmaceutical companies.

If the integration of PGx into the drug development process should result in orphan genotypes or orphan diseases, there are two main policy options which might be employed singly or in combination. The first is to rely on the existing Orphan Drug Act, with modifications as needed. The second is to rely more heavily on direct public subsidies by reshaping NIH and other private and public grant priorities to encourage the development of drugs for smaller markets. For either strategy to work, there must be sufficient rates of reimbursement for these treatments as they become available.

It would be inadvisable to pursue either option at this time. It is simply too early to tell whether these problems will occur or be of sufficient magnitude to justify the costs of such policies. Nevertheless, in anticipation of the need for such policy initiatives, appropriate groups with membership drawn from relevant public agencies and private sector actors should be formed to examine and address the grounds and extent of the societal obligation to develop new forms of therapies for groups whose health care needs would not otherwise be met. Plainly the issue of unmet health care needs extends far beyond PGx.

There is, of course, already public discussion of priorities for research, but too often it takes the form of a tug-of-war over resources by various interest groups, rather than a systematic inquiry into the underlying principles of distributive justice. There is much to be said for the idea that society has an obligation to provide equitable access to at least some “adequate level” or “decent minimum” of health care for all.61 But this is not equivalent to the assertion that everyone is entitled to whatever resources are required to assure him of a life free of disease or even of normal functioning, regardless of cost. So in considering policy options to deal with “orphan” problems that might become salient as PGx becomes an important factor in the drug development process, it should not be assumed that the societal obligation to meet health care needs is unlimited, that is, there is an obligation to supply whatever resources are necessary to provide cures for diseases that afflict very small groups. Whether or not the development of PGx highlights the problem of “orphan groups,” the problem of how to ensure that the research enterprise results in products that address the health care needs of all is worthy of more explicit and systematic examination.

III. CLINICAL PRACTICE

Even the most scientifically valid and ethically sound research does not translate automatically into improved medical practice. As PGx research advances, regulatory agencies will have to decide whether and under what conditions PGx tests and drugs for which there are PGx tests are to be approved for clinical use, physicians and pharmacists will have to learn the proper role of PGx in the choice of therapies, private insurers and government payers will have to decide whether and if so under what circumstances to reimburse for PGx tests and their interpretation, and health care administrators will have to determine how existing structures, formularies, and procedures can be adapted to the requirements of this new methodology.

A. The role of regulatory agencies: Oversight of the introduction of PGx into clinical medicine

Accuracy and safety. The first step in the process of integrating any test into clinical practice is to ensure that the test is safe, accurate, and used appropriately. Safety of the test itself is not an issue for PGx tests, since PGx tests are noninvasive, requiring only a small blood sample or a cheek swab to collect cells. So the first ethical issue is whether current oversight mechanisms are sufficient to assure the accuracy and appropriate use of PGx tests. (This Report limits its evaluation of the adequacy of oversight to the United States; an assessment of the many different oversight regimes found in various countries would require a lengthy report in itself).

PGx tests will fall within FDA’s regulatory
jurisdiction, on two distinct grounds. First, in the form of test kits, PGx tests are “diagnostics” that must have FDA approval before being sold in interstate commerce. Makers of PGx test kits will have to submit to FDA evidence of the test’s analytical validity, clinical validity, and clinical utility, so that users will be assured that they are effective for the intended purpose. (A PGx test’s analytic validity is how well it measures the presence of a genetic marker correlated with drug response. A PGx test’s clinical validity is the accuracy of the prediction of a drug response, given the presence of the genetic marker. The clinical utility of a PGx test is expected health benefit that can be achieved by knowing a positive or negative test result).

Currently, FDA only applies these criteria to test kits, not to “home brews,” that is to tests whose ingredients are assembled by the user rather than purchased in kit form. There is no good reason, however, to exclude home brews from oversight. Accordingly, the Secretary’s Advisory Committee on Genetic Testing (DHHS) and FDA are currently formulating recommendations for a process and criteria for reviewing genetic tests, whether in the form of test kits or home brews, including PGx tests.

Second, PGx tests may also fall within the FDA’s jurisdiction when they are an integral part of a New Drug Application (NDA). As noted above, a pharmaceutical company may investigate the use of a drug to counter a disease process in a pharmacogenetically-defined subgroup of the population with that disease. In applying for FDA approval of the drug, the company would have to support with appropriate data its claim that the drug is sufficiently safe and effective for the genotypic group in question. This raises the issue of what will count as sufficient safety and efficacy, a matter to be determined by the FDA. The FDA might then approve the drug, but only for those having that genotype, thus in effect requiring those who administer the drug to see that the appropriate PGx test is performed before doing so. The conditional nature of this approval would be reflected in the labeling of the drug.

FDA labeling of drugs has utilized various categories, such as indications, contraindications, precautions, and warnings. How the conditional nature of approval of new drugs with supporting PGx tests should be incorporated into labeling is an important regulatory issue requiring further attention.

**Oversight and regulation.** Although FDA regulation may be necessary to foster appropriate use of PGx tests, it is not sufficient. The category of oversight is broader than regulation. To ensure that PGx tests are employed appropriately as gatekeepers to access to drugs, physicians will have to know when to perform the tests, pharmacists will need to know which drugs should only be used in conjunction with PGx tests, and laboratories will have to provide test results to physicians in an accurate but “user-friendly” form. These broader issues are taken up later in this Report.

Finally, all laboratories performing PGx tests should meet CLIA (Clinical Laboratory Improvement Act) standards. Whether CLIA standards would require certain modifications when applied to PGx or other genetic tests is an important question that is beyond the scope of this Report, but which requires the immediate attention of policy makers. The system for regulation must allow parallel approval of a drug and a PGx test for safety or efficacy. Because the drug and the associated test are intended to be used together, and therefore must be available at the same time, the two sectors must function in a coordinated, timely fashion.

**B. Physician acceptance of PGx testing**

**The key role of the physician.** Perhaps the greatest single factor affecting the penetration of PGx into clinical practice and the pace at which it will occur will be the knowledge and acceptance of physicians. Studies indicate that many physicians lack basic knowledge of genetics and also frequently fail to take into account available information about drugs. It is therefore now commonplace to call for improved physician education in genetics, and this, no doubt, is essential.
**The division of labor.** However, it would clearly be impractical to require all physicians, or even all primary care physicians or internists, to have extensive knowledge of genetics generally or of PGx in particular. Instead, a division of labor will be necessary, taking advantage of the fact that in order to be able to administer and properly interpret a PGx test a physician need not have mastered the full range of knowledge utilized in the test. The extent and depth of knowledge the physician needs will depend both upon the tools available to him, including computer entry diagnostic and prescription technologies, and his access to the expertise of others, including pharmacists and laboratory personnel.

For example, eventually physicians will be able to send a blood sample to a laboratory that will test the DNA for dozens, perhaps eventually hundreds of markers, including SNPs (single nucleotide polymorphisms) that are known to be correlated with drug response. One option would be to require that laboratories meet high standards for accurate testing and interpretation of results, so that the information the laboratory sends back to the physician can generally simply state whether a particular drug is likely to be safe and efficacious for the patient, without including a specification of the complex genetic factors that went into this determination. Such an arrangement would require a high level of expertise in a relatively small number of persons working in testing laboratories but would not require extensive PGx knowledge on the part of tens of thousands of physicians or pharmacists. Limiting the genetic information sent back to the physician, as we suggested earlier, would also make sense as a fire-wall protection, because doing so would omit some information that is irrelevant to the therapeutic decision but which might in some cases carry the potential for psychosocial harm.

Such an arrangement is only one hypothetical illustration of how a carefully-crafted division of labor might cope with the problem of physicians’ lack of knowledge of PGx. Any such division of labor would include an important role for pharmacists in providing an independent check on physicians’ drug choices, assuming they have access to relevant PGx information.

The extent to which PGx will be integrated into clinical practice will depend in part, then, upon how user-friendly the technologies for employing this methodology are from the standpoint of physicians. And, of course, PGx tests that have high predictive value will be more attractive to physicians, other things being equal, because they will reasonably be viewed as having more impact on decisions concerning the choice of medications.

Most important, the individual physician will come to rely on PGx tests if and when he becomes convinced that the standard of practice demands it. It is therefore necessary to explore the basis and scope of the physician’s duties regarding PGx testing. When is the physician obligated to offer a PGx test and when, if ever, may he prescribe a drug for which there has been an unfavorable PGx test?

**C. Physicians’ responsibilities regarding the use of PGx testing**

**The duty to offer a PGx test.** Other things equal, the higher the predictive value of a PGx test, the more serious the risk of adverse reactions to the drug in question, and the greater the potential harm that would result from delay in effective management due to time lost taking an ineffective drug, the clearer the physician’s duty to offer the test. If, in addition, the test has received FDA approval, and especially if the test is mandatory according to the drug label, the case for asserting that the physician has a duty to offer it is all the stronger.

This is not to say, however, that the duty is limited to FDA approved tests. If there is sound, peer-reviewed, published scientific evidence that the test has high reliability and that knowing the result would be of significant benefit to the patient, the physician may be obligated to offer it even if it does not yet have FDA approval. If the test has high predictive value and significant benefit to the patient, but the patient’s health insurance does not cover it, the physician still has an obligation to inform the patient that the test is
indicated and that it can be provided at the patient’s expense.

**Informed consent.** It might be tempting to assume that the conclusions derived above regarding informed consent in the research context apply without modification to the clinical venue. If informed consent is mandatory in PGx research, should it not be required as well when PGx tests are offered in clinical practice?

Some would argue that informed consent is not required in the clinical setting, citing the fact that many diagnostic tests, including some genetic tests such as screens for Down syndrome and neural tube defect conducted on blood samples from pregnant women, are routinely administered without anything approaching informed consent, without mention of the fact that a DNA assay is being undertaken, and indeed in many cases without any informed consent at all. Some may also argue that informed consent is not required in those cases in which the payer for the care mandates the testing before the care can be provided. Yet the lack of informed consent in these cases could just as well be regarded as a deficiency. So the question remains: is informed consent necessary for all PGx tests in the clinical context?

Here it is important to note that the research and clinical contexts are relevantly different. A central element of the case for informed consent in research, as we observed earlier in this Report, is that the researcher’s interests as a researcher may conflict with those of the subject. In contrast, the assumption in the clinical context is that the physician’s role is to do what is in the patient’s best interest. Accordingly, one should not assume that if informed consent is required for PGx research then it is also necessary in the clinical setting.

Nevertheless, two facts lend support to the conclusion that informed consent is required in clinical practice as well. First, PGx tests, as already noted, can carry sensitive secondary information. Second, the public’s concern about genetic privacy is well-documented and this in itself provides a reason for treating PGx tests differently in research and clinical practice, than other tests for which informed consent is routinely omitted.

On the other side of the ledger, it might be protested that many PGx tests will not carry sensitive secondary information, especially if technologies relying chiefly on “clean” markers are developed, and that there is much to be said for avoiding both genetic exceptionalism and the unfortunate tendency to lump all “genetic tests” together.

In addition, how strong the case for informed consent in the clinical context is will depend upon what other mechanisms are in place to reduce the risk of damage from secondary information. If, for example, as a result of new regulations under HIPPA, medical records in general become more secure, and if PGx tests results are reported in such a way as to eliminate or reduce sources of secondary information that are unnecessary for conveying the drug response finding, then perhaps informed consent will not be necessary. Moreover, there is the danger that a blanket requirement of informed consent for all PGx tests, as for many other routine diagnostics, e.g., testing for hypertension or hypercholesterolemia, will degenerate into a meaningless ritual.

Until better protections for confidentiality of medical records are in place—and until the public becomes more accustomed to the medical uses of genetic information—the most reasonable course is for physicians to adopt a general policy of gaining informed consent before the administration of a PGx test. Nevertheless, depending upon how the infrastructure for protecting medical privacy evolves in the future and depending also upon whether the current patchwork of laws prohibiting genetic discrimination becomes more comprehensive, requiring informed consent for all PGx tests in clinical practice may eventually become unnecessary.

**What sort of consent?** Assuming that for the present informed consent for PGx testing in
clinical practice is the most reasonable policy all things considered, the real question is how extensive the information conveyed to the patient must be and how the risks and benefits should be presented. Here our earlier discussion of consent in the research context is relevant. In general it is probably better for the physician to tell the patient that he would like to examine a sample of the patient’s DNA to see what the likely response to a drug will be rather than to inform the patient that a “genetic test” is recommended.

Beyond this, how robust and rigorous the informed consent process should be will depend primarily upon an estimate of whether the test result will carry secondary information that will either be distressing to the patient or potentially damaging to him if others obtain it. If in most cases PGx tests do not carry potentially damaging secondary information, only a rather minimal informed consent process will be necessary.

Our earlier warning about the error of over-generalizing from the most risky genetic tests is as pertinent in the clinical as in the research context. It would be a mistake to require an informed consent process for PGx tests modeled on what is appropriate for genetic testing for serious, untreatable genetic disorders such as Huntington’s disease, for susceptibility to serious diseases such as breast cancer or colon cancer, prenatal testing for Down syndrome or neural tube defect, or carrier-status testing for cystic fibrosis or Tay-Sachs. It is difficult to imagine circumstances in which anything approaching the extensive pre- and post-test counseling that is generally appropriate for such tests would be needed for most PGx tests.66

The duty to prescribe according to PGx test results. Once the PGx test is administered and the results are obtained, how ought the physician to take the results into account in treating the patient? If the test has high predictive value, then in general the result will strongly indicate which clinical decision is appropriate. If instead the test result has low predictive value, for example, indicating a 25% adverse effect rate with considerable variation in the severity of the adverse effects, then the decision will be more complex and the physician’s duty less clear. So long as the decision the physician makes falls within the range of acceptable decisions included in the standard of practice, and the patient has been duly informed of the risks and benefits and consented to the treatment the physician recommends, the physician will not have breached a duty to the patient.

Off-label and against-label uses of drugs. An off-label use is the use of a drug for a purpose other than that for which the drug was approved by FDA. Physicians are allowed to use drugs for purposes other than those for which they were approved, if the benefits to the patient can reasonably be expected to exceed the risks. Against-label use is the administration of a drug in circumstances that are inconsistent with labeling of the drug.

In the context of PGx, an against-label use could be the administration of a drug to an individual after a reliable PGx test mentioned in the labeling yielded the result that the patient is not a good candidate for the drug. A second sense of “against-label” may also be distinguished: the drug’s labeling includes the instruction that it is not to be administered unless there has been a favorable PGx test, but the physician administers the drug without doing the test. Is against-label use of drugs (in either the first or the second sense) ever permissible? And if so, are there any circumstances in which the patient would have the right to an against-label use of a drug?

There appears to be only one circumstance in which it would be permissible for a physician to administer a drug after an unfavorable PGx test for response to that drug: there is no alternative safe and effective drug for the patient’s condition, the condition, if not treated, is a serious one, and the patient is willing in spite of the PGx test results to undergo the treatment in the hope of realizing net therapeutic benefit. Even under these conditions, the patient would not have the right that the physician administer the drug, since he cannot have a right to an action the physician has no duty to perform and the physician cannot have...
a duty to prescribe a drug for which a reliable test indicates a significant risk with regard to safety or efficacy.

Consider next the case in which a PGx test is available for the drug but the patient refuses to take it out of fear of a breach of his “genetic privacy” or for some other reason. As we have already argued, for the physician to fail to offer the test, at least if it has high predictive value and is of significant benefit to the patient, would be a violation of his duty to the patient. If the patient refuses to take the test under these circumstances, he would not have a right to have the drug administered without the test, because he cannot have a right to an action that the physician is not obligated to perform and the physician is not obligated to offer the drug without having performed the test.

One situation in which it could be argued that the physician may administer the drug even though the patient refuses to take the test would be where the drug is covered by the patient’s insurance but the test is not, the patient cannot afford to pay for the test out of pocket, and the drug is the patient’s only prospect of amelioration of a serious condition. But even in these special circumstances, the most that can be said is that it is permissible for the physician to prescribe the drug without the test (after explaining that the test is recommended for this drug), not that he has an obligation to do so or that the patient has a right that he do so.

**D. Direct marketing of and direct access to PGx tests**

**Beyond medical gate-keeping.** The discussion thus far has proceeded on the assumption that the physician will be the gatekeeper of access to PGx tests. This may not always be the case. PGx tests, as well as tests for several genetic diseases or genetic susceptibilities to diseases are already not only being directly marketed to consumers but in some cases are provided through self-administered test kits by which the individual collects a DNA sample by cheek swab and mails it to a laboratory.67 Individuals may utilize such kits either because their insurance does not cover the test, because they have concerns about having a record of a genetic test in their medical record, or for other personal reasons.

Current self-administered PGx tests use one DNA sample to test likely response to a number of drugs, including some nonprescription drugs.68 In the latter case, it would be implausible to hold that an individual who can purchase a drug without medical supervision ought not to be allowed to take a test to determine whether the drug is safe and effective for him without medical supervision, at least so long as the test meets appropriate standards of analytic and clinical validity, and the test results are conveyed in an accurate and understandable manner. If the individual has access through insurance to a prescription drug but not to a PGx test for it, there is also a strong case for allowing him to utilize a self-administered test, again assuming that the test is reliable and the significance of the results is adequately explained.

**Self-administered PGx tests.** A government sponsored report on ethical and regulatory issues in genetic testing produced by a prestigious interdisciplinary committee simply states that self-administered genetic tests are “to be discouraged.”69 Not only is this rather peremptory dismissal of the topic naive in its apparent underestimation of the power of the market forces behind such tests, but it also wrongly suggests that individuals have no legitimate interest in having access to genetic tests without reliance on a medical gate-keeper. A case can be made, however, for the presumption that competent adults have the right to information about their genotype, if the information is accurate and its significance is conveyed to them in an appropriate manner. For those who lack insurance coverage for the test in question or for those who are concerned about the risk of genetic discrimination or stigmatization posed by having a genetic test result in their regular medical record, a self-administered test may be reasonable.

**The need for safeguards.** However, if direct
marketing of and direct access to PGx tests continue to expand, the ethics and regulation of this approach will require careful scrutiny. This Report does not attempt an extended discussion of these issues, but instead will only highlight three areas of concern. First, regulation or some other form of oversight may be needed to ensure that tests are marketed to consumers in an appropriate way. There is the danger that inappropriate marketing will exploit common misperceptions about genetics, including genetic determinist thinking. Second, although concern about confidentiality of the medical record is almost certainly one reason why individuals use self-administered tests, at present there is no assurance that the laboratories to which the sample is sent will preserve confidentiality. Third, there is evidence that for some tests, parents are submitting DNA samples of their minor children. This raises complex questions about the scope and limits of parents’ fiduciary duties and rights regarding the medical care of their children. In addition, there is a more general concern: that current self-administered test techniques may allow one person to collect DNA from another and submit it for testing without his permission. Although through-the-mail tests for serious genetic diseases or for genetic susceptibility to serious disease may be more troubling than through-the-mail tests for drug response, in either case, the lack of medical supervision is worrisome in part because of the absence of regulation.

As observed in the Introduction of this Report, the basic methodology employed in PGx testing for response to medical drugs has much wider application and raises the possibility of an expansion beyond the medical realm to testing for response to dietary regimens, vitamin supplements, etc. If, as seems likely, insurers will be unwilling to pay for such nonmedical PGx tests, then the same consumer demand that fuels the market for these nonmedical chemical agents may also produce a correspondingly broad market for self-administered tests. If this occurs, then the assumption of most who have commented on PGx—that it will remain exclusively within the province of medical gate-keeping—will be utterly undermined. Absent medical supervision, a different regulatory approach will almost certainly be needed.

E. Payer-acceptance and access to PGx tests and to “PGx drugs”

Insurance coverage. Even if an extensive battery of PGx tests comes to be included in most health care insurance plans, over 40 million Americans may lack access to them simply because they have no health insurance. However, it is at present unclear to what extent these tests will be covered by private insurance or by government programs such as Medicare and Medicaid, and if they are covered, whether drugs for which PGx tests exist will be covered only if their use is preceded by PGx testing. Whether PGx becomes an important element of clinical practice will depend upon whether it is reimbursed.

In the current climate of cost-consciousness, one of the most important factors determining reimbursement decisions regarding PGx tests will be whether private insurers and government payers believe that PGx testing is cost-effective. Whether a favorable cost-effectiveness estimate is made will depend upon whether PGx testing is seen simply as an additional cost for a particular procedure viewed in isolation, or is understood to be one important component of a larger strategy of evidence-based, integrated health care whose benefits will accrue over a longer time frame and will be great enough to justify significant start-up costs. Chief among these benefits are a reduction of adverse drug reactions and of the costs of treatment and the risk of liability associated with them, and a reduction of the costs associated with inefficacious treatment.

Policy rationality versus individual patient rationality. Individual patients should in general view the integration of PGx into clinical practice as progress, since it is likely to reduce their chance of adverse drug reactions and ineffective drug therapies. However, there are circumstances in which a rational—and ethically justifiable—
drug use policy utilizing PGx may result in an individual not receiving a drug from which he would benefit.

Suppose that a managed care organization, or Medicare, or for that matter a national health system, adopts a rational drug use policy that includes the rule that a very expensive cancer drug will only be covered for those who are classified as “high-responders” according to a reliable PGx test. The justification for this rule is that given the high cost of the drug and the severity of the side-effects, and given a limited budget from which care for many individuals must be provided, responsible stewardship of resources requires providing this drug only to those who are most likely to benefit significantly from it. If this rule were not followed—if coverage was provided for “low-responders” as well as “high-responders”—then the dollars spent in providing the drug to “low-responders” would not be available for other uses that would bring greater benefits to more individuals. It is not the case that “low-responders” will receive no benefit from the drug; it is their best prospect for ameliorating their condition, but the benefits they receive will not be as great as those for “high-responders.” To take a dramatic case: administration of the drug to “high-responders” produces 5-year survival rate of 90% while its use with “low-responders” achieves a 2-year survival rate of 30%.

Even for the most rational, morally-defensible policy, there sometimes will be a divergence between what is best from the standpoint of a whole population and what is best for a particular individual. In the case at hand, you may be a “low-responder” to the drug in question, but if that drug is your only prospect for surviving you may be willing to take it anyway. If the nature of the test has been adequately explained to you, you will understand not only that “low-responders” will receive some benefit from the drug, but also that the test’s predictive value is not 100%, so that there is a chance that you will have a higher response than predicted. In these circumstances it may be rational for you to want the drug despite your unfavorable PGx test result; but it also may be justifiable for the private insurer or government program to have a policy that denies it to you.

PGx tests can only reveal probabilities of adverse reactions or probabilities of higher or lower efficacy. Deciding how low the probability of adverse reaction must be or how high the degree of efficacy must be for the drug to be used or to be reimbursable requires more than scientific knowledge; it requires ethical judgment, because where the threshold is set will reflect a particular balancing of individual versus group interest.

This discrepancy between individual rationality and rational policy is not in any way peculiar to PGx, and in fact has nothing to do with the methodology itself. It can arise in any number of contexts in the practice of medicine, wherever a policy rules out providing each patient in every instance all the services that are of any expected benefit to that individual regardless of cost.

The use of PGx tests to identify “low-responders” is clearly an improvement over a drug policy that denies everyone coverage for the drug under conditions in which the poor results for “low-responders” are aggregated with the good results for “high-responders,” resulting in an overall response rate that is deemed too low to justify costs. Nevertheless, the conflict of interest between the individual and the group is real, and increasing efforts to implement rational drug use policies, stimulated in part by advances in PGx, may make this sort of conflict more salient and more frequent. The difficulty is not with PGx, but with the incompleteness of the tools of analysis for rational drug use.

The limitations of pharmacoeconomics. Standard pharmacoeconomic analysis recognizes three main types of values to be realized in a rational drug use and/or reimbursement policy: economic (efficient use of dollars), clinical (maximal health outcomes), and humanistic. Under the heading of humanistic values, pharmacoeconomists include patient satisfaction and quality of life as estimated by the patient. However, pharmacoeconomic analysis typically incorporates these “humanistic” concerns in a
purely aggregative, utilitarian fashion, summing up benefits across all individuals affected by the policy. What this means is that the analysis is blind to the potential conflict between what is rational as a population health policy and what is rational for a particular individual. The aggregative approach is also insensitive to questions of fairness and distributive justice that arise when there is a conflict between what is rational policy for a population and what is beneficial to an individual.

The difference between a purely utilitarian, aggregative approach to allocation of medical services under conditions of scarcity and one that takes considerations of fairness into account can be illustrated by elaborations on the preceding hypothetical example. If the rational drug use policy denies you access to the drug for which you have tested as a “low-responder” is based purely on a utilitarian calculation, this means that the fact that more overall benefit (for the population for which the policy is designed) by itself is assumed to justify denying you access. In these circumstances you may complain that your interests have been ignored, or rather, sacrificed for the good of the group. You may protest that maximizing overall benefit ought not to be the only factor in a rational drug policy—that every member of the population served ought to have a fair chance at very important benefits, and that this will not be the case if the allocation is decided by a purely utilitarian calculation.

Most contemporary theorists of distributive justice would probably say that a purely utilitarian approach is defective because it is insensitive to considerations of fairness and encourages unjustified sacrifices of individuals for the sake of maximizing overall benefit. However, there is much controversy among non-utilitarian theorists as to just how considerations of fairness should be incorporated into allocation decisions, and what the appropriate standards of fairness are. For example, even among theorists who agree that the worst-off should be given some priority in allocation—that their interests should count more—there is dispute both about how one determines who the worst-off are and about how much special weight their interests should be accorded.

Furthermore, the possibility of conflicts between what is rational for the individual and what is a rational policy for a population remains even if a purely utilitarian analysis is rejected and the notion of fairness or of giving all a chance at important benefits are taken seriously. Fairness, after all, is often thought to involve a balancing of conflicting interests, not the maximizing of the interests of everyone involved. Nevertheless, conflicts between what is best for the individual and what is best for the group may be less common or, at least more ethically acceptable, if each individual can say that the policy treated him fairly, even if it did not maximize benefit for him.

PGx does not create the problem of conflicts between individual and policy rationality. However, advances in PGx may focus more attention on efforts to forge rational drug policies, with the result that the inadequacy of purely utilitarian, aggregative approaches become more apparent and the need for developing a principled consensus on notions of fairness becomes more undeniable.

GENERAL FINDINGS AND RECOMMENDATIONS

Findings
1. The risks of PGx are neither unique to PGx nor unmanageable. With feasible and appropriate safeguards, the potential benefits of PGx are worth pursuing. Given the human and financial costs of ineffective and unsafe use of drugs, it is important to develop this methodology and to integrate it into clinical practice, with appropriate protections and guidelines.

2. PGx research and the development of PGx testing take place internationally and within public and private entities. While there is a recognized need for protections and guidelines for genetic research and genetic testing, there has not been an
adequate appreciation of the particularities of PGx.

3. In order for the benefits of pharmacogenetics in drug development and clinical practice to be fully realized, informed and coordinated actions will be needed on the part of pharmaceutical companies, researchers, clinicians, insurers, and relevant government regulatory agencies.

Recommendations
1. The development of the appropriate protections and guidelines should avoid genetic exceptionalism, genetic determinism and genetic overgeneralization.

2. Harmonization, both at the national and international levels, is required in the development of appropriate protections and guidelines. These protections and guidelines must take into account the particularities of PGx and should be integrated into a comprehensive framework for the development of this methodology that includes provisions for approval and reimbursement.

3. Private and public agencies should cooperate to sponsor consensus conferences, advisory committees, and other suitable venues to ensure an on-going dialogue in which all the relevant actors required for the ethically sound and optimally beneficial use of pharmacogenetics can communicate freely with one another and coordinate their efforts.

FINDINGS AND RECOMMENDATIONS REGARDING RESEARCH

Regulatory Oversight of Research

Findings
Existing regulatory requirements for research, at least in the U.S., do not pose constraints that would prevent the successful development of PGx. However, the regulatory landscape for research is in flux. Poorly crafted requirements regarding informed consent for the collection and use of biological samples and for PGx tests or overly stringent rules regarding the confidentiality of medical information could unnecessarily limit the benefits to be derived from the integration of PGx into the drug development process.

Recommendations
In developing appropriate guidelines or regulation regarding informed consent and confidentiality of information, it is essential both to distinguish where possible between highly speculative and more likely risks, and between more serious and less serious risks, and to take into account the human and financial costs associated with efforts to reduce risks.

Informed Consent

Findings
1. Obtaining informed consent in research, even when there are only modest risks to subjects, shows respect for the dignity of the individual and provides protection against exploitation of subjects.

2. In some PGx research, where there is the possibility of group stigmatization or discrimination, genetic information may be a source of group-based harms. This raises the issue of the need for group consultation in the informed consent process.

Recommendations
1. As with all medical research, PGx researchers are ethically obligated to observe the requirement of informed consent. Research participants should be informed as to why a DNA sample is needed for the research in question, the nature of the protections of confidentiality and privacy that will be employed, the time frame of the research, potential other uses, whether the sample will be destroyed upon completion of the research, and the risks and benefits of participation.
Subjects should be given the option of disclosure of reliable, beneficial information. They should be informed as to how the research results will be disclosed to them and by whom. In addition, if the DNA sample is to be linked to the participant’s personal medical information, permission to access the latter must also be sought, and the safeguards for maintaining privacy and confidentiality of this information must also be explained. The sponsorship of the research and the possibility of commercial uses of the research data should also be disclosed. In most cases, a reasonable policy is to obtain consent to a range of related studies (conducted either by the initial researcher or by other researchers) over a defined period of time, with special provision for specific consent for studies that may be especially problematic to the subject.

2. In cases of sensitive research with groups, responsible researchers should seek to incorporate group input into the research design and informed consent process, but this should not infringe the individual’s freedom to decide whether to participate in research.

**Privacy and Confidentiality**

**Findings**

PGx research will require a sophisticated information infrastructure within which epidemiological data, individual medical records, and human biological samples can be correlated and studied over time. In order to ensure adequate protection for privacy and confidentiality while at the same time making information accessible for the benefit of the individual and society, discerning policy choices will be needed. These choices should reflect an accurate appraisal of the likelihood of psychosocial harms from PGx rather than from genetic testing in general.

**Recommendations**

The most promising strategies for protecting confidentiality of information include (a) reliance on “fire-walls” to prevent the dissemination of information to certain parties (such as insurers) for certain uses, (b) trusted intermediary entities to serve as secure repositories for and gate-keepers of access to information, and (c) laws and other public and private policies prohibiting discriminatory uses of information. As this information infrastructure takes shape, new forms of public and private oversight may be required.

**Disclosure to Subject**

**Findings**

In some cases, information that may be of significant benefit to research subjects may emerge in the course of PGx research.

**Recommendations**

PGx researchers are obligated to offer to the research subject the option of disclosure of research information when its reliability has been established and when the disclosure is of potential benefit to the subject. The sponsor and researcher should incorporate into the research protocol a plan for how the information is to be disclosed.

**Controlling the Flow of Information: Alternative Models**

**Findings**

Models for controlling the flow of information range from the researcher having knowledge of the identity of the subject from whom the sample is taken, to the sample being permanently anonymized so that no one has knowledge of the identity of the subject.

**Recommendations**

Generally speaking, the use of identified (non-coded) tissue samples and related information is not advisable. In some cases permanent anonymization may be appropriate, but its use will generally require special justification. Despite the added expense and time involved
in the process, a system of double-coding is generally preferable from the standpoint of reducing the risk of breaches of confidentiality. In such a system, there is a key-holder independent from the researcher who can provide a link between the sample and the relevant information about the subject from whom the sample comes, but neither the researcher nor the key-holder knows the identity of the subject from whom the sample comes. Whether single-coding is sufficient in a particular research study will depend upon a balancing of the possibly greater risks of breaches of confidentiality as compared with double-coding, against the benefit of its lower costs of single-coding.

**Participation in Research**

**Findings**

Recent policy efforts to expand participation in research by historically under-represented groups are compatible with the exclusion of subjects based on safety or efficacy issues in the context of PGx research.

**Recommendations**

Drug researchers should use available reliable PGx information in subject selection to reduce risk to research subjects, and may exclude potential subjects who are unlikely to respond or for whom the drug would be harmful.

**The Impact of PGx on the Research Agenda and the Availability of Drugs**

**Findings**

1. The integration of PGx into the drug development process may result in situations in which some genotypic subgroups of the population, or some disease groups, are deemed by commercial drug developers to represent insufficient market demand.

2. The prospect of such “orphan” groups may focus public attention on a distinct access problem: is there an ethical obligation to develop safe and effective therapies for groups that have health care needs that are not met by existing therapies and, if so, upon whom does that obligation fall? The widespread use of PGx testing to segment the population into those for whom existing drugs or investigational drugs are beneficial and those for whom they are not raises the question of whether the existing public processes by which groups compete to determine the targets for health care research is equitable and efficient.

**Recommendations**

1. It may be necessary to modify existing Orphan Drug legislation to promote the development of drugs for these groups. Alternatively, subsidies could be provided to encourage development of drugs for these groups. In either case, there must be sufficient rates of reimbursement for these treatments as they become available. However, any such policy initiative is unwarranted unless insufficient market demand occurs.

2. In anticipation of the need for such policy initiatives, appropriate groups drawn from relevant public agencies and private constituencies should be formed to examine and address the issues of social obligations to develop new forms of therapies for groups whose health care needs would otherwise not be met.

**FINDINGS AND RECOMMENDATIONS REGARDING CLINICAL APPLICATION**

**Regulatory Oversight**

**Findings**

In the clinical context PGx testing will serve a “gate-keeper” function, helping to determine who will have access to specific drug therapies. Because these decisions may have profound effects on an individual’s well-being, the accuracy and proper use of PGx tests are critical to the ethically acceptable use of PGx.
**Recommendations**

Current regulatory requirements and processes in the U.S. appear to be appropriate, in general, for clinical application of PGx tests. However, at least the following three areas deserve further regulatory attention: (a) FDA should extend its approval oversight to include “home brew” PGx tests, not simply test kits that are licensed and marketed; (b) FDA should ascertain the best mechanism for incorporating information about, or the need for, PGx testing in drug labeling; and (c) CLIA standards, with appropriate modifications as needed, should be extended to all laboratories that perform PGx tests.

**Physician Acceptance and Responsibilities**

**Findings**

1. Physicians lack sufficient knowledge about and decision support tools for genetics generally and in particular about when to use PGx tests and how to take the results into account in clinical decision-making.

2. In the clinical context the issue of informed consent to PGx testing is somewhat more ambiguous than in research. Generally speaking, PGx tests carry lower psychosocial risk than genetic tests that confirm the diagnosis of, or predict genetic diseases, or that identify carrier status for genetic diseases. In many cases, a PGx test, like many diagnostic tests that are now routinely administered with at most minimal informed consent, will carry no significant risk of psychosocial harm. However, depending upon the nature of the secondary information, if any, that is conveyed by the PGx test result and the social, economic, and cultural context in which the test occurs, some PGx tests may carry significant risk of psychosocial harm. In addition, there appears to be considerable public concern about genetic privacy, in part because no comprehensive system for safeguarding confidentiality and privacy of genetic information presently exists.

3. The risk of sensitive secondary information may vary depending upon the choice of genetic markers used in PGx tests.

4. There is a need to provide reasonable assurance to the public about genetic confidentiality. The use of “fire-walls” and other devices can reduce the risk of breaches of confidentiality; however, these protections will never be foolproof.

5. The integration of PGx into clinical practice will raise questions regarding standards of care for uses of PGx testing and of drugs for which there are PGx tests.

**Recommendations**

1. If the potential benefits of PGx are to be realized, physicians must become better informed about this methodology. This will require additions to medical school and postgraduate medical training curricula related to genetics and PGx, and continuing education efforts for physicians. In addition, physicians and other providers will need access to clinical decision support tools and the training to use them.

2. Protections for confidentiality and provisions for informed consent will need to be developed for PGx testing that are commensurate with the risk entailed by the test in question. In most instances, all that will be required is a simple statement that the physician wishes to test a sample of the patient’s DNA to determine whether a particular drug or class of drugs will be safe and effective for the patient and that this is the only use to which the sample will be put. In cases where the PGx test conveys sensitive secondary information, a more extensive informed consent discussion may be appropriate. As a broad generalization, the greater the reliance on markers that carry a
minimum of secondary information, the more reliable the “fire-walls” to prevent inappropriate dissemination of information, and the more comprehensive the legal protections against discriminatory uses of information, the more appropriate it is to treat PGx tests like routine diagnostic tests for which only “basic” informed consent is required. Practice guidelines will have to be developed to help clinicians distinguish between “low-risk” PGx tests that require only minimal informed consent and “higher-risk” PGx tests that require fuller informed consent. The process of developing such guidelines should be a cooperative effort, with input from test-producers, laboratories, professional organizations, and government regulatory agencies.

3. Research should be devoted to the identification of markers of high predictive value that convey the least secondary information, and preference should be given to the use of PGx tests employing these markers.

4. A sound policy approach to the issue of confidentiality will almost certainly include both fire-walls and carefully crafted legal prohibitions on discriminatory uses of PGx information.

5. The standard of care for use of PGx tests should include a duty to offer PGx testing in certain cases, the right to refuse to prescribe certain drugs if patients refuse indicated PGx testing, and the discretion to prescribe off- or against-label under certain conditions.

**Direct Marketing of and Consumer Access to PGx**

**Findings**

Demand for and access to PGx tests will not be solely a function of the decisions of physicians. PGx tests are already being marketed directly to consumers. In addition, self-administered test sample collection kits are already available which allow the individual, without the benefit of any medical supervision, to collect a DNA sample and send it to a laboratory for testing. Direct marketing of tests and self-administered DNA sample collection raise important ethical issues about which a reasoned public and professional dialogue is needed. At present the public lacks sufficient knowledge about the risks and benefits of PGx and is unlikely to be able to distinguish between PGx tests and genetic tests that have different purposes and different associated risks.

**Recommendations**

In the absence of input from a physician as a “learned intermediary,” assurance of the accuracy of tests and accurate representation to the public of the predictive value and significance of tests results is all the more important. This may require new forms of regulation and other oversight mechanisms, both public and private. FDA should undertake a thorough review of the special issues raised by the direct marketing of PGx tests to consumers, including tests that involve collection of DNA samples by the person undergoing the test. As required by existing consumer protection laws, marketers of PGx tests should represent the predictive value of PGx tests accurately and in an understandable fashion. Scrupulous fulfillment of this obligation is especially crucial in the case of direct marketing to consumers, where the protective fiduciary function of the medical professional is absent.

**Payer Acceptance**

**Findings**

1. The decision whether to prescribe a drug will depend not only upon an assessment of PGx information and other factors affecting drug response (such as the individual’s general state of health, renal function, disease severity, etc.), but also upon assumptions about the stewardship of limited medical resources. In some cases a drug use policy that is rational from the
standpoint of providing health care for a population (as in a managed care plan, Medicare, or a national health care system) may not be preferable from the standpoint of a particular patient. PGx does not create this conflict of interests. But because PGx has the potential to become a powerful tool in the context of efforts to rationalize drug use practices, its integration into clinical practice may highlight the fact that pharmacoeconomic analysis is not an ethically neutral enterprise, thereby bringing fundamental disagreements about distributive justice to the fore.

2. Whether PGx tests are included in standard insurance benefits will presumably be determined by the interplay of market forces, interest-group political competition, and evolving standards of care endorsed by the relevant medical professionals.

**Recommendations**

1. Pharmacoeconomic analysis must be enriched by considerations of distributive justice as well as cost-effectiveness analysis.

2. PGx tests that provide reliable predictions of serious adverse reactions to widely prescribed drugs should receive priority for inclusion in standard health insurance benefits, both on ethical grounds and as a way of reducing unnecessary costs.
ENDNOTES


11 Wolf, et. al., supra note 3, Roses infra note 15, and Roses, infra note 16.


14 Results of research reported by Cantab Pharmaceuticals (www.cantab.co.uk), presented at the 61st Annual Scientific Meeting of the American College of Problems of Drug Dependence. Accessed March 2002.


24 National Bioethics Advisory Commission, supra note 21, Recommendations 8, 9; Medical Research Council, supra note 22: Section 6.2.


29 45 CFR 46.116 (a)8.

30 Buchanan, et al., supra note 19.


36 Ibid.


42 For example, see First Genetic Trust (http://www.firstgenetic.net/). Accessed March 2002.

43 National Conference of State Legislatures, supra note 38.


45 National Bioethics Advisory Committee, supra note 21, Recommendations 14-16; Medical Research Council, supra note 22, Section 8.


48 45 CFR 46.101 (b)4.
49 National Bioethics Advisory Committee, supra note 21, Recommendation 9.

50 Medical Research Council, supra note 22, Section 6.

51 Knoppers, et. al., supra note 25.


61 Buchanan, et. al., supra note 19.

62 Lesko and Woodcock, supra note 1, pp. 23-34 for an illuminating discussion of the steps FDA is already taking in anticipation of the growing role of PGx in drug development and clinical practice.

63 65 CFR 25928.


66 Roses, supra note 15 and Roses, supra note 16.

67 See Genelex Corp. (www.healthanddna.com) and Ardais Corp. (http://www.ardais.com) for just two examples.

68 Ibid.


70 Cheryl Goodman, Human Genetics Laboratory, Michigan State University (personal communication).