BACKGROUNDER ON PHARMACOGENOMICS FOR THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES

Basic Science, Future Scenarios, Policy Directions

Final Report

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PREFACE AND ACKNOWLEDGMENTS

This report grew out of discussions with PhRMA staff about the growing interest in the pharmaceutical and biotechnology industries and the potential impact of pharmacogenomics on the future of these industries. The University of Washington (UW) has a wide range of multidisciplinary faculty with research interests and expertise in this area. We assembled a core team from the UW Department of Pharmacy and then enlisted the collaboration of our colleagues throughout the University for either participating on an Internal Advisory Group (IAG) or reviewing and commenting on selected sections. We are particularly grateful to the following members of the IAG: Karen Edwards, Ph.D.; Kelly Fryer-Edwards, Ph.D.; Patricia Kuszler, M.D., J.D.; Scott Ramsey, M.D., Ph.D.; Mark Rieder, Ph.D.; and Ken Thummel, Ph.D. We would also like to thank Wylie Burke, M.D., Ph.D., for her comments on parts of the report, and Alice Porter for her excellent editorial assistance.

We are also greatly indebted to an External Advisory Group (EAG) selected with the help of PhRMA. They provided review and comment on all aspects of the study, as well as on the final report. Their input was invaluable. The members of the EAG were: M.J. Finley Austin, Ph.D.; Eiry Roberts, M.D.; Wayne Rosenkrans, Ph.D.; Brian B. Spear, Ph.D.; and Christopher J. Webster, BVM&$S, M.Sc., Ph.D.

We also owe a special thanks to Clem Bezold, president of the Institute for Alternative Futures, for his advice and counsel on the development and presentation of scenario models. Randy Burkholder was the PhRMA project lead, providing ongoing intellectual support and feedback for our study plans, analyses, and report. We thank him for his many contributions. Rick Smith of PhRMA also provided key input at important stages of the project.

Research support was provided by an unrestricted grant by PhRMA to the University of Washington. We truly appreciate this support.

We began this project with an ambitious scope of work given the resources and time frame, and we have attempted to address a wide range of issues, knowing full well that we would not be able to do justice to all of them. Nonetheless, we hope that this analysis will help advance the discussion of these important, complex issues in a positive and constructive manner, and will contribute to the foundation for future such efforts.

Finally, we would like to emphasize that any opinions expressed herein are solely those of the authors and are not intended to represent the views of the sponsor, our advisors, or the university.
The completion of sequencing of the human genome in 2001 was a remarkable scientific achievement, heralded as the dawn of a new era in medicine. Pharmacogenomics, the use of genetic information to guide drug development and drug therapy, may represent one of the most important applications of genetics to medicine, and thus has received significant attention due to its potential clinical, economic, and policy implications.

Yet, there is considerable uncertainty about how quickly the science will develop and be translated into clinical practice. To add further complexity, the future will be influenced by key stakeholder interests and current regulatory and policy choices. There have been significantly diverging views of the future of pharmacogenomics, and the policy implications for the pharmaceutical industry are not clear.

Objective

The primary goal of this report is to provide an objective assessment of the likely scientific developments in pharmacogenomics and the related policy areas that the pharmaceutical and biotechnology industries in the United States will face. The primary intended audience is industry public policy staff; we thus provide both the scientific and the policy background they will need to address issues related to pharmacogenomics in a knowledgeable and constructive manner. Secondarily, others with research and policy interests in this area may also find this a useful resource.

Approach

Although the focus of this report is policy, its foundation is the basic, translational, and clinical science that will be the primary determinant of the role that pharmacogenomics will play in our health care system. We convened internal and external advisory groups with expertise in a range of scientific, clinical, and policy backgrounds to assist with the development of a current assessment of the science of pharmacogenomics and likely future scenarios in the years 2010, 2015, and 2025.

A mix of scientific, regulatory, social, policy, and other issues will shape the development of pharmacogenomics applications. We thus also provide an evaluation of the issues related to research, development, clinical use, marketing, regulation, and reimbursement of pharmacogenomics, based on a systematic review of the literature and input from the advisory groups. We also conducted a high-level stakeholder analysis, reviewing the potential key players in health policy, and discussing their perspective and incentives with respect to pharmacogenomics. Ultimately, based on our evaluation of the science of pharmacogenomics, and considering both stakeholders and key issues, we derive key policy implications for the pharmaceutical and biotechnology industries.

Findings and Implications

Scientific Progress

Currently, the ability to identify variations in our genetic code has outstripped our understanding of their biological or clinical relevance. The relationship between genetic variation and drug outcomes (termed here a “pharmacogenomic association”) is difficult to evaluate because multiple genes can interact with non-genetic factors to produce a multitude of small effects. Indeed, relatively few pharmacogenomic associations have been validated to date, and there are only a handful of marketed pharmacogenomic test kits. The primary reason pharmacogenomic testing has not seen greater penetration into clinical practice is the lack of evidence to date that testing improves patient outcomes compared to usual care—i.e., “clinical utility.” Hence, it is not yet possible to develop useful clinical guidelines for practitioners. Because of these challenges, scientists are studying larger groups of patients and using improved study designs, offering improved opportunities for the identification of novel, clinically relevant pharmacogenomic associations.

By 2010, based on the current pace of research and ongoing efforts, we expect that approximately 5 to 10 clinically relevant pharmacogenomic associations will be validated, and that several more pharmacogenic test kits approved
by the U.S. Food and Drug Administration (FDA) will be available. Many, if not most, of these findings will be in oncology, and there will likely be a shift toward associations with drug effectiveness rather than drug safety. In total, a handful of pharmacogenomic tests likely will be in routine clinical use, typically in oncology or with drugs that require careful dosing, and the average primary care clinician will see relatively little impact on his or her practice.

By 2015, approximately 10 years from now, a variety of test kits using various biological markers (such as both DNA and proteins) will be possible from a scientific/technical perspective, and point-of-care testing will be feasible when rapid test results are needed. Yet, the discovery and validation of pharmacogenomic associations will likely continue at a similar measured pace. A notable development will be the identification of clinically useful pharmacogenomic associations in drug development trials outside of oncology. We expect that 10 to 15 pharmacogenomic tests will be in routine use in clinical practice. Although the majority will continue to be in oncology, evaluating both tumor and patient genetics, several tests outside of oncology will be used by primary care clinicians to guide treatment decisions.

The next two decades will see continuing progress in the identification and validation of biological markers and the convergence of a variety of testing technologies. But, the inherent scientific complexity of the human genome and its interaction with human physiology, the environment, and drugs will continue to present challenges. Thus, even by 2025, we can expect testing technologies to be highly advanced, but our understanding of the clinical implications of test results will lag behind to a degree. Over this longer time frame, we expect an increasing number of pharmacogenomic associations will be validated, due primarily to the creation of very large epidemiological studies and pooling of these studies across countries and geographical areas. Thus, by 2025, a sufficient scientific base may be able to support the common use of pharmacogenomics, but given the likely contribution of multiple, relatively small effects from multiple genes and complex interactions with the environment, pharmacogenomics will not always explain enough of drug response to be clinically useful.

In summary, the field of pharmacogenomics will likely progress as many other novel scientific and health care technologies (e.g., biotechnology) have, requiring extensive investment over a period of decades rather than years, yet eventually providing meaningful improvements to patients’ health.

Although a variety of policy issues and stakeholders will influence the rate and extent of progress, scientific challenges will be paramount. The future of pharmacogenomics in health care will be an evolution, not a revolution.

Public Policy Issues

Many of the public policy issues related to pharmacogenomics are multidimensional, with social, ethical, legal, and economic aspects that we are just beginning to perceive. To present the wide range of issues—as well as identify “non-issues”—we established five areas of application that generally correspond to moving a drug through the research pipeline and into the marketplace: 1) research and development, 2) regulatory approval, 3) clinical use, 4) reimbursement, and 5) patient- and societal-level concerns.

“The inherent scientific complexity of the human genome and its interaction with human physiology, the environment, and drugs will continue to present challenges.”

Two concepts underlie many of the issues we identified: genetic determinism, the view that genes are the primary determinant of biological processes and outcomes, and genetic exceptionalism, the view that genetic information is fundamentally different from other kinds of medical information, and, as a result, deserves special protection, regulation, or other exceptional measures. We argue that the former is a general misconception and that, with regard to the latter, one must seriously question whether it holds generally or—more likely—will be relevant only in rare, specific instances, if ever.
We identified 19 issues, ranging from the potential impact of pharmacogenomics on the efficiency of the drug development process, to the role of FDA regulations, to issues of privacy and discrimination (see Table 4-1). Many issues that have been presented as potential barriers to pharmacogenomics were found to be more complex than may be commonly perceived. Perhaps the most important finding was that each pharmacogenomics application/test is likely to be unique, and the issues related to it should not be considered separately from other concerns; that is, most often pharmacogenomics should not be treated as being exceptional from a policy standpoint.

**Stakeholders**

To understand the nature and pace of our new knowledge about genetics, and the potential impact of this knowledge on the health care system, it is essential to characterize the perspectives and interests of key stakeholders. In Section 5, we discuss stakeholder initiatives and responses because they will influence the development, scope, and use of this new information.

We identify 15 key stakeholder groups and enumerate the key issues for them. The listing alone reveals the complexity of the policy environment in which the science of genetics and pharmacogenomics will operate in the coming decades. We all care most about how this new scientific information will affect patients and their health. Citizens—a large group with competing interests—are often the least effective stakeholders in terms of promoting their legislative and regulatory interests. As interest groups, stakeholders are generally most concerned with protecting the benefits they receive, including incomes and long-term viability. New information and knowledge can be seen as both a threat and an opportunity to those interests.

For pharmaceutical and biotechnology industries, for example, we highlight the great opportunity and challenge that pharmacogenomics presents in terms of adapting existing drug development and commercial processes. For diagnostic manufacturers, the uncertainty about regulatory reform and payer evidentiary requirements is a salient issue. Payers—public and private—face the flip side of these issues: Do they need to change coverage and reimbursement policies to encourage the development of pharmacogenomic applications and ensure their appropriate adoption? Public financiers of research and regulators will need to decide if special programs or initiatives are necessary to address the scientific challenges and barriers. These are just a few of the stakeholder issues that are listed, but the clear point emerges that if key stakeholders choose to play a proactive and constructive role, they could potentially speed up the development of pharmacogenomic applications. Conversely, they can slow things down through inaction and inconsistent and unsupportive policies.

**Conclusions and Implications**

Our review and analysis suggest the following three major findings:

- There are major scientific challenges facing the translation of basic pharmacogenomic scientific discoveries into clinical care.

- Pharmacogenomics is thus unlikely to produce fundamental changes to our health care system in the near future.

- Achieving the promise of pharmacogenomics will require both continued public support for research and effective public-private collaboration to facilitate the translation of pharmacogenomics to the bedside.

The findings derive from two major sets of challenges—scientific and non-scientific:

1. **The challenge of translational science:** Translating knowledge of gene sequences into meaningful pharmacogenomic applications is challenging for a few fundamental scientific reasons:

   - As with most common diseases, the effect of genetic variation on drug response generally is a result of complex interactions with multiple genes and non-genetic factors, and, hence, the genetic markers are often only weakly associated with drug treatment outcomes. As a
result, the effect of genetic variation on drug response is often subtle and difficult to detect.

- Our knowledge of the role of genes in specific disease processes is generally in its infancy, with multiple gene correlates but no understanding of the underlying biological mechanism.

- Genetic variants relevant to drug response can be relatively rare in the general population.

Because of these factors, identifying and validating pharmacogenomic associations will continue to be a challenging, costly, and lengthy undertaking.

2. Commercial and policy challenges: Challenging technical, business, and policy-related issues might either hinder progress in the field or potentially accelerate it, depending on how they are addressed and resolved:

- Regulatory pathways have not yet been optimized to encourage the co-development of diagnostics and therapeutics.

- Current economic incentives—as reflected in our intellectual property and reimbursement systems for diagnostics and drugs—are generally not structured to reward appropriately and consistently innovative value creation for drugs, diagnostics, and pharmacogenomics-based targeted regimens.

- The integration of pharmacogenomic diagnostic development with pharmaceutical development is difficult because of differences in the underlying business and translational science models of the two sectors.

- Genomics technologies are perceived to raise ethical, legal, and social issues to such a degree that a special National Institutes of Health program was established to address them; although specific pharmacogenomic applications may not always involve such issues, this suggests the broad range of stakeholders that will be involved in the public debates.

- Stakeholder literacy about pharmacogenomics is limited, and positions on public policy issues are not yet clearly defined.

These are significant challenges, but there are also some reasons to be optimistic. This fundamental, new biological knowledge may eventually lead to a profoundly better understanding of many diseases and ultimately to innovative diagnostics and therapeutics. In the nearer term, for example, pharmacogenomics could help to address the industry “productivity problem”—the declining number of new drugs. Many compounds that are safe and effective for many people are not safe and effective for enough people to get FDA approval. With a pharmacogenomic targeting approach, it may be possible to bring many of these “near-misses” into medical practice, benefiting many patients and the sponsoring companies as well.

In the long term, the field of pharmacogenomics may represent the first step in a chain reaction of basic science knowledge—cascading through proteomics, metabolomics, and other biomarkers—that will gradually yield medical breakthroughs. This enthusiasm is warranted, given the potential of this technology, but it must be tempered by acknowledgment of the long path that new technologies must travel before they can be integrated into mainstream medical practice.

“These are significant challenges, but there are also some reasons to be optimistic. This fundamental, new biological knowledge may eventually lead to a profoundly better understanding of many diseases and ultimately to innovative diagnostics and therapeutics.”
What are the most significant implications for the pharmaceutical industry regarding public policies and development and commercial strategies? We highlight the following ones:

- Pharmaceutical and biotechnology companies will need to add a systematic evaluation of potential pharmacogenomic and other biomarkers as part of their due diligence research and development processes.

- Substantial federal government support for basic research generally will be critical before translational private research activities are viable.

- The pharmaceutical and biotechnology industries will be major beneficiaries of this basic research, and should participate actively in the public discussion of priorities.

- Companies will need to provide a rationale to regulators why they have or have not included pharmacogenomics or other biomarkers in their clinical trial development programs.

- The pharmaceutical, biotechnology, and diagnostic industries have not taken a unified or proactive position on appropriate regulatory processes and initiatives, and it may not be possible to reach a consensus. Still, it is an opportune time to begin a policy review and discussion.

- For pharmacogenomics-targeted pharmaceuticals to have greater commercial viability, the pharmaceutical, biotechnology, and diagnostic industries must engage in the public policy debate on national coverage and reimbursement issues for such drugs and tests.

How these policy areas play out could profoundly affect the development and use of pharmacogenomics-based therapies. As key stakeholders, the pharmaceutical and biotechnology industries can influence—through developing well-informed and scientifically sound public policy positions—the speed of these exciting scientific discoveries, their impact on clinical practice, and, ultimately, the benefits in terms of improved patient health.
INTRODUCTION
SECTION 1. INTRODUCTION

1.1 Background

The remarkable scientific achievement represented by the completion of sequencing of the human genome in 2001 was understandably heralded as the dawn of a new era. Only a year before, Francis Collins, director of the National Human Genome Research Institute, hypothesized that:

“In the next five to seven years, we should identify the genetic susceptibility factors for virtually all common diseases—cancer, diabetes, heart disease, the major mental illnesses—on down that list.”1,2

While this has not yet come to pass, no one doubts that this new knowledge will ultimately bear fruit in a wide array of applications profoundly improving our understanding of disease and our ability to prevent and treat it. The excitement in the news media is almost palpable, as virtually every day we are greeted with headlines about how a specific disease or behavior is correlated with some genetic marker.

While the field of pharmacogenomics, defined here broadly as the use of genetic information to guide drug development and drug therapy, presents undeniable promise, there is also a growing appreciation of the challenges in translating this new knowledge into clinical applications. Not only are the scientific hurdles greater than many initially believed, but it is also clear that non-scientific factors play an important role. In a recent article, Webster and colleagues conclude:

“Pharmacogenomics is on the threshold of making a major impact in commercial labs and in the clinic. But, despite its promise and the heavy investment made in the technology, many companies still question whether there is a coherent business, health policy, or regulatory model emerging to shape the future development of pharmacogenomics.”

And even more recently, the report Personalised Medicine: Hopes and Realities from The Royal Society cautions:

“Pharmacogenetics is unlikely to revolutionize or personalize medical practice in the immediate future.”

Thus, there is considerable uncertainty about how quickly the science will develop and can be translated into clinical practice. To add further complexity, the future will be influenced by key stakeholder interests and current regulatory and policy choices.

1.2 Purpose

The purpose of this report is to provide pharmaceutical industry staff with the scientific and policy background they need to address issues related to pharmacogenomics in a knowledgeable and constructive manner. Secondarily, others with research and policy interests in this area may also find this a useful resource.

1.3 Science as a Foundation

A mix of scientific, regulatory, social, policy, and other issues will shape development of the applications of pharmacogenomics. However, it is fundamental scientific and clinical knowledge that are critical to the long-term success of any health care technology; this report thus emphasizes the primacy of the basic scientific research and clinical translation issues.

We also recognize that the extent and direction of scientific knowledge will be significantly influenced by a multitude of issues and stakeholders, and consider these influences explicitly in formulating this report.

“A mix of scientific, regulatory, social, policy, and other issues will shape development of the applications of pharmacogenomics. However, it is fundamental scientific and clinical knowledge that are critical to the long-term success of any health care technology.”
1.4 Organization of the Backgrounder

First and foremost, this backgrounder aims to be a continuing resource for its readers. We have organized it so that readers may easily access information regarding the science or policy and stakeholder issues of particular interest at a given moment.

While the report aims to guide the reader through the science, policy issues, stakeholders, and implications, each section may be referred to independently, assuming the level of background provided in Section 2, a primer covering the basic science and terminology needed to understand pharmacogenomics in a policy context.

Section 3 reports the results of a future scenario development exercise conducted with multidisciplinary experts.

Section 4 defines and describes 19 key issues of policy relevance, highlighting the key pros and cons and providing a summary assessment of the potential impact.

Section 5 identifies the key stakeholders and the most important issues they face in terms of the potential impact of pharmacogenomics.

Finally, Section 6 assesses the implications for the pharmaceutical and biotech industries, in particular, and more generally draws out the broader implications for society.

Section References

GENETIC SCIENCE PRIMER
2.1 DNA and Genetics: The Basics

The basic operating units for most living organisms are cells. Each cell contains the necessary information to develop and maintain life within its natural environment in the form of DNA (deoxyribonucleic acid), a long, threadlike molecule (see Figure 2-1). The total complement of DNA for an organism—constituting all of its hereditary or genetic material—is called its genome.

DNA is arranged in a linear sequence of side-by-side base pairs, each of which is composed of one of four possible nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C).

DNA contains four nucleotides, or bases: adenine, thymine, guanine, and cytosine, which are designated by the shorthand A, T, G, and C. Genes—the basic units of heredity—are defined by the order of these bases. The human genome consists of three billion pairs of bases, stored in 23 pairs of chromosomes—physically separate threads of DNA. In total, these chromosomes house from 30,000 to 35,000 genes. The information in these genes is used as a “blueprint” for making about 100,000 proteins, the molecules that essentially do all the work in the body (see Figure 2-2). The information stored in genes is transferred to making proteins by RNA, a molecule similar to DNA, the levels of which can be increased or decreased in a process called gene expression.

The human genome and non-genetic (environmental) factors interact to produce a person’s phenotype—the outward appearance or physical characteristics, such as blond hair or the presence of a disease. The genome sequence is relatively static, but the process that produces the phenotype is dynamic and consists of interacting networks of molecules, with the activity and amount of genes and proteins regulated by complex feedback mechanisms in response to the environment.

2.2 Genomics and Human Health

2.2.1 Gene Discovery

The first step in understanding the relationship between genes and human health is the identification or discovery of genes that are relevant for human health. Gene discovery uses two primary approaches, involving either the study of related individuals (technically termed a linkage analysis) or non-related individuals (a case-control study). These two methods provide information about the location of genes, but further molecular techniques must be used to “isolate” (or characterize) the gene, describe its nucleotide sequence, and understand its function. The identification of genes provides the opportunity both to develop therapies to target the proteins they express or the genes themselves (i.e., via gene therapy) and to study the impact of variation in their DNA sequence on human health.

* Underlined terms are defined in the Glossary at the end of this section.
2.2.2 Types of Genetic Variation

In general, human beings are very alike in that two unrelated people have 99.9 percent similarity in their genomes. But, the remaining 0.1 percent contributes to many of the differences that do exist between people, from eye color to drug response. The majority of the variation in the human genome can be attributed to differences at the single nucleotide level—i.e., one person has an A, whereas another has a T at a specific base pair. This type of variant is termed a single-nucleotide polymorphism, or SNP. Based on the 0.1 percent difference between individuals, each person has approximately 3 million unique changes (i.e., SNPs) in their DNA. Groups of SNPs that tend to be inherited together are termed haplotypes. The genome can also vary in other ways, owing to the insertion or deletion of a DNA base pair, the insertion or deletion of larger DNA segments including entire genes, or the addition of extra copies of existing genes. Ultimately, these changes in DNA can have health consequences if they alter either 1) how a protein works or its stability (protein function), or 2) the number of RNA copies of a gene that are made (gene expression) and thus the amount of protein produced (protein expression). When a DNA variant is located in an area that contains the instructions for building of a protein, it is said to be in the coding region. When it is in an area that contains the instructions for when and how much protein to produce, it is said to be in the regulatory region. The impact of a DNA variant thus depends on the type of change and where in the genome it is located.

“The first step in understanding the relationship between genes and human health is the identification or discovery of genes that are relevant for human health.”

2.2.3 Identifying Genetic Variation: Testing Technologies

The technologies for detecting DNA variation are rapidly advancing. Although there are multiple types of genetic tests, they essentially all measure the two basic characteristics of DNA variation: changes in the sequence of a gene, and changes in the amount of a gene that is expressed. These variations can be detected using a variety of approaches, including:

1. Genotyping: any test designed to detect a specific, known genetic variant (e.g., an SNP), using traditional molecular biology techniques
2. Sequencing: an approach to discover or identify multiple genetic variants, using DNA sequencing instruments
3. Protein expression assay: a qualitative measure of the amount of protein, typically using a method termed immunohistochemistry or IHC
4. Gene copy number assay: a quantitative measure of the number of copies of a gene, typically using a method termed “FISH” (fluorescence in-situ hybridization)
5. Gene “chips”: a powerful technology for identifying thousands of genetic variants (i.e., SNPs) or measuring the expression level of thousands of genes. This process involves the placement of thousands of short DNA probes on a single chip, using techniques developed to produce computer microprocessor chips.

2.2.4 Connecting Genetic Variation to Human Health

Although we are able to detect many genetic variants, the majority of genetic variation has little or no influence on a person’s health. But, a small portion of DNA variation can play a role in who might or might not get a disease or have a certain drug response. A key approach used to study the relationship between genetic variation and human health is the association study, in which the frequency of genetic variants is compared in patients with and without a specific health outcome, such as a disease or an adverse drug reaction. Types of association studies include cohort studies, in which patients are categorized based on genetic variant, and case-control studies, in which patients are categorized based on health outcomes (or phenotype). These study designs are necessary because a randomized clinical trial (RCT) cannot be used to evaluate directly these associations, as patients
(obviously) cannot be randomly assigned to have a genetic variant. But, association studies can be conducted using data collected during clinical trials.

Although a genetic variant may be associated with the likelihood of a disease or drug outcome, it is not necessarily true that all patients with the variant will experience the outcome. This concept is termed gene penetrance, and it is defined as the proportion of people with a gene variant who actually develop the phenotype associated with the variant (e.g., an adverse drug reaction or a disease). High penetrance variants have been identified in a few well-known monogenetic diseases. For example, in Huntington’s disease, a fatal neurodegenerative disorder, about 99 percent of patients with the disease gene variant will develop the disease in their lifetime, unless they die from unrelated causes prior to disease onset. Other examples of monogenetic diseases include sickle cell disease, caused by the beta hemoglobin (abbreviated HBB) gene. In contrast, the great majority of disorders such as cancer, cardiovascular disease, and mental illness are caused by complex interactions between multiple genes and non-genetic or environmental factors. For example, both high cholesterol and family history are risk factors for heart disease, but they don’t guarantee an individual will develop disease. This is best exemplified in studies of identical twins since it is possible to assess the environmental effects because each individual is born with the same DNA sequence. The concordance of disease in identical twins is only 20 to 40 percent for medical disorders and 40 to 60 percent for behavioral disorders. These complex interactions make evaluating the relationship between genetic variation and human health challenging, as discussed in more detail in the next section.

2.3 Defining Pharmacogenomics

2.3.1 Definition

It has long been known that the same drug at the same dose can produce a different response in different patients. Several non-genetic factors can cause such variations, including diet, age, bodyweight, and kidney and liver function (see Figure 2-3). But, the contribution of one’s genes to drug response has recently received increased attention as understanding of the human genome and the tools of molecular investigation have improved. Pharmacogenetics and pharmacogenomics are two common terms used to describe the interaction of genes and drug response. The terms derive from pharmacology and genetics or genomics, and they describe the combination of traditional pharmaceutical sciences with knowledge of genes, proteins, and SNPs. The two terms have been defined in multiple ways by various authors and organizations, and they are often used synonymously.

In this backgrounder, we will use the term “pharmacogenomics” and define it as the use of human genomic concepts for the development and clinical application of pharmaceuticals. Pharmacogenomics seeks to 1) improve drug treatment by more accurately predicting drug response in a given patient, thereby decreasing adverse drug reactions and increasing drug effectiveness, and 2) streamline drug development through drug target identification and more efficient clinical trials.
2.3.2 Genetic Variation and Pharmacogenomics

The human genetic variations of interest in pharmacogenomics are of two types:

1. Heritable variation in the germline, for example, variation that is passed from one generation to the next (i.e., parent to child), and

2. Non-heritable, acquired variation in body (somatic) tissue—acquired mutations typically seen in cancers.

The distinctions between these types of genetic variations are important and help define when and how tests are conducted for genetic variation as well as how to use the information gained in testing. Note that genetic variation in disease pathogens, or infectious diseases, can also play a role in drug therapy and is sometimes considered a pharmacogenomic interaction. This approach is currently used in drug treatment for AIDS and hepatitis C, but is not addressed further in this document, which is focused on human genomics.

2.3.3 Heritable (Traditional) Pharmacogenomics

Heritable genetic variation can ultimately produce pharmacogenomic effects through changes in proteins involved with human disease and drug response. One class of proteins is enzymes, which catalyze chemical reactions within the body. The mechanism of action of many drugs is to inhibit enzyme function, but in contrast, some enzymes are responsible for the metabolism and elimination of drugs from the body. Membrane transporters are proteins involved in moving molecules (including drugs) into or out of cells. Cell receptors are proteins generally on the surface of cells that bind to a specific factor such as a neurotransmitter, hormone, or drug and initiate a cellular response. Variation in the structure, function, stability, or amount of these proteins can thus lead to changes in the metabolism of drugs, drug levels within the body and within specific cells, and the effectiveness of drug action at the intended target.

2.3.4 Acquired (Somatic) Pharmacogenomics

Genetic variation can also be acquired throughout a person’s lifetime through spontaneous mutation in individual cells that is then passed on to daughter cells during cell division. These types of mutations tend to build up over time, and when mutations occur in certain types of genes, e.g., oncogenes or tumor-suppressor genes, cancer can result. These cells are genetically distinct from normal body tissue, and information about their genetic makeup may help identify patients more likely to require chemotherapy or respond to a specific drug.

“The contribution of one’s genes to drug response has recently received increased attention as understanding of the human genome and the tools of molecular investigation have improved.”

2.3.5 Application of Pharmacogenomics to Clinical Practice

In standard medical practice, patients with a given disease or condition are given a drug based on what works best for most people with similar characteristics. If the drug does not work or causes adverse side effects, then the dosage can be altered or an alternative medication can be tried. Thus, to a certain extent, drug therapy is already “individualized” using non-genetic information. Pharmacogenomics would introduce a genetic test into this scenario in an effort to better predict patient response. For example, when a genetic test reveals a person to be a poor metabolizer of a specific drug, a lower dosage may be prescribed, or another drug may be used. Applications of pharmacogenomics are often grouped into two categories: those involving drug metabolism and drug levels (pharmacokinetics); and those involving drug targets and drug effectiveness (pharmacodynamics). Pharmacogenomics thus has the potential to increase the probability of achieving the “right drug” and the “right dose” more efficiently than with a traditional approach.

Examples of current applications of pharmacogenomics are shown in Box 2-1. These examples are drawn from the limited set of currently utilized pharmacogenomic tests. Other notable examples, for which the FDA has recently added pharmacogenomic information to the label, include UGT1A1, CYP2C9/VKOR, and TPMT, and they are discussed further in the next section.
2.3.6 Application of Pharmacogenomics to Drug Development

Pharmacogenomics has the potential to influence several areas along the drug development pipeline from target selection to product launch. The two primary areas likely to be affected are drug target identification and the clinical trials process. As the field of genomics progresses and genes that play a role in disease processes are identified, the proteins that are expressed by these genes can be investigated as potential drug targets. An estimated 500 drug targets are believed to exist, and genomics could increase this number up to 5,000. This application of genomics to drug development would thus be more of a quantitative, rather than qualitative, change to the current process. A deeper understanding of pharmacogenomics may also help streamline the clinical trials process. It is possible that the size and cost of a clinical trial could be reduced if patients more likely to respond to a drug or less likely to experience an adverse drug reaction could be preferentially enrolled, although knowing how to identify these patients using pharmacogenomics markers before conducting a trial with a novel drug is extremely challenging. We explore these ideas further in Section 4 of this report.

2.3.7 Scientific Complexity and Challenges

Although many of the concepts underlying pharmacogenomics are straightforward and logical, the challenges inherent in connecting genetic variation and drug response are complex. Much of the initial progress in pharmacogenomics involved single-gene (monogenetic) variants with large effects. But, the multigenic nature of most diseases, interactions with non-genetic, environmental factors, and the relatively low frequency of many genetic variants make progress in the field difficult. These issues are discussed in the next chapter on current scientific challenges and likely future scenarios.

Section References

Genetic Science Glossary

- **Association study**—A study of the correlation between a (genetic) marker and a disease or condition. The marker and the condition are said to be associated if the frequency of the marker in people with the condition is higher than would be expected by chance alone.

- **Base pair**—Two bases which form a “rung of the DNA ladder.” A DNA nucleotide is made of a molecule of sugar, a molecule of phosphoric acid, and a molecule called a base. The bases are the “letters” that spell out the genetic code. In DNA, the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively. In base pairing, adenine always pairs with thymine, and guanine always pairs with cytosine.

- **Case-control study**—An association study design using non-related individuals and based on health status where individuals are classified as having the outcome (case) or not (control).

- **Cell receptors**—A receptor is a protein on the cell membrane or within the cytoplasm or cell nucleus that binds to a specific factor, a ligand, such as a neurotransmitter, hormone, or other substance, and it initiates the cellular response to the ligand. As all receptors are proteins, their structure is encoded into the DNA.

- **Chromosomes**—Threadlike “packages” of genes and other DNA in the nucleus of a cell. Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mothers and half from their fathers.

- **Coding region**—DNA that contains instructions for making proteins (or other cell products such as RNAs).

- **Cohort study**—A study design in which a population cohort is prospectively defined and divided according to the presence or absence of an exposure variable (gene variant) of interest and then followed over time for the occurrence of pre-specified outcomes (disease or health condition).

- **DNA (deoxyribonucleic acid)**—The double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.

- **DNA sequence**—The linear order of the base pairs in a segment of DNA.

- **Enzymes**—Proteins that act as catalysts, speeding the rate at which biochemical reactions proceed but not altering the direction or nature of the reactions.

- **Genes**—The functional and physical units of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

- **Gene expression**—The process by which proteins are made from the instructions encoded in DNA.

- **Gene therapy**—A novel approach to treat, cure, or ultimately prevent disease by changing or repairing defective genes.

- **Genetic test**—The analysis of human DNA, RNA, chromosomes, and those proteins and metabolites used to detect heritable or somatic disease-related genotypes or karyotypes for clinical purposes.

- **Genome**—The entire DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA found separately in the mitochondria within cells.

- **Genomics**—The study of the functions and interactions of all the genes in the genome, including their interactions with non-genetic (environmental) factors.

- **Genotype**—A person’s genetic makeup, as reflected by his or her DNA sequence for a specific gene base-pair.

- **Haplotypes**—A set or combination of gene variants or linked genetic markers found on a single chromosome, which tend to be inherited together in a given individual.

- **Linkage analysis**—A gene-hunting technique that traces patterns of disease in high-risk families, in an attempt to locate a disease-causing gene by identifying genetic markers of known chromosomal location that are co-inherited with the trait of interest.

- **Membrane transporters**—Proteins that go completely through a cell membrane and carry specific nutrients, ions, drugs, etc., across the cell membrane.

- **Monogenic**—Controlled by a single gene, as opposed to multigenic.

- **Multigenic, polygenic**—The involvement of many genes in the expression of a trait.
Genetic Science Glossary – Continued

- **Mutation**—A permanent structural alteration in DNA. In most cases, DNA changes either have no effect or cause harm, but occasionally, a mutation can improve an organism's chance of surviving and passing the beneficial change on to its descendants.
- **Nucleotides**—Sub-units of DNA or RNA consisting of a nitrogenous base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate molecule, and a sugar molecule (deoxyribose in DNA and ribose in RNA). Thousands of nucleotides are linked to form a DNA or RNA molecule.
- **Oncogene**—A gene that normally directs cell growth but when altered allows uncontrolled cellular growth.
- **Penetrance**—The likelihood or probability that a particular genotype will be expressed in the phenotype. A penetrance of 100 percent means that the associated phenotype always occurs when the corresponding genotype is present. Similarly, if only 30 percent of those carrying a particular gene (such as a disease-causing mutation) exhibit a phenotype (the disease), the penetrance is 30 percent.
- **Pharmacodynamics**—The study of the biochemical and physiological effects of drugs and the mechanism(s) of drug action.
- **Pharmacogenetics**—The study of how people's genetic makeup affects their response to medicines.
- **Pharmacogenomics**—The application of genomic concepts to the development and clinical application of pharmaceuticals.
- **Pharmacokinetics**—The study of the absorption, distribution, metabolism, and excretion of a drug.
- **Phenotype**—The observable traits or characteristics of an organism, for example, hair color, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.
- **Polymorphism**—A common (traditionally >1 percent within the population) variation in the sequence of DNA among individuals.
- **Proteins**—Large complex molecules made up of one or more chains of amino acids. Proteins perform a wide variety of activities in the cell.
- **Protein expression**—The amount of proteins genes generate.
- **Regulatory region**—A region of the genome that does not encode a protein but affects the expression of a gene.
- **RNA (ribonucleic acid)**—A chemical cousin of DNA, RNA is responsible for translating the genetic code of DNA into proteins.
- **Single-nucleotide polymorphisms (SNPs—pronounced “snips”)**—One-letter variations in the DNA sequence.
- **Tumor-suppressor gene**—A gene that normally restrains cell growth but, when missing or inactivated by mutation, allows cells to grow uncontrolled.
SECTION 3
CURRENT STATE OF THE SCIENCE AND LIKELY FUTURE SCENARIOS
SECTION 3. CURRENT STATE OF THE SCIENCE AND LIKELY FUTURE SCENARIOS

3.1 Introduction

This section provides an assessment of the state of the science of pharmacogenomics (PGx) and likely future scenarios for progress in the field. The science related to PGx is defined broadly here as scientific research and findings in genome sequencing, gene discovery, genetic epidemiology, clinical science, and clinical practice. As discussed in the previous section, significant scientific complexities are involved in the translation of PGx findings to clinically effective interventions. Although the evolution of this field is uncertain, it is nonetheless possible to project potential scenarios based on progress to date and consideration of fundamental scientific challenges.

The objective of these forecasts is not to provide precise timelines for the development of specific technologies and clinical applications but to provide “ballpark” estimates of the future landscape. These assessments are useful, indeed almost necessary, given the widely divergent views of the future of PGx. For example, one perspective is that “hospitals and doctors will use these [genetic testing] kits at the point of care to determine how a patient will respond to a drug. Personalized medicine is coming faster than people realize.” In contrast, Sir David Weatherall, chair of The Royal Society’s report Personalised Medicine: Hopes and Realities, stated, “With the human genome sequenced, some people are expecting personalized medicines within a few years, but the reality is still many years away.” Thus, an assessment of the science will provide a foundation for an evaluation of the potential impact of PGx on the health care system.

In addition, factors such as regulation, economic incentives, and public perceptions will clearly have an important influence on the pace of scientific discovery and technology transfer to clinical practice. These factors are outlined at the end of this section.

3.2 Approach

To collect expert opinions on the science of PGx, we convened a roundtable discussion of our Internal Advisory Group. (See Appendix B for a list of the participants.) The group assessed current PGx scientific knowledge and challenges and explored likely 5-, 10-, and 20-year scenarios (corresponding to 2010, 2015, and 2025). We then obtained feedback from our project’s External Advisory Group and conducted subsequent rounds of revision and review using a modified Delphi consensus approach. Although not a full or formal alternative futures exercise to develop a base set of forecasts, this process can be considered a preliminary step in such an undertaking.3, 4

Our internal group consisted of experts in gene analysis technologies and discovery, genetic epidemiology, pharmacogenomics, clinical practice, law, economics, and ethical, social, and policy issues. All participants had significant research experience evaluating the impact of genetics and PGx on their respective fields. External group members were employed in the pharmaceutical and diagnostics industries, had a variety of expertise, and were in key positions pertaining to PGx in their respective organizations. We also consulted with an expert in future scenarios development, who offered suggestions and reviewed our plans and report.

The results of the exercise are summarized at the end of this section in Table 3-1. We discuss each time frame in detail in the rest of this section. The rest of this section presents our sense of the most likely developments for 2010, 2015, and 2025.

“We define a pharmacogenomic association as the correlation between a genetic variant and an outcome from drug therapy.”

3.3 Scientific Domains

We identified three major PGx scientific domains: 1) testing technologies, 2) pharmacogenomic associations, and 3) clinical utility and utilization. These domains are similar to other frameworks developed for the evaluation of genetic and PGx testing, such as the ACCE criteria (analytic validity, clinical validity, clinical utility), and ethical,
legal, and social issues (or ELSI). Each domain is described in more detail below, and likely scenarios for each are presented in subsequent sections.

3.3.1 Testing Technologies

We define testing technologies as scientific discoveries and related technological developments that enable the identification of genetic variants—in this case, with particular relevance to PGx. As discussed in the previous section, pharmacogenomic tests can measure different types of genetic variation using a variety of approaches (genotyping, sequencing, protein/gene expression assays, and gene chips).

It is also useful, however, to categorize PGx tests by their intended use:

1) Research use, conducted in research settings
2) Clinical use but conducted in niche labs (“home-brew” tests, or testing services)
3) Clinical use, conducted in typical central or hospital clinical labs
4) Clinical use, conducted at the point of care (e.g., a doctor’s office)

The regulation of genetic tests is determined in part by their intended use. Research use-only tests are not subject to regulation, unless the research involves evaluation of the test device itself. Laboratory-developed tests or “home-brew” tests are intended to inform clinical care, and thus must be conducted in a Clinical Laboratory Improvement Amendments (CLIA) certified lab, thus meeting certain personnel, quality control, and proficiency requirements, although none of these are specific for genetic testing. These tests are considered medical services (as opposed to devices), however, and thus the FDA generally does not regulate them directly. The FDA instead regulates the manufacture of the building blocks used in their making, termed “analyte-specific reagents” (ASRs) and consisting of antibodies, nucleic acid sequences, and other biological or chemical reagents, for quality, documentation, and restrictions on sales to qualified laboratories. Tests designed for use in typical clinical labs or at the point of care are directly regulated by the FDA, and termed in vitro diagnostics (IVDs), or “test kits.” IVDs may be classified as Class I, II, or III depending on similarity to existing tests and risks posed to patients, for example as a result of false positive or false negative test results.

3.3.2 Pharmacogenomic Associations

We define a pharmacogenomic association as the correlation between a genetic variant and an outcome from drug therapy. As discussed in the previous section, establishing the validity of a PGx association is challenging. There are several reasons for caution when evaluating a reported genetic association: 1) patient groups may have differences other than the specific genetic variant of interest (e.g., “population stratification”), 2) the evaluation of multiple genetic variants and multiple outcomes in a study can lead to chance positive findings, and 3) the effect of genetic variation on drug outcomes may be relatively small, necessitating large samples of patients to detect a statistically significant result.

In addition, association studies are subject to publication bias—the tendency to publish only positive findings. There is, thus, no standard definition of a “valid” association, and reviews of pharmacogenomic associations have reported widely different findings depending on definitions of validity.

While it is difficult to characterize a valid association, in general, this means the findings have been consistently replicated, ideally by multiple investigators in multiple patient populations. Recent proposals have been put forth for a process for determining the validity of complex tests such as gene expression profiles.

3.3.3 Clinical Utility and Utilization

We define clinical utility as the actual benefit a patient could receive from testing, and clinical utilization as the actual use of pharmacogenomic testing in clinical practice. Realizing the clinical benefits from PGx will require more than efficient testing technologies and valid pharmacogenomic associations. An effective clinical treatment based on the PGx test result must also be available. Identifying the treatment may be easy to do — e.g., by providing or avoiding a specific drug in certain patients. But, when treatment options are limited, or patients are already closely monitored, the incremental benefit that could be provided by a treatment based on PGx testing may be difficult to identify and measure.
Ideally, a pharmacogenomic test and the subsequent treatment strategy would be evaluated in a prospective randomized clinical trial (RCT). Such trials may not be warranted, however, in cases where the potential for clinical benefit of testing is clear and there is an obvious treatment intervention. In either case, the availability of scientific and clinical evidence for the effectiveness of treatment modifications based on pharmacogenomic tests likely will be a key driver in the acceptance and use of these tests by practicing physicians.

3.4 Current Scientific Knowledge

3.4.1 Testing Technologies

The ability to identify genetic variants has outstripped our understanding of their biological or clinical relevance, and thus genetic testing itself generally does not present a significant barrier in the field. For example, gene chips currently being used in research settings are capable of testing for hundreds of thousands of genetic variants in a single assay.13 Most pharmacogenomic testing services that are currently available, however, detect a more limited number of variants using straightforward genotyping approaches. A multitude of pharmacogenomic testing services are available directly from diagnostic labs. These are home-brew tests developed by a testing company for use in its own labs and not for resale on the market. Many home-brew testing services and some test kits are actively marketed to physicians, and some are available to patients directly over the Internet. Although home-brew testing services are generally not regulated by the FDA, they are receiving some scrutiny.14 Examples of pharmacogenomic home-brew testing services currently available include those for cytochrome P450 drug metabolizing enzymes (CYPs),15,16 TPMT,17-19 UGT1A1,20,21 antibiotic-induced hearing loss testing,22,23 and gene expression profiling in breast cancer.24,25

There are currently a handful of marketed pharmacogenomic test kits, including two types of Her2-neu tests for trastuzumab (Herceptin®) therapy, and the AmpliChip Genotyping test, which identifies 31 genetic variants in two drug metabolism genes, as discussed in the previous section. The most recent pharmacogenomic test kit is for detecting variants in the UGT1A1 gene, which is involved in the metabolism of the colon cancer drug irinotecan.26 Currently, there are no point-of-care pharmacogenomic (or any genetic) tests, although research activity is under way in this area.26 Another test kit that can be considered pharmacogenomic-based is qualitative protein expression testing for epithelial growth factor receptor (EGFR) in colon cancer treatment with cetuximab (erbitux, BMS/Imclone)17 (PharmDxTM test from DAKO).26 This test kit has also been used in clinical trials of EGFR tyrosine kinase inhibitors in lung cancer treatment, but has not been validated for this indication.29,30

3.4.2 Pharmacogenomic Associations

The relationship between genetic variation and drug outcomes (i.e., efficacy and safety) is the primary focus of current pharmacogenomics research. Few pharmacogenomic associations have been extensively validated to date. In addition to trastuzumab, well-known and often cited examples include: 1) TPMT variants and toxicity to the anti-cancer drug 6-mercaptopurine in children with acute lymphoblastic leukemia,31,32 2) CYP2C9 and VKORC1 variants and dose requirements of the blood thinner drug warfarin in patients with clotting disorders,33,34 and 3) UGT1A1 variants and toxicity to the anti-colon cancer drug irinotecan.35 These associations have been reproduced in various studies and are generally accepted in the scientific and clinical community as valid. In addition, the FDA recently required the addition of information about pharmacogenomic effects to the labeling of each of these drugs, although testing was not required. Validation of the gene expression profile assays currently available for guiding breast cancer chemotherapy is ongoing. Both the MammaPrint and Oncotype DXTM tests have been validated using retrospective analyses, and prospective validation studies are currently being conducted.36-38

A variety of other pharmacogenomic associations related to drug metabolism or safety are of continuing interest, including the relationship between (1) HLA and adverse drug reactions to the anti-HIV drug abacavir,39-41 thymidylate synthetase and 5-FU chemotherapy toxicity,42 (2) MDR
gene and immunosuppressants, and (3) CYP3A4/5 variants and drug disposition. The validity and clinical utility of these associations are not yet clear. A more general assessment of the association between P450 drug-metabolizing enzymes variants and the broad variety of drugs they metabolize is challenging. For example, the AmpliChip test identifies variants in the CYP2D6 and CYP2C19 genes, which play a major role in the metabolism of up to 25 percent of marketed drugs. But only a few clinically relevant associations have been validated, e.g., between CYP2D6 and side effects to the ADHD drug atomoxetine (Strattera, Lilly), and response to codeine. In contrast, although of great interest, the influences of CYP2D6 variants on antidepressant therapy outcomes have not been consistently identified. Thus, there is not currently a solid evidence base for hopes that pharmacogenomics will lead to widespread decreases in the incidence and cost of adverse drug reactions.

Numerous other pharmacogenomic associations have been and are still being explored, but have not been consistently reproduced. For example, one study indicated a significant relationship between an alpha-adducin gene variant and diuretic antihypertensive response, but two recent (as yet unpublished) studies failed to identify such an association. The association between the CETP polymorphisms and statin therapy outcomes has been widely studied, but a recent meta-analysis failed to validate the association. Some other examples of pharmacogenomic associations that have not been consistently reproduced as of yet include: ACE gene polymorphisms and antihypertensives, beta-receptor polymorphisms and both asthma and heart failure medications, and serotonin transporters and antidepressants. Treatment of patients with the Philadelphia chromosome in chronic myeloid leukemia (CML) with imatinib (Gleevec, Novartis) is a validated association and sometimes considered a pharmacogenomic application, but it is more diagnostic in nature.

Lastly, very recent studies have identified a variety of promising new prospects for clinically meaningful associations, although validation and prospective evaluation studies have not been conducted. Examples include associations between the CYP2D6 drug metabolism gene and response to tamoxifen therapy in breast cancer; the beta adrenergic receptor gene and response to bupindolol in heart failure; the CYP3A5 drug metabolism gene and toxicity from the chemotherapeutic drug vincristine; the OCT2 transporter gene and elimination of metformin in diabetes; and the serotonin 2A receptor gene HTR2A and response to antidepressant treatment.

“The most likely reason that pharmacogenomic testing has not seen greater penetration into clinical practice is the lack of evidence to date that testing improves patient outcomes compared to usual care.”

3.4.3 Clinical Utility and Utilization

Currently, pharmacogenomics is rarely used in clinical practice. A pharmacogenomic test is routinely used with only one drug (Herceptin) of the top 200 drugs by sales, and none of the top 200 drugs by prescription volume. Although valid associations have been identified and tests are available, routine pharmacogenomic testing with 6-mercaptopurine, warfarin, and irinotecan therapy is conducted only at a limited number of academic research centers, and testing has not been required by the FDA despite labeling changes. Clinical utilization of the AmpliChip is less clear as it has recently entered the market and does not have a specific indication. Lastly, clinicians are just beginning to evaluate the role of the Oncotype DX and MammaPrint gene expression assays in adjuvant breast cancer chemotherapy treatment decisions. For example, 550 Oncotype DX test results were ordered in 2004 and 7,000 in 2005.

The most likely reason that pharmacogenomic testing has not seen greater penetration into clinical practice is the lack of evidence to date that testing improves patient outcomes compared to usual care — i.e., clinical utility. This lack of evidence has several causes, including: 1) the paucity of prospective randomized clinical trials evaluating pharmacogenomic tests, 2) the challenges of identifying valid associations.
to study, 3) the challenge of identifying a treatment strategy that will provide an incremental benefit over usual care, 4) in some cases (e.g., warfarin) the limited availability of a test kit or test results within a clinical decision-making time frame, and 5) genetic variation that may not account for the majority of variation in drug-related therapeutic outcomes. Randomized trials of pharmacogenomic testing are just beginning with warfarin therapy, CYP2D6 for antidepressant use, and Oncotype DX, and they will likely have an important impact on the future prospects for these tests. The recent FDA approval of a UGT1A1 test kit may increase its use and evaluation in clinical trials.

Because of the lack of clinical applicability and routine use of pharmacogenomic tests, few treatment guidelines exist, although pharmacogenomic-based dosing algorithms have been developed and are currently being evaluated for some drugs (e.g., warfarin). The U.S. Centers for Disease Control and Prevention (CDC) has sponsored an initiative, Evaluation of Genomic Applications in Practice and Prevention, which is developing an assessment process for pre- and post-market evaluation of the effectiveness for DNA-based genetic tests.

Below we present an overview of likely developments in PGx at 5-, 10-, and 20-year time points. These forecasts represent an assessment of the most likely scientific developments and what they mean for PGx. They don’t assume as rapid a set of changes as some of the authors cited above, nor are they as cautious as The Royal Society estimates. The collected forecasts for this scenario are also presented in Table 3.1.

3.5 2010 Forecasts

3.5.1 Testing Technologies

Within the next five years, rapid technological advances in the analysis of individuals’ genes that is currently being done in research settings will likely make their way toward diagnostic use. Gene chips capable of evaluating up to 500,000 individual genetic variations (SNPs), able to identify a significant portion of the variability in an individual’s genome, are currently available in the research setting for less than $1,000. Indeed, the current goal is to develop technologies for the complete sequencing of the human genome. The National Institutes of Health recently presented an RFA entitled “Genome Sequencing Technologies—The $1000 Genome.” These tests may be ordered directly by patients, with actual testing taking place in-house by the testing laboratory. Several more FDA-approved pharmacogenomic test kits will likely be available, but by 2010 we expect this number will be in the range of 3–5 rather than greater than 10. It is possible that point-of-care assays, which would allow testing in physicians’ offices, will be available for one or two pharmacogenomic tests, although there will be technical and regulatory challenges in their development. In the research setting, the development and utilization of assays for other molecular biomarkers such as proteins (proteomics) and endogenous metabolites (metabolomics) will continue to expand.

3.5.2 Pharmacogenomic Associations

Over time, our understanding of specific pharmacogenomic associations will change as additional studies are performed and the quality of studies improves. Some will be found to be highly clinically relevant, while the validity of others may come into question. Based on the current pace of research and ongoing efforts, it is reasonable to expect that 5–10 clinically relevant pharmacogenomic associations will be validated in the next five years. Many of these associations will be in oncology, and there will likely be a shift toward associations with drug effectiveness rather than drug safety. By 2010, several associations may have been identified and validated during Phase III clinical trials in the drug development process, although these trials are generally not large enough to conduct association studies, and so may be confined to oncology applications in which a tumor genome is being studied. Large, collaborative association studies may just be getting started in 2010 and be engaged in collecting informed consent, enrolling patients, and addressing clinical and sample collection issues. Research studies evaluating pharmacogenomics, proteomics, and combinations of biomarkers will become more common, but they will face challenges due to the high number of markers and their time-varying nature.
3.5.3 Clinical Utility and Utilization
In 2010, a handful of pharmacogenomic tests likely will be in routine clinical use, e.g., similar to the current utilization of testing with Herceptin® therapy. Again, these will most likely be in oncology or with drugs that require careful dosing, such as warfarin, and thus the average primary care clinician will see relatively little impact on his or her practice. For such tests to achieve acceptance by clinicians and attain standard-of-care status, they likely will have been evaluated in a prospective clinical trial and shown to improve patient outcomes. Treatment guidelines or evidence-based recommendations for pharmacogenomics for several therapeutic areas will be available, but in many cases, they may indicate that there is insufficient evidence to recommend testing. Studies will support the importance of both clinical and genetic information in making treatment decisions for drugs that have pharmacogenomic tests associated with them.

A novel, pharmacogenomic-based drug outside of oncology may arise, either from an intended pharmacogenomic-based drug development program or as a consequence of unintended identification of a responder (or non-responder) subgroup.83,84

3.6 2015 Forecasts

3.6.1 Testing Technologies
By 2015, it is likely that testing technologies will be developed for a variety of biological markers, often in combination (e.g., genotyping, gene expression, and proteomics). Thus, a wide variety of test kits will be possible from a scientific/technical perspective. Point-of-care testing will be feasible for pharmacogenomic applications that require rapid results.

3.6.2 Pharmacogenomic Associations
Also within the next decade, the pace of discovery and validation of PGx associations will continue at a similar level. Several associations may be identified in drug development trials outside of oncology. Results from large association studies will likely reveal cumulative small effects from multiple genes as well as from environmental factors.

3.6.3 Clinical Utility and Utilization
By 2015, it is likely that 10–15 pharmacogenomic tests will be in routine use in clinical practice. Although the majority will continue to be in oncology—evaluating both tumor and patient genetics—several tests outside of oncology will be used by primary care clinicians to guide treatment decisions. In addition, several of these tests may be intended for use with novel, “pharmacogenomic” drugs. Because of the increased utilization and available data, treatment and reimbursement guidelines will be developed for most of these tests.85 Importantly, the scientific evidence will support the role of PGx testing as a complement to other clinical information, rather than being deterministic with regard to treatment strategies. The exception will be in cases in which, because of drug mechanism of action, a drug will be expected to work optimally only in patients with certain genetic profiles.

3.7 2025 Forecasts
The further ahead the future is envisioned, the greater the variability and potential impact of factors external to the science. Nonetheless, since it is widely accepted that genomics will unfold in health care over decades, rather than years, a 20-year perspective is warranted.

3.7.1 Testing Technologies
The next two decades will see continuing progress in the identification of biomarkers and the convergence of a variety of technologies. The ability to assay a multitude of markers in an efficient fashion may enable the development of novel statistical analysis methods and epidemiological study designs. However, the inherent scientific complexity of the human genome and its interaction with human physiology, the environment, and drugs will continue to present challenges. Thus, in 2025, we can expect testing technologies to be highly advanced, but our understanding of the clinical implications of test results will lag behind.
3.7.2 Pharmacogenomic Associations

In the next 20 years, it is possible that many validated pharmacogenomic associations will be identified, due primarily to the creation of very large epidemiological studies and pooling of these studies across countries and geographical areas. With sample sizes ranging from 100,000 to 1 million patients, these studies will be able to detect small effects and gene-gene and gene-environment interactions. They may also be supported by novel testing technologies, statistical analysis methods, and study designs. The size of some of these pharmacogenomic effects will be so small, however, that they may not justify, clinically or economically, modification or addition of treatment. The ability to more specifically diagnose common diseases such as hypertension based on molecular markers and mechanism of disease may offer one of the greatest hopes for improving health outcomes with the use of genomics. How well pharmaceutical treatments can be targeted to specific sub-diagnoses likely will determine the magnitude of the role of pharmacogenomics itself.

“The ability to more specifically diagnose common diseases such as hypertension based on molecular markers and mechanism of disease may offer one of the greatest hopes for improving health outcomes with the use of genomics.”

3.7.3 Clinical Utility and Utilization

In 2025, a sufficient scientific base may be able to support the common use of PGx. But given the likely contribution of multiple, relatively small effects from multiple genes, the time-varying nature of gene and protein expression, and interactions with the environment, PGx often will not always explain enough of the variation to be useful. In other words, drug therapy, even for drugs for which a PGx test is available and an association validated, will not be guided by genetics alone. PGx will be more of an evolution, rather than a revolution, in health care.

3.8 Non-Science Change Drivers

Future development, interpretation, and use of PGx will clearly depend on a complex set of interacting factors. Major concerns include the perceived lack of economic incentives for investment in research and development in PGx and adverse ethical, legal, or social consequences. Non-science factors that may speed scientific progress in this area include: 1) investment by public/private partnerships to conduct very large association studies, 2) changing patent protection for diagnostic tests, 3) additional regulatory/patent incentives to develop drugs for smaller, targeted patient populations, 4) efficiency in drug development due to PGx, 5) anti-genetic discrimination legislation, and 6) demand for and reimbursement of PGx tests and drugs, both by traditional health care payers and providers and individual patients and consumers.

We organize these factors into the following five broad categories:

Factors inherent in the science, including,

• stability of the underlying paradigms for science and R&D;
• increasing appreciation of the complexity of genomics science, including gene-environment interactions, and of questions about the incremental value added by emerging genetic interventions, including PGx; and
• the need for research that better translates findings into practice.

Factors and issues related to the science, including,

• low levels of both provider and patient/consumer genetic literacy;
• fluctuating levels of public financing for research, along with regulatory constraints as to types of research;
• uncertain adoption curve of the science into clinical practice;
• conflicts between the scope of some potential uses of genetic services and prevailing payment and financing programs, i.e., susceptibility testing without therapy; and
• bioethical and public and community concerns about the potential scope of the technologies.

Factors associated with enabling technologies, including,

• the rate and scope of the adoption and use of electronic medical records, point-of-care health information, and development of disease management programs based on the availability of more targeted risk information;
• the availability and affordability of “genome-on-a-chip” technologies;
• the extent, utility, and use of Web portals and other media as information and marketing channels for these technologies; and
• the expanded use of testing kits and sample generation technologies increasing both accessibility and affordability.

Factors and trends in the health care delivery system, including,
• changing revenue mix across three major sources: private insurance, public payment, and consumer spending;
• continued erosion of purchaser/employer funding;
• impacts of consumer spending through consumer-driven health accounts; and
• levels and scope of technology assessment by both private and public payers.

Factors from the policy environment, including,
• the possibility of regulatory reform affecting the FDA and the federal Centers for Medicare and Medicaid Services, in particular;
• the availability of risk capital financing for novel medical technologies;
• expected delivery system reform initiatives affecting both types and levels of financing; and
• the potential transformation of health insurance companies from medical management to asset management organizations.

The host of issues raised by the interaction of these factors with the science of PGx are discussed in the subsequent sections. The scenario presented here is a “best estimate,” most likely forecast for the science of PGx. These factors in various combinations could lead both to different scenarios for the science, and equally important, to different scenarios for the use and impact of PGx.
### Testing Technologies

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 (Current)</td>
<td>* Essentially not a barrier for most research, although sample collection is challenging.</td>
</tr>
<tr>
<td></td>
<td>* “Whole genome scans” are currently being conducted in research settings.</td>
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<tr>
<td></td>
<td>* Four commercial PGx test kits are available (2 Herceptin tests, Amplichip; UGT1A1).</td>
</tr>
<tr>
<td></td>
<td>* Many labs offer in-house (“home brew”) PGx testing services.</td>
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<tr>
<td></td>
<td>* Point-of-care PGx assays are not available.</td>
</tr>
<tr>
<td>2010 (5 years)</td>
<td>* “Whole genome scans” are available for clinical research and potentially direct to consumers (e.g., 500,000 SNP chip for &lt;1,000).</td>
</tr>
<tr>
<td></td>
<td>* Several more PGx test kits are available.</td>
</tr>
<tr>
<td></td>
<td>* Point-of-care assays may be available for a few PGx tests.</td>
</tr>
<tr>
<td></td>
<td>* Use of proteomics has increased and involves the study of biologically more relevant biomarkers.</td>
</tr>
<tr>
<td>2015 (10 years)</td>
<td>* A multitude of biological markers are studied using various assay technologies, often in combination.</td>
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<tr>
<td></td>
<td>* Thus, a wide variety of test kits may be possible.</td>
</tr>
<tr>
<td></td>
<td>* Point-of-care testing is feasible.</td>
</tr>
<tr>
<td>2025 (20 years)</td>
<td>* Optimistic: Paradigm changes are possible due to continuing progress in and convergence of various technologies, including bioinformatics, proteomics, metabolomics, gene chips, and computer hardware and software that will enable a “systems biology” approach.</td>
</tr>
<tr>
<td></td>
<td>* Pessimistic: These technologies may not necessarily surmount challenges of inherent biological complexity.</td>
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</table>

### Pharmacogenomic Associations

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2005 (Current)</td>
<td>* There are perhaps 5 to 10 validated PGx associations, depending on definition.</td>
</tr>
<tr>
<td></td>
<td>* Most are related to drug metabolism.</td>
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<tr>
<td></td>
<td>* Association studies often are difficult to evaluate because they:</td>
</tr>
<tr>
<td></td>
<td>– are underpowered;</td>
</tr>
<tr>
<td></td>
<td>– explore multiple outcomes, leading to chance positive findings;</td>
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<tr>
<td></td>
<td>– have poor exposure data;</td>
</tr>
<tr>
<td></td>
<td>– lack well-defined phenotypes; and</td>
</tr>
<tr>
<td></td>
<td>– are not validated in other populations (i.e., population stratification).</td>
</tr>
<tr>
<td></td>
<td>* Negative findings are often not published (publication bias).</td>
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<tr>
<td>2010 (5 years)</td>
<td>* There are 5 to 10 additional validated PGx associations, mainly in oncology.</td>
</tr>
<tr>
<td></td>
<td>* Several (3 to 5) associations may be identified during the drug development process.</td>
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<tr>
<td></td>
<td>* There is continued movement from studying drug metabolism to drug targets.</td>
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<tr>
<td></td>
<td>* Design of association studies is improving along with stricter peer-review and editorial oversight.</td>
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<tr>
<td></td>
<td>* Larger (e.g., 10,000s to 100,000s of patients) association studies are in the enrollment phase; few data are yet available.</td>
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<tr>
<td></td>
<td>* Association studies involving proteomics and metabolomics are complicated by the time-varying nature and increased number of biomarker candidates.</td>
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<tr>
<td>2015 (10 years)</td>
<td>* Similar pace of validated PGx associations occurs.</td>
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<tr>
<td></td>
<td>* Several (3 to 5) associations are identified during drug development process outside of oncology.</td>
</tr>
<tr>
<td></td>
<td>* Data from larger association studies become available.</td>
</tr>
<tr>
<td></td>
<td>* Findings of larger association studies likely reflect cumulative small effects from multiple genes and from environmental interactions.</td>
</tr>
<tr>
<td>2025 (20 years)</td>
<td>* Optimistic: Results from larger association studies identify many complex but valid PGx associations.</td>
</tr>
<tr>
<td></td>
<td>* Pessimistic: The size of these effects may not always be clinically meaningful. The complexity of interaction of genetics with non-genetic factors may lead to the identification of few validated PGx associations.</td>
</tr>
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</table>

### Clinical Utility and Utilization

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2005 (Current)</td>
<td>* PGx tests are routinely used with only 1 of the top 200 drugs by sales (Herceptin).</td>
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<tr>
<td></td>
<td>* Oncologists see some impact on practice with gene expression assays.</td>
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<tr>
<td></td>
<td>* Other than Herceptin, no comparative, prospective randomized trials have demonstrated the utility of PGx testing.</td>
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<tr>
<td></td>
<td>* Few, if any, major guidelines or recommendations exist for their use.</td>
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<td></td>
<td>* PGx is perceived as having special value compared to clinical data, although this view may not be supported by the science.</td>
</tr>
<tr>
<td>2010 (5 years)</td>
<td>* Three to five RCT-evaluated, FDA-approved test kits are routinely used (&lt;5 percent of top 200 drugs).</td>
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<tr>
<td></td>
<td>* There may be one novel, non-oncology PGx-based drug.</td>
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<tr>
<td></td>
<td>* Most clinicians continue to see little impact on their practice.</td>
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<tr>
<td></td>
<td>* Several guidelines or recommendations exist for PGx use.</td>
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<tr>
<td></td>
<td>* PGx continues to be perceived as having “special value,” although its equivalent role with clinical data is appreciated more (e.g., treatment algorithms include both PGx and clinical data).</td>
</tr>
<tr>
<td>2015 (10 years)</td>
<td>* An additional 5 to 10 RCT-evaluated, FDA-approved test kits are routinely used (&lt;10 to 20 percent of top 200 drugs).</td>
</tr>
<tr>
<td></td>
<td>* Several of these tests may be for novel, PGx-based drugs.</td>
</tr>
<tr>
<td></td>
<td>* Several of these tests may be for common, chronic conditions (non-oncology).</td>
</tr>
<tr>
<td></td>
<td>* Many clinical areas have guidelines or recommendations regarding use of PGx tests.</td>
</tr>
<tr>
<td></td>
<td>* PGx is viewed as complement to traditional clinical/environmental factors in treatment decision-making due to results from larger association studies showing comparable importance of these factors.</td>
</tr>
<tr>
<td>2025 (20 years)</td>
<td>* Optimistic: Significant scientific and clinical evidence to support common utilization of PGx by clinicians and patients/consumers.</td>
</tr>
<tr>
<td></td>
<td>* Pessimistic: PGx may not be one of the primary drivers in health care decisions (e.g., even if PGx is used, the effect on drug selection, dose, size of target population, and clinical outcomes may be relatively moderate for each case).</td>
</tr>
</tbody>
</table>

*Erbilix (cetuximab) and Gleevec (imatinib) could be considered; testing currently not common with warfarin or Straterra (atomoxetine). Camptostar (irinotecan) not in top 200, nor is testing currently standard.

PGx=pharmacogenomics; RCT=randomized controlled (clinical) trial.
Section References

1. “Gentris receives $5 million investment; announced shortly after FDA guidance on pharmacogenomic data submission, funding will help Gentris deliver on the promise of personalized medicine,” Business Wire, April 27, 2005.


76. Tonner, B., “GSK’s Allan Roses says PGx is not only here, it’s already paying off,” GenomeWeb Daily News, April 6, 2006.

KEY PUBLIC POLICY ISSUES
SECTION 4. KEY PUBLIC POLICY ISSUES

4.1 Introduction: Purpose and Approach

The purpose of this section is to identify, describe, and summarize key public policy issues likely to emerge as pharmacogenomic products move out of the research stage and into the marketplace. Many of these public policy issues are multidimensional, with social, ethical, legal, and economic aspects that we are just beginning to perceive.

We identified these issues in three stages. First, we developed a list of potential issues by reviewing the literature for intersections between PGx and the traditional disciplinary areas—scientific, ethical, legal, social, economic, and policy. But most issues fall into multiple areas, making it difficult to discuss a specific issue without referring to several others. For this reason, we organized issues into groups of mutually exclusive categories. We circulated a draft list of issues to both an Internal Advisory Group (IAG) and an External Advisory Group (EAG) for review and comment, including a priority ranking.

We then integrated these lists into a final version and expanded the remaining issues to include a detailed summary and analysis statement. We sent these write-ups to the IAG and EAG for additional review and comment.

To present the wide range of issues—including important issues as well as myths and “non-issues”—we established five general sequential areas of application that roughly correspond to moving a product through the pipeline and into the marketplace: 1) research and development, 2) regulatory approval, 3) clinical use, 4) reimbursement, and 5) patient- and societal-level concerns.

The issues addressed in this section are listed in Table 4-1, which can serve as a table of contents and reference to facilitate finding specific issues of interest.

4.2 Background: Underlying Concerns of Genetic Determinism and Genetic Exceptionalism

Two underlying concerns affect many of the issues discussed in this section: 1) To what extent do genes alone determine a specific biological or clinical outcome? and 2) Is genetics sufficiently different from other medical information to require a special policy response? These views are usually characterized as follows:

- **Genetic determinism**: The view that genes are the primary determinant of biological processes and outcomes; and

- **Genetic exceptionalism**: The view that genetic information is fundamentally different from other kinds of medical information, and, as a result, deserves special protection, regulation, or other exceptional measures.

We consider each briefly in turn.
### TABLE 4-1. SUMMARY LIST OF KEY ISSUES

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Subtopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>DEVELOPMENT OF PHARMACOGENOMIC TESTS AND DRUGS</td>
<td>I-1 Efficiency of drug development: Will PGx improve the efficiency of the drug development process?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I-2 Rescuing “failed” drugs: Will PGx enable pharmaceutical companies to rescue “failed” or recalled drugs?</td>
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<tr>
<td></td>
<td></td>
<td>I-3 Economic incentives for development: If the market sizes for PGx drugs are smaller than for non-targeted drugs, will the financial incentive for PGx drug development be stifled?</td>
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<td></td>
<td></td>
<td>I-4 Rare and “orphan” diseases: Will the designation of “orphan” drug status to some PGx drugs provide financial incentives to address unmet needs for the treatment of rare diseases?</td>
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<td></td>
<td></td>
<td>I-5 Gene patenting: How might “gene patenting” affect the future development of pharmacogenomic tests and drugs?</td>
</tr>
<tr>
<td>II</td>
<td>REGULATORY APPROVAL OF PHARMACOGENOMIC TESTS AND DRUGS</td>
<td>II-1 PGx labeling: Will the FDA require the inclusion of pharmacogenomic data in drug labels, and, if so, what will be included?</td>
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<td></td>
<td></td>
<td>II-2 PGx test evidence: Will the FDA modify the evidentiary standards for regulatory approval of stand-alone pharmacogenomic tests?</td>
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<td></td>
<td>II-3 Labeling and risk management: Will PGx drugs be restricted by the FDA to use in their PGx-defined populations?</td>
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<td></td>
<td></td>
<td>II-4 Duty to inform: Will drug developers be required to inform consumers about PGx information?</td>
</tr>
<tr>
<td>III</td>
<td>CLINICAL USE OF PHARMACOGENOMIC TESTS AND DRUGS</td>
<td>III-1 Test interpretation: Who will interpret PGx tests for patients?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III-2 Informed consent for tests: Should informed consent for PGx testing differ from other types of testing (e.g., non-genetic)?</td>
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<td></td>
<td></td>
<td>III-3 Physician liability: Will doctors incur liability due to the availability of PGx tests?</td>
</tr>
<tr>
<td>IV</td>
<td>PAYMENT POLICIES FOR PHARMACOGENOMIC TESTS AND PGx-TARGETED DRUGS</td>
<td>IV-1 Test and provider reimbursement: How will PGx tests be reimbursed?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV-2 Reimbursement for PGx-targeted drugs: Will reimbursement for PGx drugs be restricted based on PGx test results? What evidence will be needed to establish coverage? Will cost-effectiveness be a criterion?</td>
</tr>
<tr>
<td>V</td>
<td>PATIENT- AND SOCIETAL-LEVEL IMPACTS OF PHARMACOGENOMIC TESTS AND DRUGS</td>
<td>V-1 Clinical trial informed consent: Should PGx research study subjects whose DNA has been stored be informed about clinically relevant findings arising from or after the study?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V-2 Privacy and discrimination: Will the use of PGx tests lead to stigmatization or genetic discrimination in life insurance, health insurance, or employment?</td>
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<tr>
<td></td>
<td></td>
<td>V-3 Ownership: Who owns genetic information—patients, PGx test developers, drug developers, family members, or others?</td>
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<td>V-4 Public knowledge: Is the public knowledge of PGx adequate?</td>
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<td></td>
<td>V-5 Global health inequalities: Will PGx-based drug development focus on genotypes that are most common in populations able to afford medications? Will this exacerbate global health inequalities?</td>
</tr>
</tbody>
</table>
A common misconception is that genes are the primary determinant of most biological outcomes. Most scientists and scholars would reject this idea, but there remains a widespread tendency to oversimplify complicated situations and causal relationships, attributing everything to DNA. The fact that a few diseases, such as Huntington’s disease and cystic fibrosis, have a strong genetic basis has no doubt contributed to the misconception that single genes frequently cause disease—what has been called the “monogenic view.” When science topics are presented in the news media, whether about the causes of cancer and obesity or differences between the races and sexes, the genetic factors and causal relationships, attributing everything to DNA.

It seems to be becoming more widely understood that because of the complex, multi-factorial nature of most diseases, genetics is almost non-existent, and most phenomena that we think of as genetic are a result of complex interactions among genetic and environmental factors and thus are poorly predicted by genes alone.

While we have achieved great strides during the Human Genome Project in identifying genes that vary across individuals, as yet this work has not resulted in a significant number of improved medical treatments, let alone improved health outcomes. It seems to be becoming more widely understood that because of the complex, multi-factorial nature of most diseases, genetics alone is likely to be very limited in its ability to predict important biological and health outcomes.

“Most phenomena that we think of as genetic are a result of complex interactions among genetic and environmental factors and thus are poorly predicted by genes alone.”

The term “genetic exceptionalism,” the belief that genetic information about an individual is different from other medical information and therefore deserving of different treatment, was coined in the early 1990s and has been debated ever since. Genetic information is often perceived as more sensitive than other types of medical health information. For example, many states have passed laws, and there have been attempts to pass federal legislation banning the use of genetic risk information in health insurance underwriting; in contrast, there are no specific laws banning discrimination on the basis of cholesterol level (not a disease in itself but a risk factor for stroke and heart attack). A second example involves the institutional review boards appointed to protect individuals used in research. They may ask for a separate signature line on an informed consent for planned genetic analyses but not for other types of tests conducted as part of a medical study. A third example is seen in arguments to keep genetic test results separate from patient medical records.

It is sometimes argued that genetic tests are different because they not only give information about the person tested, but also, to some degree, about their blood relatives. In fact, any information for a trait that is heritable—it family history or a diagnostic blood test—could provide some information about the health of other family members. And some non-heritable traits (such as having tuberculosis) could provide information on family members due to shared environments.

Specifically, four characteristics of genetic tests are frequently cited to argue for exceptional treatment of genetic information in particular cases. None of these characteristics is, however, unique to genetic tests.

- **Predictive of future health:** Non-genetic factors — e.g., plasma cholesterol levels, blood pressure, or exposure to radiation — can be just as predictive.

- **Permanent and unchangeable:** Exposure to second-hand smoke or pollution or a severe sunburn can irreversibly affect risk for certain diseases, such as skin cancer or asthma.

- **Uniquely identifying:** Fingerprints, dental films, voiceprints, and other personal data can yield highly predictive information.
Informative about family and community members:

There are many examples of non-genetic predictors, such as family history of diseases (e.g., heart disease, tuberculosis) due to common environmental influences.

This perception is not surprising given that the large majority of currently available genetic tests pertain either to rare cases of single-gene disorders where the relationship between the gene and health outcome is very strong, or to paternity and forensic DNA testing. Our current experience with genetic data and testing has therefore been biased toward genetic tests that deliver information more highly predictive than for many common medical tests. Conversely, we have no or very limited exposure so far to other applications of PGx tests that are less predictive but still potentially useful, such as tests to help adjust drug dose.

Regardless of the extent to which genetic information may be exceptional, it is commonly viewed and treated as such, a situation that influences policy. Thus, the potential impact of this general perception must be kept in mind in considering each specific issue.

4.3 The Issues

In this section, we address 19 policy issues, each with a self-contained discussion so that the user of this back grounder can go directly to specific questions of interest.

I. DEVELOPMENT OF PHARMACOGENOMIC TESTS AND DRUGS

I-1. Efficiency of drug development:

Will PGx improve the efficiency of the drug development process?

PGx information could allow for smaller, shorter, faster, and cheaper clinical trials with improved success rates. Although there is potential for such efficiency, it is unclear given the complexities of drug development how significant or pervasive these effects might be. An understanding of the relationship between a genetic marker and drug efficacy could enable the design of a clinical trial that is enriched with likely responders, thus improving the chances of finding a clinically and statistically significant benefit.

As a result, fewer patients would be required for the trial, decreasing enrollment times and cost. An additional benefit of PGx might be the exclusion of patients more likely to experience an adverse event, thus improving the risk-benefit ratio of the drug. In practice, however, this will not be practical in many situations since rare, significant adverse effects sometimes show up only after a drug is in wider use.

But the identification and validation of a PGx marker and test to predict drug efficacy or toxicity may require a significant amount of time and resources, including large clinical epidemiological studies prior to targeted drug development. The exception to this situation may be when the PGx marker itself is inherently involved in the mechanism of the drug. Such is the case for trastuzumab (Herceptin®), the breast cancer drug, which targets breast cancer tumor cells over-expressing the HER2 protein on their surface. Trastuzumab attaches to cells that over-express HER2 and kills them. About 25 percent of women with breast cancer have tumors of this type.

Another reason that clinical trial times may not be reduced is that manufacturers may be required to evaluate the safety of a drug in patients without the designated PGx efficacy markers for the FDA to assess safety in the overall population that might receive the drug, even if inappropriately. But such safety studies would still generally require sample sizes (i.e., number of patients exposed to the drug) comparable to a standard clinical trial conducted for FDA approval.

In summary, PGx may improve the efficiency of the drug development process for selected drugs, but it will not likely lead to a paradigm shift in the clinical trials process. The potential efficiency gains achieved by restricting the study population must be balanced against the goal of having the drug approved for the widest possible patient population.

Given that PGx is still early in its application and uncertain in its impact, it will also introduce additional complexity to the inherently complex nature of the drug development process. On balance, with the additional information that new genetic knowledge provides, some efficiencies in the drug development process may be achievable over time, although the net impact remains speculative.
I-2. Rescuing “failed” drugs:

Will PGx enable pharmaceutical companies to rescue failed or recalled drugs?

Increasing PGx knowledge may result in the ability to bring a drug to market that was previously thought to lack an appropriate efficacy or safety profile. About 77 percent of new, candidate pharmaceutical products are not approved. These failures are frequently due to lack of demonstrable efficacy or the presence of adverse effects in a small number of patients. “Rescuing” such drugs would require that efficacy — or the adverse effects — be shown to correlate with a genetic marker. A narrowed definition of the target population could, in effect, rescue drugs that were previously discarded. The social benefit of this would not be greatly reduced drug development costs but rather the additional health benefits achieved in those who can safely receive the targeted therapy. Assuming such failed drugs could be rescued, the drug manufacturer would be able to recoup some of its research and development investment.

But evaluating PGx markers for the catalogue of previously failed drugs, and obtaining regulatory approval for successful candidates, would be challenging. Because drug compounds are patented before regulatory approval, many older drugs will already be off-patent, and manufacturers will have less incentive to invest additional resources. Novel patent extensions or data exclusivity could help address this issue when rescue possibilities are significant enough to justify the costs of additional PGx studies.

PGx-based drug rescue may be more promising for drugs that are in the development stages. But in drugs for which PGx is used to address safety concerns (including those threatened with removal from the market), a significant challenge will be the development of a risk management strategy to restrict a drug’s use to the appropriate patient population. Absent such a strategy, the history and perception of the rescued drug as unsafe may hinder its utility because of provider fears of increased liability. Unfortunately, recent experiences with non-PGx drugs suggest successful risk management plans are difficult to implement, even with stringent measures. For example, because of the additional hurdles that sometimes accompany a risk management program, if other therapies are available, physicians are likely to avoid using the rescued drug without first exhausting all other treatment options.

In summary, drug rescue as a result of growing PGx knowledge offers promise, particularly for drugs that have faced efficacy challenges during development and have been shelved. Addressing safety issues will be more challenging, and will require effective risk management strategies and changing practice patterns to include testing.

“Because drug compounds are patented before regulatory approval, many older drugs will already be off-patent, and manufacturers will have less incentive to invest additional resources.”
I-3. Economic incentives for development:

If the market sizes for PGx drugs are smaller than for non-targeted drugs, will the financial incentive for PGx drug development be stifled?

Currently, the pharmaceutical industry generally relies on a “blockbuster” model to finance the majority of its research and development: The 30 percent of drugs that earn more than the average cost of developing a new drug generate more than 50 percent of revenues in a given year. Because broader clinical indications lead to greater revenues and a greater likelihood of recovering the high costs of research and development, there is a strong incentive to develop and market drugs that can be used by a wide variety of patients. At the same time, it is widely recognized that for many drugs, only a minority of patients achieve a clinically significant response.

Although a PGx test might reduce the number of patients who receive a drug, it is not necessarily true that total revenues would decrease proportionally—or at all. The revenue that could be generated would depend on a variety of factors, including whether the drug is already on the market, pricing flexibility in the market, and other competitive factors.

The effectiveness of such a drug in a targeted population would be higher on average than in a non-targeted population. The targeted drug would thus provide more value per patient; and a similar cost-effectiveness level could potentially be maintained even with higher up-front treatment costs. However, manufacturers’ ability to adjust for product use in the targeted population is limited in practice for drugs that are already on the market. In addition, this may necessitate a greater shift in emphasis to value-based decision-making by payers. On the other hand, even for products already on the market, there are some economic incentives for targeting. For example, if a drug with a current 10 percent market share in a broad indication is found to be highly efficacious in 20 percent of the patient population with a specific PGx marker, revenues might be significantly increased. Even “blockbuster” drugs often have a minority market share that might be expandable with proof of superiority in a subset of patients.

It is also possible that a new PGx test that targets a subgroup of responders could increase the sales of a drug for which adverse drug events make physicians and patients reluctant to use a drug. If such events could be predicted based on PGx, the drug would be more valuable in the marketplace, and sales could increase because the uncertainty about adverse events would be reduced, encouraging many more patients to use a drug than previously. But as in the case of drugs “rescued” from safety problems, carefully developed risk management plans would need to be developed and implemented to foster appropriate utilization.

Development of a targeted drug in combination with a PGx test may also present a more positive scenario for drug manufacturers. If an accurate PGx test could be developed together with the drug, then the drug developer would have a better estimate of the market size and overall cost-effectiveness of the drug and could plan accordingly. If the drug developer also develops the test, additional value and revenue could be captured in the process of screening (i.e., testing) the larger pool of potential patients. The FDA’s recent guidance on Genomic Data Submissions suggests that the drug sponsor consider developing the screening test and drug concurrently, thus allowing for a more efficient review as well as potentially yielding a drug that may be more effective and or safer. How often it will be technically feasible to develop a PGx test in parallel with a drug, however, is not clear.

In summary, for drugs already on the market, a new PGx-based test would tend to lead to a reduction in market size based on sheer number of patients, but this does not necessarily mean there would be no economic incentives to create, discover, and develop a companion test. Total revenues will not always be reduced due to novel approaches to co-development of drugs and tests, greater market share, or higher prices for the drug. First-in-class drugs launched with a companion PGx-test for appropriate targeting should be in a better position to achieve revenue in line with the total value created. Effective strategies for particular products and companies will depend on the specifics of the situation.
I-4. Rare and “orphan” diseases:

Could the designation of orphan drug status for some PGx drugs provide financial incentives to address unmet needs for the treatment of rare diseases?

There is often a limited financial incentive to develop drugs for rare diseases. As private enterprises, pharmaceutical companies often must focus their research efforts on diseases for which unmet medical need is combined with an ability to pay. Hence, research and development activity tends to be focused on relatively common diseases of the developed world. This issue is not unique to PGx.

To encourage development of drugs for underserved populations in the United States, orphan drug legislation provides regulatory and legislative support in the form of tax benefits and market exclusivity to drug developers. Similar provisions are in place in the European Union and other developed countries. The federal Orphan Drug Act defines rare diseases as those that (a) affect fewer than 200,000 persons in the United States, or (b) affect more than 200,000 persons in the United States but for which there is no reasonable expectation that the cost of developing the drug will be recovered from U.S. sales.

The development of PGx tests could be similarly encouraged under the Orphan Drug Act. In cases where a PGx-defined population is small, a PGx drug targeting this population could be designated as an orphan drug. Indeed, FDA spokesperson Michael Dreis stated that pharmacogenomic drugs would not be treated differently from “any other orphan drug submission.”

While orphan drug legislation has induced the development of drugs for rare diseases, the path to orphan drug status is not always smooth. How orphan disease populations are defined can be a contentious issue, and determining the proportion of the population with a specific genotype may be even more difficult. As such, it is not clear if orphan drug status would be determined solely by the number of people with the specific genotype or by both the prevalence of the indication as well as the genotype. To date, there has not been an effort to define an “orphan genotype.”

Many more drugs have been qualified for orphan drug status than was originally anticipated. And critics of the provision claim that it has been abused by industry to convert niche indications into blockbuster products. In cases where drugs approved under the Orphan Drug Act do generate high profits, there has been backlash over the high cost of those drugs, with some suggesting that “unreasonable” profits be limited. Additionally, there is concern that if many PGx drugs do obtain orphan status, the cost to the government with respect to tax benefits may be unsustainable. This controversy will no doubt continue and could affect how orphan drug status may be applied to PGx applications.

“In summary, existing orphan drug provisions would apply to targeted PGx products in principle, and this could encourage the development of PGx therapies targeted to smaller or less-affluent sub-populations. But continuing controversy about these programs could lead to reforms that would similarly affect PGx. In any case, laws such as the Orphan Drug Act cannot ensure that all genetic subgroups have drugs developed for them, but they may serve to counteract some of the disincentives that could arise from market segmentation.

I-5. Gene patenting:

How might “gene patenting” affect the development of pharmacogenomic tests and drugs?

The advantages and disadvantages of patenting genes and gene variants is a controversial topic. The proponents of gene patenting argue that patents produce innovation, and they provide the potential intellectual property rights necessary to encourage the investment of capital for their discovery. The emergence of the biotechnology sector is often provided as evidence for this stance. But those who
argue against gene patents contend that they limit access to valuable scientific advances that could be used for research and development of commercial products or to promote basic scientific research.9

Gene patenting may create difficulties in the diagnostics market; it could be difficult to create competing PGx-based diagnostics because it would often be necessary to test a genetic variant (sequence) patented by another entity.10 Furthermore, the polygenic nature of genes and the need to develop multiple-gene assays and algorithms may present complex problems given our current patent system.11 It is possible that the development of a PGx-based diagnostic or treatment could be forestalled by the licensing costs associated with accessing numerous, already-patented genetic sequences. Yet, without patents, the incentive to invest to develop new tests is reduced.

But there will often be the potential for shared financial gain, which has already begun to promote collaboration. One example is “patent pooling,” which the U.S. Patent and Trademark Office defines as “an agreement between two or more patent owners to license one or more of their patents to one another or third parties.” A patent pool could facilitate the collection of necessary tools to practice a certain technology through “one-stop shopping,” rather than obtaining licenses from each patent owner individually. But it is only a proposal and has not been enacted.12

In summary, the patenting of genes and genetic sequences provides a critical incentive for the development of PGx tests, though the size of the genome and the role of multiple genes in complex diseases adds an additional layer of complexity to patent-holder negotiations that could hamper the development of PGx-based drugs. As with most technologies, a better understanding of the pros and cons of gene patenting will gradually unfold as more real examples and related case law are developed. Different stakeholders will hold different views, as some would prefer to have free access to what others consider their intellectual property. This applies not only to PGx-based tests, but to other innovations as well.

II. REGULATORY APPROVAL OF PHARMACOGENOMIC TESTS AND DRUGS

II-1. PGx labeling:
Will the FDA require the inclusion of pharmacogenomic data in drug labels, and if so, what will be included?

The FDA-required label for each prescription drug provides information on its appropriate use, dose, route of administration, safety, and efficacy. FDA rules state that “if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug.”12 Clearly, this language could apply to PGx tests but not to them alone. Beyond this language, no specific regulations require PGx information to be included in the label. In 2003, however, the FDA's Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science addressed the question of pharmacogenomic labeling. The subcommittee stated that information should be included in the label if there is: 1) a polymorphic receptor, drug-metabolizing enzyme, or transporter involved in the kinetics of the drug, 2) evidence to show that it has a consequence in terms of the side-effect profile or lack of efficacy, and 3) a way to test for the particular variant.13

At this stage, the lack of evidence of the clinical consequences of PGx variation remains a significant barrier to inclusion of PGx information in drug labels. Furthermore, there is no clear evidentiary standard for when to include such information based on non-randomized controlled studies. For example, the warfarin and 6-mercaptopurine labels recently have been modified to include information about PGx, but testing was not mandated. Nonetheless, there are currently about 20 drug labels that carry references to treatment implications potentially caused by genetic differences.14 Lacking the clear evidence on the clinical benefits of testing in practice, the FDA has, for the most part, refrained from the explicit requirement of a genetic test prior to prescribing a drug.
In summary, there are a limited number of examples of drug labels referencing PGx, and they refrain from requiring a test in clinical practice. In the future, when a drug is co-developed with a PGx test, testing information will be included prominently in the package insert, as with the breast cancer drug Herceptin®. But a specific test being mandatory is likely to be rare, unless serious safety issues are involved.

II-2. PGx test evidence:

Will the FDA modify the evidentiary standards for regulatory approval of stand-alone pharmacogenomic tests?

Mirroring the pace of advances in molecular medicine, overall laboratory testing has grown in terms of the number of tests, capital expenditures, and profile in clinical care. A recent study reported that diagnostics influence 60–70 percent of downstream treatment decisions, and as much as $56 billion was spent on laboratory diagnostic services in 2005. The regulatory environment will be crucial to ensure appropriate use of laboratory testing for this growing and influential sector of health care.

Laboratory tests can be categorized into two major types: “home-brew” tests that are developed in-house for use by the developer and cannot be sold to other clinical laboratories; and test kits that are developed as commercial products to be sold on the open market. They differ in how they are regulated. Home-brew tests are regulated by the federal Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Act (CLIA). CLIA requires that tests demonstrate good analytic performance but not necessarily good clinical performance. In other words, the test must accurately detect the marker it specifies, but it need not provide direct evidence of clinical benefit in terms of the patients’ health.

Home-brew tests are also regulated indirectly through the regulation of the building blocks used in their making, termed analyte-specific reagents (ASRs) and consisting of antibodies, nucleic acid sequences, and other biological or chemical reagents. The FDA regulation of ASRs includes quality control, labeling, and restrictions on sales to high-complexity laboratories. Test kits, on the other hand, are regulated by the FDA and are subject to pre-market approval, during which they must provide evidence of their safety and effectiveness for identified uses. But test kits are not often required to provide the same level of evidence that the FDA mandates for other devices that carry significant risk (such as prospective controlled trials for implantable defibrillators). While laboratory tests usually pose little direct risk of injury or death, they often lead to a cascade of clinical decisions and procedures that have incumbent risks for patients. For example, women whose genetic tests show BRCA mutations (indicating a higher predisposition to breast cancer) may choose to have prophylactic mastectomies and oophorectomies. Thus, by virtue of potential impact on clinical treatments, PGx tests could also represent a class of laboratory assays that could pose risks for patients.

Many tests, including PGx tests, are brought to market as home-brews and therefore circumvent a large portion of the regulatory process. In response to the regulation gap for home-brew tests, two committees released reports in the late 1990s recommending increased oversight of genetic tests.

Though it appears that the FDA has the right to regulate all laboratory testing, including home-brew tests, it has not
yet chosen to do so. The potential for increased use of laboratory tests in clinical decision making, the potential risks associated with certain types of testing, including PGx, and the ability of clinical labs to avoid pre-market review for home-brew tests together have created concern over the current level of regulation for laboratory testing. The recent draft FDA guidance on “In Vitro Diagnostic Multivariate Index Assays” (September 2006) is a first step in the direction of increasing the regulation of home-brews.

In summary, the FDA appears to have regulatory authority over all laboratory tests, including home-brew tests. With the increase in laboratory testing and its heightened role in clinical care, it seems likely that the FDA will increase evidentiary requirements for laboratory tests generally and PGx tests specifically.

II-3. Labeling and risk management:

Will PGx drugs be restricted by the FDA to use in their PGx-defined populations?

The issue of risk management and restricted indications for drugs is not unique to PGx, but it is relevant insofar as 1) pharmacogenomics could be used to try to minimize risk, and 2) using PGx to minimize risk may be risky in and of itself. Risk management in the context of PGx involves the assessment of the benefits and risks of a PGx drug in the subgroup for which it is intended as well as for potential use in other, “off-label” populations. Prohibition by the FDA of off-label use based only on efficacy (or lack thereof) is unlikely. But when the safety of a drug in a non-target population is unknown or a concern, regulation or risk management strategies are likely. For example, the FDA recently issued three guidance statements (although not specific to PGx) on managing and minimizing risk.

From these guidance statements, it is still clear that the dominant paradigm for risk management will likely remain similar to the current situation in which labeling is one of the FDA’s major regulatory tools and liability exposure is the primary means of discouraging questionable prescribing practices.

In summary, with the trend toward the collection of pharmacogenomic information in the drug development and clinical environments, risk management approaches based on pharmacogenomics will receive more attention, especially in cases of drugs with significant adverse events. But given the paucity of PGx applications, the rarity of many of the gene variants, and the difficulty of linking them causally to uncommon adverse events, risk management based on PGx is likely to be uncommon for the foreseeable future.

II-4. Duty to inform:

Will drug developers be required to inform consumers about PGx information?

The “duty to inform” consumers typically is discharged through the “learned intermediary,” which in most cases is a health care provider, such as a physician or pharmacist. This will be the case with the majority of PGx tests and products. Nonetheless, the volume of direct-to-consumer (DTC) advertising is growing. For example, some vendors, including medical labs such as Genelux, are currently marketing PGx tests directly to patients, often over the Internet.

According to a recent New Jersey Supreme Court decision, if pharmaceutical manufacturers are engaging directly with consumers, then they create and are therefore bound by the duty to inform them. The FDA in 21 CFR 202.1 sets the rules that govern DTC advertisements for pharmaceuticals. The duty-to-inform issue for industry involves primarily product claims in DTC ads. The FDA states that these ads should contain a “fair balance” of risks and benefits associated with the product, inform consumers that they should consult with their physician, and should be understandable to the public. The FDA regulations do not contain specific language addressing the inclusion of PGx information—a not-surprising situation given the current stage of development of PGx. But given the FDA language and insofar as PGx information becomes known and recognized as relevant to understanding risks and benefits, manufacturers will be obliged to include such information. The FDA requirement for the advertisement to be understandable to the public will be particularly problematic in the case of PGx, due to its inherent complexity and the general public’s lack of basic knowledge about genetics.
In summary, although there is no specific case law or regulation to date, current legal language and trends imply a duty to inform consumers about “known” (included in the prescribing information) risks for PGx subgroups in any relevant DTC advertisements. This duty would seemingly be met through appropriate attention to the risks in such advertisements. Given that most PGx services and products will be ordered and prescribed by licensed health care providers, serving as learned intermediaries, the duty to disclose in DTC advertising is likely to be limited.

III. CLINICAL USE OF PHARMACOGENOMIC TESTS AND DRUGS

III-1. Test interpretation:
Who will initiate and interpret PGx tests?
Primary care and specialty clinicians, medical geneticists, genetic counselors, nurses, and pharmacists are all candidates to play a role in PGx test interpretation and communication with the patients. Certified genetic counselors and medical geneticists typically discuss (non-PGx) genetic test results, such as prenatal screening and tests for breast cancer risk genes (BRCA 1 & 2). But PGx markers tend to imply risks that are similar to other risk factors involved in drug prescribing, and therefore, traditional providers of clinical information will likely be able to provide this information to patients for most PGx tests. There may be exceptions: For example, when a PGx variant is associated with other disease risk, this may warrant a higher level of counseling. Clinical pharmacists (PharmDs) are highly trained with regard to inter-patient variation in drug response and represent an alternative potential provider source for PGx information, particularly in regard to drug metabolism and pharmacokinetics. Pharmacists may be well-situated to discuss these types of PGx test results with patients—potentially in a similar fashion to the way drug-drug interactions are monitored and managed, even in retail pharmacy settings. Pharmacists will, however, face the same time and experience limitations that physicians face. DTC marketing of PGx tests could also create additional complexity and challenges for the clinical community and its role in the provision and interpretation of PGx test results.

In summary, physicians are the most likely health care professionals to provide patients with the interpretation of PGx test results, although pharmacists and genetic counselors will also likely play a role. In instances where FDA-approved labeling does not provide clear guidance, the development of evidence-based guidelines for the use and interpretation of PGx tests results could be very helpful, and efforts are now being undertaken in this area by the CDC and other organizations. Direct marketing of PGx tests to patients, and accessibility of the tests, could lead patients to bring test results to physicians, which could be counterproductive, especially if the tests actually have poor predictive power.

III-2. Informed consent for tests:
Should informed consent for PGx testing differ from other types of clinical testing (e.g., non-genetic)?
Because gene variants may have more than one effect or manifestation among patients, some of the gene variants tested in PGx tests will hold clues not only to drug response but also to disease or disease severity. This is not necessarily dissimilar from other diagnoses that can have secondary implications or even stigma attached. Laboratory-based tests used in the clinical setting typically are not preceded by a formal informed consent, although arguably implicit consent is present. That said, more comprehensive and documented consent processes are increasingly incorporated into genetic testing and other complex diagnostic procedures. The question of whether PGx tests will be treated more like a cholesterol test or more like a test for the breast cancer
risk gene BRCA 1&2 is critical. The answer will depend in part on whether the risk prediction of PGx testing is similar to that of currently available non-genetic laboratory tests with similar ease of interpretation. Informed consent procedures will be clarified as more PGx tests are in use. Tests that reveal additional potentially life-altering genetic information may be handled by genetic counselors (their traditional expertise) and include an involved informed consent process, while others will be treated as traditional diagnostic tests, handled by physicians, with verbal, rather than written informed consent.

Complicating the question of informed consent is its somewhat unsettled status in medicine, society, and law, especially in the United States. Over the past several decades, the United States has become increasingly devoted to the concept of individual rights. In the broad societal context, this is evidenced by our dedication to civil and political rights. In the medical context, the long-standing dominance of the health care provider in medical decision-making is being progressively offset by an increasing role for patients and dedication to individual autonomy. Indeed, the strong DTC marketing movement is a testament to the power of the patient in health care decision-making.

In law, this changing power equation has produced an unsettled landscape with respect to informed consent standards of liability. In case law, inadequate informed consent as a theory for malpractice liability was not fully enunciated until 1957. Initially, the standard of care with respect to informed consent was a professional, physician-based standard. But in 1972, the landmark case of Canterbury v. Spence ushered in a new approach: The jury is instructed to consider disclosure from the perspective of what a reasonable patient would have wanted to know. Currently, about half of the jurisdictions recognize the professional-based standard, while the other half use a patient-based standard. Further complicating the concept of informed consent liability is the trend to expand the scope of the duty to disclose. Several jurisdictions have found that a provider’s success rate and level of expertise in the contemplated intervention should be disclosed to the patient.

In the case of PGx, the standard of care with respect to informed consent will be critical in determining what will need to be disclosed to patients using the products and services. At a minimum, providers will be required to be sufficiently well-versed in the science to conform to the professional standard of care. This may make it difficult for primary care physicians to adopt PGx products and services. The half of the jurisdictions that use a liability standard based on patient perspective may demand a greater burden of disclosure in informed consent. Moreover, the trend toward more disclosure under both standards will likely continue and further enhance the scope of disclosure.

In summary, the question of specific informed consent for PGx tests is still unresolved because there have been so few examples. It is further complicated by the unsettled nature of informed consent in medicine, law, and policy. Indirect regulation of medical practice and the standard of care with respect to informed consent and negligence through tort law occurs at the state level and are thus likely to be piece-meal and subject to variation across the states.

III-3. Physician liability:
Will doctors incur liability due to the availability of PGx tests?

It is the physician’s duty to prescribe drugs competently according to known safety and efficacy information and to warn patients about any risks involved with them. Therefore, deviations from either of these duties can result in a malpractice lawsuit for the prescribing physician. Liability for inadequate informed consent has been discussed above, but increased liability exposure may also accrue on the basis of negligent administration of the PGx tests and services.

“Tests that reveal additional potentially life-altering genetic information may be handled by genetic counselors ... and include an involved informed consent process, while others will be treated as traditional diagnostic tests, handled by physicians, with verbal rather than written informed consent.”
Any time that additional or new risk information is included in a drug label, there will be an increase in liability for those charged with dispensing the drug in question.

Providers are expected to be knowledgeable about the indications and contraindications associated with the care that they provide. Future cases involving PGx tests and services are likely to conform to case law involving failure to account for drug-drug interactions, which are clearly listed in the product label.

Unlike informed consent liability, the standard for medical negligence liability is relatively stable and uniform. The standard requires the provider to deliver care consistent with that of a reasonably prudent practitioner, taking into account circumstances and resources. Assuming that a PGx test is available and detailed in a drug label, the physician will have a duty to take that information into consideration when determining the planned care. When a PGx test is available but not included in the drug label (or necessarily validated), the situation is less clear.

In summary, physicians could in theory incur increased liability exposure with the increasing inclusion of PGx information in the product label, though more precise targeting might allow for more carefully honed therapy decisions and result in a net reduction of the number of lawsuits in practice. At this early stage, assessment of overall liability burden is speculative.

**IV. PAYMENT POLICIES FOR PHARMACOGENOMIC TESTS AND PGx-TARGETED DRUGS**

**IV-1. Test and provider reimbursement:**

*How will PGx tests be reimbursed? How will providers who prescribe and interpret the tests be paid?*

Currently, no new, special provisions have been proposed for the reimbursement of PGx tests for either clinical laboratories or physicians. This is testimony to the fact that PGx and other biomarkers are simply new pieces of the diagnostic puzzle. They provide new information and generate resource costs just like other tests.

Payers could be expected to apply the current paradigm that is used for diagnostic tests in general. New tests would be “cross-walked,” or matched, to existing diagnostic tests and test procedures based on perceived technical similarity in terms of level of effort and complexity. This kind of reimbursement is inherently a “cost-based” system rather than a “value-based” one — i.e., new tests are not necessarily reimbursed based on the value they bring to patients. To be sure, diagnostic manufacturers may be able to develop and produce some PGx tests that are commercially successful — when long-run marginal cost is less than the expected payment level under the current system. But if the reimbursement model for PGx follows the diagnostic test model, the incentives for developing a stand-alone PGx test may be relatively weak. Generating the scientific and clinical evidence necessary to validate new PGx tests could be expensive due to the generally greater difficulty in identifying and validating PGx markers. Without payments and reimbursement closer to the incremental value generated, the rewards and hence incentives for PGx test development may be muted. Of course, this is true for any new diagnostic test.

The ability to capture greater value on a sustained basis not only depends on clinical performance, but will also be a function of relevant regulatory processes and intellectual property protection, which are needed to deter entry by follow-on competitors. Genomic Health’s Oncotype DX™ test for predicting breast cancer recurrence risk represents an important early example of a “home-brew” diagnostic launch accompanied by a value-based, cost-effectiveness argument to support reimbursement. But the regulatory environment for home-brews may change, as reflected in the recent (September 2006) draft FDA guidance on “In Vitro Diagnostic Multivariate Index Assays.” And some diagnostics manufacturers may choose to market some tests directly to consumers to avoid the costly and difficult process of clinically validating the PGx test as well as to obtain higher reimbursement than payers are willing to give.

The focus on market size as one of the key determinants of drug revenues causes potential competition between drug developers and PGx test developers. PGx tests developed for a drug already on the market will segment that market, and could create disincentives for a drug manufacturer in
the absence of flexible, value-based reimbursement. As a result, prospects for tests developed in tandem with drugs seem to be more promising. If companies can align and synchronize the drug development timeline with the diagnostic development timeline, PGx tests could be developed in parallel with drugs. But this requires solid evidence before Phase II trials that the PGx biomarker is predictive, so that it can be validated in phases II and III.

Academic center researchers often operate at the cutting edge of the basic science, and they can help identify potential PGx test and response correlations. But these associations are not necessarily causal, and they need to be validated in clinical studies. The diagnostics and pharmaceutical industries will play a critical role in translating this new knowledge into clinical applications. The current reimbursement system for diagnostics diminishes the incentive to discover and develop these applications from the point of view of the diagnostic manufacturer. The drug manufacturer would be in a better position to develop value from a co-developed PGx-based diagnostic-drug combination, but development costs could be increased to develop and validate the PGx marker.

With regard to provider payment and reimbursement, the current fee-for-service coding system could easily accommodate these tests, as their reimbursement level is based more on time spent, location, and specialty for “cognitive” services.

In summary, payers are likely to try to apply existing reimbursement frameworks to reimburse PGx tests. As these are not set up to reward highly innovative tests with greater reimbursement, this may not provide additional economic incentive to develop PGx tests. Some test developers may understandably attempt to utilize home-brew status and stronger intellectual property protection to capture greater value. Drug manufacturers have some potential to capture the additional value created by co-developed diagnostic-drug products, though the utility of this strategy will depend in good part on the technical feasibility of parallel development.

IV-2. Reimbursement for PGx-targeted drugs:
Will reimbursement for PGx drugs be restricted based on PGx test results? What evidence will be needed to establish coverage? Will cost-effectiveness be a criterion?
Currently, insurers can specify the conditions under which reimbursement is provided for new drugs. These conditions can include proof that a patient has a specific disease, which may be based on the results of one or more diagnostic tests. The general standard of “reasonable and necessary” care is often applied so physicians can follow general community norms of care, which affords them some flexibility. Payers often put restrictions on the coverage of certain medications, through either tiered co-pay systems, restricted formularies, or “prior authorization” requirements (e.g., the patients must have a certain diagnosis or have tried another drug first). If a PGx test were highly predictive—if patients who test “negative” have not been shown to benefit—the implementation of prior authorization requirements would be likely, particularly for expensive drugs. But when the results of PGx tests are less clear, as is often the case, it may be difficult for payers to place restrictions based on the test.

Whether this PGx-testing is likely to be mandatory or only recommended will depend, among other factors, on the disease or disorder in question. If the purpose of PGx testing is to reduce adverse events, then it may be required as a pre-condition for treatment with a specific drug, as part of a risk management plan. Conversely, if the purpose of a PGx test is to predict efficacy, the necessity of the testing will vary by geography or by institution, due to varying community standards.
New PGx tests for targeting already-marketed drugs could greatly reduce drug revenues, particularly if the target is some subgroup of responders (rather than just eliminating a small subset at risk for adverse events). As discussed above, this can raise average cost-effectiveness of the treated population and, by raising the average value of the therapy, justify a higher price on economic grounds. Payers may be reluctant to provide greater reimbursement based on this greater value, however. If PGx tests can be developed to accompany drug launch, drug manufacturers will be in a better position to justify higher prices in a subgroup when they enter the market and make their initial value arguments.

Several ethics papers have cited concerns about restrictions on the use of PGx-based drugs because of cost-effectiveness. This is not an issue unique to PGx. The primary concern is that restricting access to a linked PGx diagnostic and drug based on cost-effectiveness would amount to a kind of “genetic discrimination.” This might raise unique issues if patients’ reaction to denial of coverage based on their genetics, rather than, say, cholesterol level, is very different. But if the PGx tests are validated and contained either in the label or as part of the standard of practice, it is difficult to see why payers would have a problem enforcing the denial.

Cost-effectiveness is just one of several criteria that most public and private payers consider in making coverage and reimbursement decisions. The most often used criteria are drug safety, efficacy, and direct drug price; others include potential for misuse, liability, and equity. At best, in the United States, cost-effectiveness is an implicit criterion applied in a non-standard way. Indeed, cost-effectiveness standards and criteria are currently in their infancy. Thus, the use of cost-effectiveness to guide reimbursement of PGx drugs is less likely because most payers do not use cost-effectiveness as an explicit criterion in general.

New PGx tests could also raise important questions for formulary design and drug choice, not just for payment. For example, how will payers incorporate PGx information into policies designed to drive utilization patterns (e.g., tiered co-pays)? These issues have received very limited attention, but it is clear that payers may increasingly attempt to encourage or limit utilization to patients in PGx-defined subgroups. What are some possible ways forward that meet payer needs for cost containment and physician/patient need for PGx-informed choices?

“In New PGx tests could also raise important questions for formulary design and drug choice, not just for payment.”

In summary, payment and coverage policies for PGx-targeted drugs are likely to be similar to those of other drugs in which prescriptions are related to diagnostic tests, such as in cholesterol measurement. Reimbursement for PGx drugs will not likely be restricted based upon cost-effectiveness alone but also upon efficacy and safety issues. Furthermore, as payers would reasonably expect patients to have tests measuring their lipid levels before being prescribed cholesterol-lowering drugs, they would expect them to have a PGx test before being prescribed drugs whose performance depends on their genetic makeup.

V. PATIENT- AND SOCIETAL-LEVEL IMPACTS OF PHARMACOGENOMIC TESTS AND DRUGS

V-1. Clinical trial informed consent:
Should PGx research study subjects whose DNA has been stored and used during a study be informed about clinically relevant findings arising from or after the study?

Patients or subjects participating in clinical trials are required to provide their informed consent, indicating that they understand the potential risks of the study as well as its potential benefits. This requirement is not unique to PGx. It has become increasingly common in clinical studies to store subjects’ tissue or blood for DNA analysis, to address either the study question or future research questions. In the many study repositories, the tissue or blood has been “anonymized” before it has been “banked.” In other words, the samples have been stripped of subject identifiers, and future studies will not be able to link back to the subjects. This fact is critical, given that “biobanked” PGx information may be linked to other health-related genetic information.
One genetic sequence, mutation, or anomaly may have multiple health-related associations—a characteristic called pleitropy. In the case in which a biobank has samples with a subject identifier included in its holdings, additional studies on the materials might require consent from the subject. Typically, the possibility of such downstream studies and the procedure for subsequent consents are laid out in the consent process during the initial subject recruitment.

Overall, the “duty to warn” is driven by whether there is foreseeable harm that can be avoided. This concept of duty to warn of potentially useful genetic information has been litigated in two cases, both of which evolved in the context of medical practice, not research. One case, *Safer v. Pack,* determined that a provider knowing of a genetic danger had a duty to warn the primary patient’s family members. The other case, *Pate v. Threlkel,* concluded that any such duty was discharged with disclosure to the primary patient. The former case was later countermanded by legislative action to limit the duty to disclose only to the patient. Any duty to disclose to affected third parties would likely be further chilled by current privacy regulations under the federal *Health Insurance Portability and Accountability Act* (HIPAA).

“In genetic discrimination is generally thought to be more problematic for genetic testing that predicts disease than for PGx testing because of the stigmatizing nature of diseases such as breast cancer, Huntington’s disease, and Alzheimer’s—which are traumatic, costly, and often debilitating.”

In the context of an anonymized research biobank, a duty to warn would be further muted by the fact that there is no mechanism to contact those at risk of harm and therefore no breach of duty—even if some new and clinically relevant information might be discovered. In the unlikely event that an identifiable tissue were stored with a known gene variant for which current research has shown a validated link with clinically relevant outcomes, the duty to warn would exist only if the researchers have agreed to provide such downstream knowledge to the subject. Current research practice does not usually include such a provision. Indeed, informed consent often specifically states that trial subjects will not be contacted regarding any individual PGx results.

In summary, although one could theorize a duty to warn subjects in PGx studies about new risk information, current federal research regulations governing informed consent and HIPAA-related procedural methods in the collection and storage of study tissues lessen this issue’s potential impact.44

**V-2. Privacy and discrimination:**

**Will the use of PGx tests lead to stigmatization or genetic discrimination in life insurance, health insurance, or employment?**

“Genetic discrimination” is defined as discrimination on the basis of an individual’s genetic information, as opposed to discrimination based on an observable medical condition. While a person may have a genotype that predisposes him or her to a disease or condition, the person may not develop the medical problem for many years, if ever. Genetic discrimination would most likely manifest itself in the realm of life insurance, health insurance, or employment. Currently, several states have passed antidiscrimination laws, and the U.S. Congress has made several attempts to pass genetic privacy and genetic antidiscrimination laws.

The primary reason that genetic discrimination is a “hot” issue is that many people believe it is unfair for individuals to be denied access to insurance or jobs on the basis of something over which they have no control. Genetic discrimination is generally thought to be more problematic for genetic testing that predicts disease than for PGx testing because of the stigmatizing nature of diseases such as breast cancer, Huntington’s disease, and Alzheimer’s—which are traumatic, costly, and often debilitating.

Most legislative efforts to prevent genetic discrimination focus on health insurance and employment. Ironically, there is virtually no evidence of genetic discrimination in the insurance market. This is because the vast majority of health care coverage is not subject to traditional underwriting practices. Moreover, even if it were, genetic science as yet is too speculative and uncertain to meet actuarial standards for reliability.
Some health policy makers have expressed concerns that patients who have genotypes indicating a higher likelihood of adverse events, or requiring more expensive drugs, will be labeled “difficult to treat” and have difficulty obtaining health insurance or employment because of fears of additional costs to an employer-based health plan. But there is only limited anecdotal evidence of instances of genetic discrimination and no case law to speak of.

In theory, genetic discrimination is more problematic for life insurance than for health insurance because it commonly uses probabilistic, actuarial information at a more individual level; health insurance, in contrast, is typically provided at the group level. Both life and health insurers have some incentive to base coverage decisions on genetic test data insofar as these data provide reliable information about future risk. In the health insurance market, this incentive is countered by the volatility of the market and the beneficiary tendency to frequently reevaluate health plans substitutes. Private health plans generally have annual open enrollment periods with the set of offered plans changing each year in terms of premiums and covered services.

From the insurance perspective, there is a concern about adverse selection: when insurers are not allowed access to genetic risk information but individuals who are at high risk purchase more insurance, based on their knowledge of personal genetic risk. This is a particularly viable concern in the life insurance context, which does not exhibit the same volatility as health plan coverage. Because the traditional model of life insurance is based upon accurate risk assessment and knowledge equality, this knowledge asymmetry could erode the insurance model.

Currently, the fears of genetic discrimination appear to be overemphasized, and the risks related to PGx are likely to be even further attenuated. Once PGx tests are more common, it is still unlikely that PGx information would be used in determining eligibility for health insurance. This is not only because it is unclear whether a patient would ever need to use the drug indicated in the PGx test, but also because the nature of genetic information is probabilistic, not deterministic. Even if the patient used the drug, the event predicted by the PGx test may not occur.

In summary, genetic discrimination is a hot topic and a concern for the public. But given the prevalence of the group health insurance model, the relative lack of PGx applications, and the absence of case law to date, this issue is a function more of fear than of reality at this time.

V-3. Ownership:
Who owns genetic information — patients, PGx test developers, drug developers, family members, or others?

The issue of ownership of genetic information has persisted for many years with no clear resolution. Genetic information is at once very personal and at the same time shared with one’s family, and to a larger degree, with all of humanity.

It is useful to distinguish between genetic information that is applicable and useful across many people and an individual’s unique DNA sequence. Through a patent, individuals or companies can obtain intellectual property rights (“ownership”) for the use of a specific gene in a specific application. A patent is a time-limited right given to an inventor to exclude others from using, making, or selling an invention. To be patentable, the “invention” must be novel, non-obvious, and useful. In patenting genes, the novelty requirement can be fulfilled by the DNA by being “purified” or isolated away from the cell. The non-obvious condition can be met through the need to invent and use complex methods to derive and isolate the DNA sequence. Finally, the useful condition can be met through showing a specific, substantial, and credible utility. In the past, the usefulness requirement could be fulfilled by simply showing that the gene can be used as a probe to find other genes. But the criteria for showing usefulness in the context of gene patents have become increasingly more stringent. The key case regarded as opening the door to patenting human genes was Diamond v. Chakrabarty in 1980, in which the U.S. Supreme Court held that living matter, in this case genetically engineered bacteria, could be patented. Since that time, more than 2,000 gene patents have been issued. This growing stringency is in part a reaction to issues that have arisen in relation to these early patents.

In summary, ownership of genetic information will likely follow two seemingly independent paths. On one side,
genetic information found as part of the clinical experience for patients will fall under increasingly strict privacy rules exemplified by the recent push toward medical privacy and anti-genetic discrimination legislation. On the other side, researchers and commercial entities will continue patenting genes and DNA discovered experimentally, and will thereby obtain the protection offered through the intellectual property system. The definition of credible utility will certainly be subject to interpretation and may well evolve in the course of litigation and debate.

V-4. Public knowledge:

Is the public knowledge of PGx adequate?

Public understanding of PGx and its relevance to health is an important issue, particularly because genetic testing is available directly to consumers. It is not likely that most individuals are familiar with the details or limitations of PGx, but it is likely they have heard of “designer” and “genetic” drugs from exposure in the lay media.\textsuperscript{50,51}

The public does seem to have considerable interest in genetics and some interest in PGx, mostly through the media-generated concept of “designer” drugs. For example, a focus group of Americans indicated that if cost, privacy, and discrimination problems were solved, PGx-based prescriptions are preferable to raced-based prescriptions.\textsuperscript{52} Furthermore, a citizen’s focus group in Iceland indicated concerns about the cost of drugs developed using PGx and the implications for health care inequalities.\textsuperscript{53}

These concerns may be influenced by the concept of genetic determinism. A perception that a PGx test provides definitive information could lead patients to stop or modify their drug regimens inappropriately. Alternatively, patients may perceive themselves as candidates for drug regimens based upon their genetic profile, when, in fact, use of the drugs may be contraindicated for non-genetic factors. Although efforts such as CDC’s EGAPP\textsuperscript{54} process are under way, public education programs will become increasingly important.

In summary, knowledge levels about PGx in the general public remain low in part because PGx tests are rarely used in clinical practice. There is some awareness about the field in general. The need to inform the public will rise in parallel with the development and clinical application of additional PGx drugs.

V-5. Global health inequalities:

Will PGx-based drug development focus on genotypes that are most common in populations able to afford medications? Will this exacerbate global health inequalities?

Given global inequality in the distribution of income and wealth, investment in PGx research will continue to focus on genetic variation that is relatively common in the United States and other developed countries.\textsuperscript{57} This could well exacerbate existing health disparities, despite providing new knowledge and medicines for future populations. Several mechanisms may address this issue.

Many in the developed and developing worlds are working together to address the health consequences of the unequal global distribution of wealth and access to medical care and technology. Governments and private philanthropies are funding public and private research to address the diseases of the developing world, such as malaria and tuberculosis. These often cutting-edge efforts apply the latest in scientific knowledge, including genetics. New PGx knowledge might well help generate improved treatments or cures for some developing world diseases. The challenge is to help translate this knowledge and make it affordable for the less fortunate.

Issues of wealth inequality and unequal access to health care are not fundamentally about genetics or PGx. But to the extent PGx-based drugs and tests might receive higher per unit prices because they are able to identify responders effectively, this raises the access barrier a bit higher for anyone who must pay out-of-pocket.\textsuperscript{55,56} On the other hand, drugs and tests are commonly priced differentially around the world, based in part on ability to pay. Global poverty and inequality are issues that must be addressed to provide access to the fruits of our new knowledge.

In summary, although the initial applications of PGx are likely to focus on diseases of the developed world, recent
basic research efforts to address diseases of the developing world are attempting to use all the latest tools of genetics and PGx. Thus, over the longer term, the developing world should benefit in absolute, if not relative, terms from growing knowledge of genetics, PGx, and related fields of biology. The nature of the impact will depend on our ability to address the broader economic issue of poverty.

Section Notes and References

12. Specific requirements on content and format of labeling for human prescription drugs, 21 CFR 201.57.
42. Safar v. Estate of Pudl (New Jersey Supreme Court 1996).
43. Part v. Theliddle, 661 Sn 2d 278 (Fla. 1995).
STAKEHOLDER PERSPECTIVES AND ISSUES
SECTION 5.
STAKEHOLDER PERSPECTIVES AND ISSUES

To understand the nature and pace of our new knowledge about genetics, and its potential impact on the U.S. health care system, it is essential to characterize the perspectives and interests of key U.S. stakeholders. This report focuses on the nature and quality of the science and research, but we also review stakeholder initiatives and responses because they will influence the development, scope, and use of this new information.

This report does not attempt a comprehensive explanation or prediction of how the interests and actions of the numerous stakeholders will play out. Rather, this section enumerates the important PGx-related issues for key stakeholders, as an overview and starting point for those who wish to delve more deeply into the stakeholder concerns. This listing reveals the complexity of the policy environment in which the science of genetics and PGx will operate in the coming decades.

We begin with a few general observations about some key cross-cutting issues and challenges that PGx is likely to pose for stakeholders.

We all care most about how this new scientific information will affect patients and their health. Citizens—a large group with competing interests—are often the least effective stakeholders in terms of promoting their legislative and regulatory interests. Specific, disease-related patient groups can be far more effective. As interest groups, stakeholders are generally most concerned with protecting the benefits they receive, including incomes and long-term viability. New information and knowledge can be seen as both a threat and an opportunity to those interests.

In Section 3, the most likely future scenario projects a modest but continuing expansion of PGx clinical applications over the next couple of decades. Under such a gradual process, stakeholders would have some time to address this impact on the health care system. But for those who would support a more rapid expansion of PGx-related applications, there are several key challenges that must be met in the near term:

- Greater federal research support for continuing basic research on genetics, biomarkers, and molecular medicine would be needed to support an acceleration of current trends.
- Given new basic knowledge, both private and public sector resources would be needed to validate and translate gene-phenotype associations into clinical applications. For example, public-private sector partnerships may be necessary to conduct the large genetic epidemiology studies needed to validate and test gene-disease-outcome associations.
- Payers must provide strong signals that they will adequately reward both diagnostics and therapeutic innovation. For example, they are increasingly requesting evidence-based dossiers to support applications for drug coverage. Similar trends are likely to affect targeted drugs and their companion diagnostics. If payers don’t reward innovation with appropriate payments, the incentives to develop the evidence base would be hindered.
- Regulators must strike the right balance in setting standards that are achievable without being burdensome.
- Pharmaceutical and diagnostic companies must confront business integration issues related to PGx- and biomarker-based targeted therapies, or “personalized medicine.”
- The lack of general literacy in genetics among providers and consumers may slow the adoption of new PGx-based technologies.

With this backdrop, what are some of the more specific and relevant stakeholder issues and needs?

Table 5-1 lists the stakeholders in the order reviewed in this section and some useful Web links to selected organizations that either represent the sector or provide educational materials about it.
In this section, we review the issues from the perspectives of the following 15 stakeholder groups or sectors:

1. Pharmaceutical manufacturers
2. Biotechnology manufacturers
3. Diagnostics manufacturers
4. Clinical laboratories
5. Providers—traditional genetic services
6. Providers—physicians
7. Hospitals
8. Providers—pharmacists
9. Purchasers—employers and groups
10. Public payers
11. Private payers
12. Patients and consumers
13. Public financiers of research
14. Academic health centers
15. Regulatory policymakers

We list the key issues that PGx presents for each stakeholder and highlight critical issues that we believe represent a major, if not the major, challenge for them.
<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Key Organizations</th>
<th>Web Links</th>
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<td>Biotechnology manufacturers</td>
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<td></td>
<td>American College of Medical Genetics</td>
<td><a href="http://www.acmg.net">www.acmg.net</a></td>
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5.1 Pharmaceutical Manufacturers

Scientific knowledge of biological processes is the foundation for the innovative research and development processes of pharmaceutical manufacturers. As one of the most promising areas of genomics science, PGx raises a number of scientific and commercial challenges and opportunities for them.

Today, little in the operating environment for the pharmaceutical sector is stable. Consolidation and acquisition activity is increasing, mostly to fill developmental pipelines, and the regulatory environment is under pressure because of issues of drug safety and industry productivity. Moreover, revenue sources, both public through infrastructure and research and private through patient revenue and risk capital investment, are volatile as to level and mix. For these and other reasons, systemic and institutional change are increasingly likely.

Specific PGx-related issues:

- The ultimate impact of PGx on pharmaceutical R&D—including the likelihood of success, the costs of drug development and the time to market—is unknown.

- The pharmaceutical industry generally has used a high risk/high reward “blockbuster” model of financing that may not foster PGx development because a likely impact of PGx applications will be to reduce the scale of markets.

- PGx is cutting-edge basic research, and, as such, a good deal of its progress will be achieved based on support for government-sponsored academic research. But the long-term impact of this basic research will have a great deal to do with how effectively the pharmaceutical industry is able to leverage its comparative advantage at translational research and development.

- Though barely measurable today, an increased use of PGx to determine the scope of prescription drug markets could create incentives for drug companies either to build internal diagnostic capability or to partner with diagnostic developers.

- The pharmaceutical (and diagnostic) industry may need to engage payers, regulators, and policymakers to advocate for and encourage payment policies that adequately reward the development of PGx-based therapies.

PGx may represent a great opportunity for the pharmaceutical industry, despite slow progress to date. But because of its potentially disruptive character as a business model, its integration poses other challenges. A critical issue for pharmaceutical companies is how to incorporate PGx into existing drug discovery and development processes while aligning with future marketing and strategic positioning models.

5.2 Biotechnology Manufacturers

Not surprisingly, biotechnology manufacturers of new drugs face many of the same challenges as the pharmaceutical industry. Indeed, the line between the pharmaceutical and biotechnology sectors continues to blur as many of the largest pharmaceutical companies develop and market biologics, engage in market-related partnering, and, in some cases, acquire biotech assets and companies. But given that many biotech developers are smaller and frequently focused on cutting-edge science, companies in this sector are likely to be more aggressive developers of PGx, even though they may lack sufficient scale to explore and exploit most PGx opportunities.

Specific PGx-related issues:

- The emerging complexity of genomics science and the slow pace of progress make access to capital a constant and critical challenge.

- Biotechnology companies, often lacking depth in both human and capital resources, are more affected by inconsistent and restrictive science policy—for example, as to stem cell research—and budgetary constraints for publicly funded research.

- Uncertainties in the regulatory environment and the lack of consistent administrative and assessment processes used by payers also represent potential barriers to the growing use of PGx in biotechnology.

A critical PGx issue for the biotech industry is how to translate new developments in the emerging science of genomics and PGx into existing development and commercial models rapidly enough to ensure a steady flow of risk capital.
5.3 Diagnostics (Dx) Manufacturers

This sector is likely to undergo substantial change as diagnostics takes a more central place in the future of our medical care system. Some argue that the completion of the sequencing of the human genome has brought a much greater focus on Dx discovery, though evidence of this impact is lacking as yet. On the policy and regulatory fronts, the emerging interest in the use of these biomarkers to measure the effects of therapy throughout the course of treatment will add value to the sector. Despite these opportunities, reimbursement rates remain low, and assessment processes are uneven and inconsistent. Moreover, the Dx industry is not yet well-equipped — or at least incentivized — to address the challenge of evidence-based clinical practice.

Specific PGx-related issues:

- To date, despite significant promise, there are very few examples of PGx-based diagnostics with demonstrated clinical utility. Developers often face skeptical payer and provider communities that are wary of PGx “hype.”

- Dx developers generally have not invested substantially in the resources and infrastructure needed to support the evidence-based technology assessment models now being taken up by many payers, especially in light of concerns about the “added value” of genetic testing and the lack of resources for counseling and interpretation. Payer requirements for coverage decisions are variable and still not well-defined.

- Payers will continue to be reluctant to support predictive and susceptibility testing, though such services may become more available to consumers as the use of a consumer-directed health insurance model provides consumers with subsidies to purchase these services.

- Gene patents provide a critical incentive for innovation, but difficulties in licensing them may be a significant barrier to the development of multigenic prediction tools.

A critical PGx issue for diagnostic manufacturers is uncertainty about regulatory reform, payer requirements for evidence of value, and the limits on payment levels in relation to those requirements.

5.4 Clinical Laboratories

The regulatory environment of the clinical laboratory business may be changed indirectly over the next few years if ongoing reviews of the U.S. drug safety system lead to broader reforms. That said, PGx testing will generate more transactions overall, and so it is likely to be favorable for this sector. Consumer markets also offer opportunities for PGx testing. Clinical labs operate in a complex environment, with both independent and hospital-based competitors, and they are often viewed as commodity producers with less political and economic leverage than stakeholders in larger sectors such as the pharmaceutical and hospital supply industries.

Specific PGx-related issues:

- Clinical laboratory companies face substantial uncertainty as to future regulation and payment environments. They often have little leverage on pricing, and hence are dependent on payer responses to new technologies such as PGx.

- The fragmentation of this sector and rising demand for tests may create conditions for sector consolidation through mergers and acquisitions.

- As payers continue to expand use of consumer-directed health products, direct consumer demand for PGx tests is likely to increase, creating new opportunities to develop and market these types of products.
A critical PGx issue for clinical laboratories is how to meet payer demands for evidence (directly, or through a marketing partner) without the infrastructure to produce it and with reimbursement levels that are insufficient to support infrastructure costs.

5.5 Providers of Traditional Genetic Services

Professional status and reimbursement issues are chief concerns for this stakeholder sector. These professions, including genetic counselors, medical geneticists, nurse geneticists, and laboratory technicians, have delivered medical care services in relative obscurity for years. But with a greater integration of genetic services into mainstream medical care, the roles and accountabilities of these providers will necessarily change. These providers are more likely to have a role in genetic disease testing than in routine PGx tests, which will be handled by physicians.

Specific PGx-related issues:

- The field includes three general limitations that must be overcome: the historic focus on Mendelian conditions; lack of health care system knowledge; and inconsistent reimbursement experience.

- Securing a broader, more important role in our health care delivery system is compromised by the low numbers of these providers, their limited training in complex disease protocols, and the lack of independent status as health care providers for many of them.

- Ensuring the utility of these providers’ special knowledge and experience will be challenged if and when genetics moves into mainstream medical practice.

Critical PGx issues for genetics providers are professionalism and marketplace recognition. More and better-educated health care personnel will be required, especially in addressing the genetics of complex diseases. Of central concern is the control of both education and practice and required levels of training.

5.6 Providers—Physicians

For most physicians (excluding the small numbers of medical geneticists and most genetic counselors), the questions about PGx are primarily practical.

Specific PGx-related issues:

- Most clinicians lack an in-depth knowledge of genetics, and the majority lack what could be called even basic “genetic literacy.” This is understandable, given the limited volume of patients presenting with genetic conditions or with conditions that can be treated with PGx interventions.

- Despite the expected growing demand for genetic services, many continuing education curricula and graduate health professional training programs have been very slow to adopt genetics.

- Additional practice challenges include lack of supporting information technology and uncertainties about reimbursement related to PGx services.

Given the gradual emergence of PGx applications, critical PGx questions for clinicians are: (a) What is available today for patients; (b) What is in the pipeline; (c) How soon should clinicians learn about developments; (d) How do they learn more about them; and (e) Who is going to pay for them?

5.7 Providers—Hospitals

Of all health care system stakeholders, hospitals must adopt the most strategic, long-term perspective because of the need for long-term planning for facilities, institutional information technology, and human resources. Long-term planning in these areas could eventually be significantly
affected by genomics medicine, though this may take many years, especially since most drugs that might be affected would be prescription outpatient drugs.

Specific PGx-related issues:

• Telemedicine development and facilities planning are major opportunities, but long-term planning remains at issue, particularly if, as expected, genetics practice skews more toward outpatient services. Further, changes in modes of clinical practice, including the increasing use of PGx-related specialty drugs, would have to be accommodated.

• The uneven evolution of PGx creates substantial positioning challenges, partly because expanding use of genetic diagnostics is likely to arrive ahead of needed institutional and information technology infrastructure.

• Hospitals also face significant marketing challenges. Because genetic medicine is ultimately “subgroup” medicine, hospitals must plan ahead for changing patient and treatment profiles, more consumer engagement, and the concomitant opportunities that may lie with segmented markets.

• Children’s hospitals, having provided genetic services for decades, are in a special category. They face unique challenges in terms of leveraging existing genetic-testing expertise (particularly in lab work), uncertainties about the response of community hospitals, and the competitive challenge of specialty hospitals.

Hospitals, in general, face the challenges of long-term strategic capital planning for genetic services, in terms of both facilities and processes, all in a time of changing revenue mix from private to public and consumer sources.

5.8 Providers—Pharmacists

As the use of PGx eventually expands, greater demands will be placed on pharmacists for patient and consumer information and for assistance in patient decision-making for complex choices about both testing and therapy. At this early stage, it is not clear how often a PGx-based prescription will require special pharmacist monitoring or counseling; it could be rare. Critical issues here are access to decision-support information technology and the need for patient/consumer education and counseling tools. Electronic medical record (EMR) products will partly meet this need, but the use of EMRs is still very limited. Who, then, will provide these services and who will pay for them?

Specific PGx-related issues:

• There will be new needs for professional training on PGx. Although pharmacists are probably better trained in PGx than are physicians, they would need additional training as new applications are approved. As they do with drugs, pharmacists would be expected to do more patient education.

• There is a clear need for expanded information technology for efficient decision support for pharmacists, as well as consumers.

• Pharmacists face the perpetual challenge of securing adequate reimbursement and payment for patient and consumer education.

A critical challenge of emerging PGx for pharmacists will be meeting the information needs of consumers and securing remuneration for the additional, complex clinical services they would provide.

5.9 Purchasers—Employers and Groups

Purchasers — mostly private employers, including self-insured companies with administrative services only (ASO) accounts — and purchasing groups will in most cases defer to clinical and payer expertise on PGx. Most employers, and especially the small to mid-size firms, do not have sufficient knowledge about health care services in general, much less about genetics and PGx. As a result, purchasers as a group are unlikely to influence the market for PGx to any significant degree. Nonetheless, they could indirectly have a major, negative impact if national income growth or their market growth deteriorates to the point that they take an even harder look at new, cost-increasing innovation.
Specific PGx-related issues:
- Pharmacy benefit managers and benefits consultants must be committed to promoting the use of PGx when it is cost-effective and particularly when savings are achievable.
- Many employers may be wondering if genetics literacy for employees could be important because genetic information will affect their work lives beyond health care—touching on issues including fears of job discrimination, disabilities, worker safety, and toxic exposures.

A critical issue for purchasers is to manage the cost-effective use of PGx in drug therapy by effectively managing payer, provider, and advisory relationships.

5.10 Public Payers

The positions that CMS and state governments take on PGx will, of course, have an important impact on PGx development. The likelihood that these agencies will move swiftly and decisively, even if substantial marketplace demand exists, is compromised by ongoing federal-state conflict, prevailing demands on resources for existing programs (particularly Medicare Part D), and heightened demands for engagement on health care and regulatory reform initiatives.

Specific PGx-related issues:
- It will be important to determine the proper role of government in providing leadership to the health system on coverage policies for genetic services and PGx.
- Government’s position on developing and establishing protocols for payment based on evidence will be influential in encouraging the appropriate use of new technologies, but may also negatively impact their development, if evidentiary requirements are set too high.
- Improved collaboration between regulatory and research agencies is needed to ensure optimal translation of research into practice.
- Government will play a prominent role in encouraging the wider use of information technology, including EMR, to improve health care efficiency.
- Government support for basic science research plays an essential role in the production of new knowledge.

A critical issue facing public payers is facilitating the appropriate adoption of PGx into routine practice through health care policy and financing decisions, despite increasing pressure on financing.

5.11 Private Payers

Decisions made in the private sector will have an important influence on the evolution of PGx over the next 5 to 10 years. Their decisions may be even more influential than those of public payers. This is due partly to the differing nature of criteria for coverage (especially cost-effectiveness), partly to the demographics of covered populations, and finally to the fact that private payers have been given significant incentives to enroll Medicare beneficiaries in Part D and Medicare Advantage. At the same time, private payers face great challenges: They are under considerable pressure to contain costs; they have dissatisfied consumers, and; they are viewed poorly by the public. The uneven roll-out of Part D has not helped the image of either private or public payers.

“Government’s position on developing and establishing protocols for payment based on evidence will be influential in encouraging the appropriate use of new technologies, but may also negatively impact their development, if evidentiary requirements are set too high.”
Payers have been mostly unmoved by the prospects of PGx because a compelling clinical and business case hasn’t been made, or at least a case sufficiently compelling to offer “first mover” advantages. Although payers are still awaiting sufficient evidence to support reimbursement of PGx, there is an emerging interest in reimbursing PGx when favorable clinical utility data are available. Adequate programs to evaluate new services consistently are still largely undeveloped. In other words, payers are caught in a tension between embracing PGx if it can save them from paying for expensive drugs, particularly newer oncology and biotech drugs, and still wanting to remain competitive by providing patients and providers access to the latest innovations.

Specific PGx-related issues:

• Payers must decide whether to include PGx in benefit plans given that the evidentiary base is underdeveloped and that there is a lack of demonstrable consumer and purchaser demand.

• How and when to evaluate PGx diagnostics could affect incentives to develop new PGx-based regimens. Assessment capabilities in this area may expand along the lines of existing pharmacy and therapeutics committees.

• It may be helpful to PGx innovation to develop ways to minimize uncertainty and transaction costs through development of consistent and clear evidentiary standards for coverage and reimbursement based on value added.

• Another incentive to innovation may be to ensure maximization of opportunities for proactive clinical management of PGx, specifically through effective pharmacy benefit management of Medicare Part D.

• Payers must determine whether to include certain genetic and PGx services in their consumer-driven health care products.

5.12 Patients and Consumers

Given the attention given to genetics in the media, including forensic and paternity testing, consumers are generally aware of our ability to identify specific genes. On the other hand, the vast majority of patients are generally unaware of specific PGx applications. Consumers are eager for health care innovation, as evidenced by the increased real levels of spending that we continue to observe. And this will translate to demand for PGx innovations if they can be shown to provide medical benefit, even if small. Indeed, consumers may even use more of their own dollars to purchase PGx products as the role of consumer-directed health insurance products expands.

Specific PGx-related issues:

• The public is ambivalent about the nature of genetic information, particularly about the putative effects of genetic discrimination.11

• Today, patients, their doctors, consumers, and their families lack both reliable information and tools, such as EMRs, to facilitate their integration into consumer purchasing and decision-making.

• It is unclear whether some genetic services, including PGx, will be purchased, or at least sought by consumers through use of consumer-directed health funds.

• Great uncertainties persist about consumer attitudes and perspectives on genetics, in general because these technologies raise many value questions about their use and scope.

A critical PGx issue for patients and consumers is obtaining clear, objective information about PGx tests and their implications.

5.13 Public Financiers of Research

Two traditional and central activities of government in relation to health care are to support basic and applied research on health care and to foster collaboration among government, the private sector, and the research communities to support translational research to improve health care services. Two important examples of this are the NIH investment in
the Human Genome Project and the Pharmacogenomics Research Network. New research includes a massive epidemiological study to provide the genetic information needed to relate genes to health outcomes. The degree to which these programs are focused on PGx, as against other needs, will be a significant factor in the development of these technologies.

Specific PGx-related issues:
- Maintaining focus and consistency becomes more difficult in light of continued deterioration in public financing for research and support, along with fluctuating private financing, especially for early stage biotechnology companies.
- It is unclear whether government, delivery system stakeholders, and researchers have the ability and willingness to collaborate more effectively to encourage PGx innovation and application.
- During the presidential electoral cycle, health care reform initiatives could also impede progress of PGx.

Related critical issues are how strongly and consistently government will provide funds for basic science research, including specifically research into the evidence supporting the use of genetic and PGx applications.

5.14 Academic Health Centers
Academic health research centers rely on both public and private funds to support their basic and applied research activities. Taxpayers provide a substantial share of support, either through federal agencies such as the NIH or through state tax-supported programs. Support from private endowments and student fees are a major element as well.

Currently, 85 percent of NIH’s budget of $28.5 million supports U.S. university-based scientists. But appropriations have not kept pace with inflation since 2003.

Specific PGx-related issues:
- The availability of grants and other resources to support undergraduate and graduate training of the next generation of scientists is an important issue for academic health centers.
- Restrictions on the use of patented research tools might hinder the progress of PGx science.
- Support for translational research is also essential.

A critical issue for academic health centers is how strongly and consistently federal and state governments will provide funds for basic science research on genetics, PGx, and related fields.

5.15 Regulatory Policymakers
The nature and — often more significantly — the consistency of public regulation can either promote or deter sector development and performance. The FDA has established an initiative in genomics, which has generated excellent educational materials. The agency has also recently issued a guidance on Genomic Data Submissions and a draft concept paper on co-development of PGx diagnostics and drugs. This guidance encourages voluntary submissions, but actually designates “known valid biomarkers” on which information should be provided in applicable submissions. It is not clear how much organizational energy and how many resources will continue to support PGx. Reform initiatives focused on both the regulation and financing of health care will occupy policy agendas over the next few years, leaving less room for deliberative action on programs related to PGx.

Specific PGx-related issues:
- It is not clear whether a sufficient focus on PGx issues and needs can be maintained in a politicized policy and electoral environment.
- Pressures could arise related to the federal Orphan Drug Act if the number of drug candidates flowing from R&D that meet statutory criteria substantially increases.
- FDA diagnostics regulations, including policies for home-brew PGx tests, are being reconsidered in light of the potentially significant clinical implications of these new technologies.

A critical PGx issue facing regulators is establishing appropriate evidentiary requirements for the development of PGx diagnostics, as well as for trials that concurrently test PGx-diagnostic validity while determining the efficacy and safety of PGx-targeted therapies.
Section Notes and References

SECTION 6

KEY FINDINGS AND IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY AND PUBLIC POLICY
SECTION 6. KEY FINDINGS AND IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY AND PUBLIC POLICY

6.1 Key Findings

The objectives of this report are to provide a basic background on the science behind PGx, an overview of related policy issues, and an assessment of the likely future. Our review and analysis suggest the following three major findings:

• There are major challenges facing the translation of basic PGx scientific discoveries into clinical care;

• Pharmacogenomics is thus unlikely to produce fundamental changes in our health care system in the near future; and

• Achieving the promise of PGx will require both continued public support for basic science research and epidemiological studies, and effective public-private collaboration to facilitate the translation of pharmacogenomics to the bedside.

Pharmacogenomics and “personalized medicine” do, in general, hold significant promise. Indeed, in a speech at a recent biotechnology meeting, U.S. Secretary of Health and Human Services Michael Leavitt laid out an optimistic vision:

“The next ten years will be seen as a signal point of transition in health care. Medicine will be transformed from an instinctive art of alleviating symptoms to a science of personalized health care. The next decade will be viewed by future generations as the time when treatments became preventive, predictive, and personalized … A decade from now, we will have a health care delivery system in which doctors, pharmacists, and other health care providers customize treatment and management plans for individual patients based on vast amounts of information that is readily accessible at clinics and hospital bedsides—information like medical history, genetic variability, and even patient preferences.”

Notwithstanding this promise, Secretary Leavitt and others believe that the current constellation of public-private research activities operating under existing regulatory and payment incentives is unlikely to produce this profound change in the next decade. Although several current federal initiatives—such as the FDA’s Critical Path Initiative, the NIH Roadmap project, the NIH trans-institute Genes and Environment Initiative, and the American Health Information Community—aim in part to accomplish this goal, significant challenges remain.

These public and private initiatives will encounter two sets of important barriers:

1. The challenge of translational science: Translating knowledge of gene sequences into meaningful pharmacogenomics applications is challenging for a few fundamental scientific reasons:

• As with most common diseases, the effect of genetic variation on drug response generally is a result of complex interactions with multiple genes and non-genetic factors, and hence the genetic markers are often only weakly associated with drug treatment outcomes. As a result, the effect of genetic variation on drug response is often subtle and difficult to detect.

• Our knowledge of the role of genes in specific disease processes is generally in its infancy, with multiple gene correlates but no understanding of the underlying biological mechanism.

• Genetic variants relevant to drug response can be relatively rare in the general population.

Because of these factors, identifying and validating pharmacogenomics associations will continue to be a challenging, costly, and lengthy undertaking.

2. Commercial and policy challenges: Challenging technical, business, and policy-related issues might either hinder progress in the field or potentially accelerate it, depending on how they are addressed and resolved:

• Regulatory pathways have not yet been optimized to encourage the co-development of diagnostics and therapeutics.
Current economic incentives—as reflected in our intellectual property and reimbursement systems for diagnostics and drugs—are generally not structured to reward appropriately and consistently innovative value creation for drugs, diagnostics, and pharmacogenomics-based targeted regimens.

The integration of pharmacogenomic diagnostic development with pharmaceutical development is difficult because of differences in the underlying business and translational science models of the two sectors.

Genomics technologies are perceived to raise ethical, legal, and social issues to such a degree that a special NIH program was established to address them; although specific pharmacogenomic applications may not always involve such issues, this suggests the broad range of stakeholders that will be involved in the public debates.

Stakeholder literacy about pharmacogenomics is limited, and positions on public policy issues are not yet clearly defined.

“Achieving the promise of PGx will require both continued public support for basic science research and epidemiological studies, and effective public-private collaboration to facilitate the translation of pharmacogenomics to the bedside.”

These are significant challenges, but there are also some reasons to be optimistic. This fundamental, new biological knowledge may eventually lead to a profoundly better understanding of many diseases and ultimately to innovative diagnostics and therapeutics. In the nearer term, for example, pharmacogenomics could help to address the industry “productivity problem”—the declining number of new drugs. Many compounds that are safe and effective for many people are not safe and effective for enough people to get FDA approval. With a PGx targeting approach, it may be possible to bring many of these “near-misses” into medical practice, benefiting many patients and the sponsoring companies as well. In the long term, the field of pharmacogenomics may represent the first step in a chain reaction of basic science knowledge—cascading through proteomics, metabolomics, and other biomarkers—that will gradually yield medical breakthroughs. This enthusiasm is warranted, given the potential of this technology, but it must be tempered by acknowledgment of the long path that new technologies must travel before they can be integrated into mainstream medical practice.

In the following section, we address the internal and external implications of these challenges for the pharmaceutical and biotechnology industries, keeping in mind our principal aim of informing those who will participate in future policy discussions.

### 6.2 Implications for the Pharmaceutical Industry

Looking first at the quality of the science and research to date, and weighing the impact of all the other factors bearing on its utility, what are the most significant implications for the pharmaceutical industry regarding public policies and development and commercial strategies? There are research and development, regulation, pricing and reimbursement, marketing, and health policy issues, each of which we discuss below.

#### 6.2.1 Implications for research and development

New knowledge about genes that affect drug targets and drug response in turn affects research and development investments and processes in the pharmaceutical and biotechnology industries. First, in cases such as trastuzumab (Herceptin®) for breast cancer or imatinib (Gleevec®) for CML (chronic myelogenous leukemia), new genetic knowledge played a direct role in definition of the target. Thus, new knowledge can generate new targets. Second, there will be situations in which genetic makeup of the individual or the tumor affects the response (efficacy or safety) to given compounds. CYP2C9 and VKORC1 mutation status for
warfarin and UGT1A1 testing with irinotecan are examples. The second instance differs from the first in that diagnostic PGx testing becomes part of the standard clinical protocol; under these circumstances, both the validity of the test and the efficacy and safety of the drug will be tested to a degree through the co-development process. This can, however, add substantial complexity and cost to the research phase. At this point, it is unclear how the marketplace will evolve, whether along the lines of co-development, joint venturing, separate development, and so forth. But it is likely that payers will require formulary submissions that address test validity and utility in addition to drug efficacy and safety.

The development phase of clinical trials for a new PGx-targeted therapy could also be affected in numerous ways. In some instances, smaller and faster trials may be feasible because the target population would be expected to exhibit higher rates of response. On the other hand, special or additional studies to validate the PGx marker will be needed. And requirements to establish a minimum level of safety dictate some requirements on the duration and size of trials. At this early stage, it is not clear what the net impact of PGx will be on costs and duration of trials during the development phase.

Co-developing a PGx test and a drug is also demanding in that, historically, these organizational processes have been specialized in diagnostic and pharmaceutical companies. The utility of a test has to be likely before its results can be used to define the inclusion or exclusion of patients in a drug trial. Testing both simultaneously—the validity of the PGx predictor and the drug response—adds some risk and complexity to the testing process. The pharmaceutical companies that would conduct these trials would have to deal with challenges of integrating diagnostic test development processes into their clinical development plans. At a minimum, pharmaceutical companies will need to add a systematic review of potential PGx and other biomarkers as part of their due diligence R&D processes. This will require more resources and time, but it is unclear whether the function is specialized enough that companies will need diagnostic experts supporting each product team.

Finally, at this stage of our knowledge of genetics, we are finding many associations or correlations of genes and phenotypes that are spurious in a causal sense. After further studies, these correlations are often not replicated, and no causal role of the gene in disease development or drug response is found. Sorting out these associations and determining which are causal will consume considerable time and resources, often requiring extremely large-scale, prospective epidemiological studies. Substantial federal government support for these kinds of basic research studies would be critical before translational private research activities are viable. The pharmaceutical and biotech industries will be major beneficiaries of this basic research, and they would be wise to participate actively in the public discussion of priorities. In addition, opportunities for public-private collaborations to validate biomarkers should be explored.

6.2.2 Implications for regulation

The leadership at the FDA is clearly engaged with the potential of PGx to improve drug development, addressing the “medical product pipeline problem,” as evidenced by the Critical Path Initiative1,2 and the Genomics Data Submission.3 The latter encourages companies to collect genomics data voluntarily in clinical trials and report this information in new drug application submissions. The latter encourages companies to collect genomics data voluntarily in clinical trials and report this information in new drug application submissions. This guidance also distinguishes between “known valid biomarkers” and those that are probable or less certain. Companies are required to submit data on known valid biomarkers in the relevant disease area.
Under the Critical Path Initiative, the FDA has recently identified 76 opportunities, grouped under six areas:

- Better Evaluation Tools (33)
- Streamlining Clinical Trials (12)
- Harnessing Bioinformatics (8)
- Moving Manufacturing into the 21st Century (13)
- Developing Products to Address Urgent Public Health Needs (5)
- Specific At-Risk Populations (5)

At the top of this list of 76 opportunities is “Biomarker Qualification”:

“The process and criteria for qualifying biomarkers for use in product development should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers.”

This suggests that even regulators recognize the lack of consensus on how to validate biomarkers; at this early stage, industry faces uncertainty about what the requirements will be.

These FDA initiatives indicate that companies will be actively scrutinized from a regulatory perspective for due diligence with respect to biomarker evaluation. At a minimum, companies will need to explain why they have or haven’t included PGx or other biomarkers in their clinical trial development programs. To do this, they will need to address these questions proactively, in the pre-clinical phases of drug development.

A related set of issues concerns FDA regulation of tests. As described in Section 3, there are a few marketed PGx test kits with FDA approval, and a greater number of PGx tests are available as less-regulated home-brews. If the FDA exercises authority to regulate the home-brews, the PGx playing field will change, increasing evidentiary requirements, especially regarding ultimate clinical utility and impact. At the moment, this part of the regulatory environment is uncertain. The pharmaceutical, biotechnology, and diagnostic industries have not taken a unified position on this, and it may not be possible to reach a consensus. Still, it is an opportune time to begin a policy review and discussion.

6.2.3 Implications for marketing and regulation

The FDA regulates the promotion of tests and drugs for which it has approval authority. The availability of companion PGx diagnostics raises the issue of how they will be listed in the label of the corresponding drug. Will a specific manufacturer’s test or a class of tests be mentioned? Will they be required, or will they be listed only as potentially providing additional useful information for clinicians and patients? The latter appears to be the case in the recent label for warfarin. In general, linking a specific PGx biomarker test to use of a drug may raise concerns for pharmaceutical manufacturers. First, having multiple test suppliers could increase competition and lower the price of the test. Second, greater flexibility in drug labeling could encourage improvements in the quality of the test over time. But if a drug manufacturer also owned the companion diagnostic, then the company might want this information in the label, as it would tend to make competitive entry more difficult for both diagnostics and drugs.

“A broader question is how the advent of targeted therapies might affect current marketing practices for widely used drugs, such as detailing through sales representatives and direct-to-consumer advertising. The marketing model for small, orphan, specialty drugs such as Gleevec (reaching fewer than 10,000 patients) for PGx-targeted therapies would be scaled back considerably if not require a fundamentally different approach. This approach would most likely differ as a function of market size (in terms of number of potential patients).
6.2.4 Implications for payment and reimbursement

The payment and reimbursement systems for drugs and diagnostics haven’t fundamentally changed in the recent past, but “high” drug prices in particular are a topic of great interest in the news media and the Congress. The new Medicare Part D drug benefit has provided improved coverage for many beneficiaries, but the “doughnut hole” in coverage will also leave many bearing significant co-pays. Some drug manufacturers have publicly announced their efforts to address these problem areas through medical need programs that reduce costs for those who can’t afford to pay.

“As key stakeholders, the pharmaceutical and biotechnology industries can influence — through a well-informed and scientifically sound public policy position — the speed of these exciting scientific discoveries, their impact on clinical practice, and, ultimately, the benefits in terms of improved patient health.”

By definition, PGx-based targeted therapies are likely to lead to higher per-patient clinical value of drugs among the smaller set of targeted users. In theory, then, value-based reimbursement should result in about the same level of total revenues. Indeed, aggregate benefit may be higher because it would reflect that all patients (even non-users) are better off due to reduced uncertainty. The total value created is due to the combination of an innovative test and an innovative drug, and how that value is apportioned in the marketplace to the drug or test manufacturer will depend on a complex set of interacting factors, including reimbursement policies and intellectual property, among others. But both the test and the drug will need to receive appropriate levels of reward through coverage and reimbursement policies to justify the costs and risks of developing the innovations.

In the United States, drug manufacturers have some flexibility to establish a price based on “value” at launch. Of course, they have to work to convince payers, providers, and patients of the value in terms of better health outcomes or cost savings. For the reasons described earlier, introduction of new PGx tests hold the potential to alter dramatically the value equation for pharmaceuticals or drug/diagnostic combinations. This shifting environment requires payer and public understanding of the need for reimbursement policies with sufficient flexibility to adjust to these altered value equations. Without it, manufacturers would have much less incentive to discover such subgroups from a commercial perspective.

Diagnostic manufacturers may face even greater limitations on their ability to capture the extra value created with innovative PGx diagnostic tests. They currently operate in an “administered” pricing and reimbursement system, where the reimbursement for a new test is based on perceived complexity and cost in comparison to existing tests. New tests are linked to existing tests via a coding system that does not account for their impact on health outcomes. Most new tests that are approved do not provide the kind of evidence of clinical benefit that new drugs provide. It is a chicken-and-egg problem: Test manufacturers must develop tests that are commercially sustainable, but generating more evidence in development costs more, and if there is no extra reward to recover these costs, PGx test developers will have limited incentive to invest in them. Further, if test developers seek value-based payments that greatly exceed administered reimbursement levels, they will have difficulty obtaining provider and patient adoption.

Identifying PGx markers, validating them, and demonstrating their clinical utility is often challenging, costly, and risky. Unless payment and reimbursement systems are structured to reward value creation from PGx-targeted therapy, the incentives for finding PGx subsets for existing drugs may be severely curtailed. Co-development of a diagnostic with a therapeutic by a drug manufacturer offers the incentive of increased predictability of revenues, but only if making the test-drug linked therapy is feasible from a scientific, technical perspective. Drug companies will have a much better chance of capturing a greater share of the value they create over the product life cycle if they launch the product with an indication that provides the greatest...
aggregate benefit, even if for a smaller number of patients. Drug companies are already under pressure because of the perception of high drug costs, so fostering a constructive policy dialogue on the topic of ensuring adequate reimbursement for targeted PGx therapies is difficult. At the same time, public opinion polls suggest that Americans are supportive of basic medical research and appreciate the health benefits that have been achieved from innovative drugs and diagnostics.

For PGx-targeted pharmaceuticals to have greater commercial viability, the pharmaceutical, biotechnology, and diagnostic industries must engage in the public policy debate on national coverage and reimbursement issues for drugs and tests. If they don’t participate, they face an increased risk of deleterious reforms that would focus reimbursement even more on costs rather than value. Reforms are likely to push for more evidence on clinical utility and cost-effectiveness, which will increase compliance costs to some degree.

6.2.5 Implications for health policy

Given the uncertainties about the pace of PGx innovations and their impact on clinical practice, it is uncertain whether the pharmaceutical and biotechnology industries will proactively address the policy issues identified here. But it is clear that the FDA is taking a proactive stance and that payers are putting increasing pressures on suppliers to provide evidence of clinical utility and economic value. Since genetics is generally not “exceptional,” policy reforms based on broader concerns will have implications for PGx.

The pharmaceutical and biotechnology industries have several opportunities to participate in discussions about policy changes that could have important implications for PGx-targeted therapy. These include FDA efforts regarding the Critical Path Initiative, biomarker requirements for drug development programs, and changes in evidentiary requirement for test validation. A second area concerns efforts to reform payment and reimbursement, particularly for tests. Health insurance reforms that encourage consumer-driven health care could affect the demand for genetic tests as more people use tax-free dollars to buy genetic pre-disposition tests and other such products. A variety of incentives, such as increased market exclusivity, are frequently proposed to provide greater reward and incentive for innovation. Ethical, legal, and social issues, such as genetic discrimination, privacy, and ownership of genetic information, will need to be sorted out. Public spending on the basic science that underlies PGx will remain a key issue. And as this report’s review of the science makes clear, identifying and developing PGx biomarkers will continue to be significant challenges.

How these six policy areas play out could profoundly affect the development and use of PGx-based therapies. As key stakeholders, the pharmaceutical and biotechnology industries can influence — through a well-informed and scientifically sound public policy positions — the speed and impact of these exciting scientific discoveries, their impact on clinical practice, and, ultimately, the benefits in terms of improved patient health.

Section Notes and References
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