

Pharmacogenomics: A Primer for Policymakers

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OVERVIEW — Researchers are exploring how genetic variations among individuals may help explain why a drug can work well in some people and poorly (or not at all) in others, including those who appear to have the same disease. Pharmacogenomics, as this new field is called, aims to help physicians make use of genetic tests to distinguish among patients whose genetic characteristics predispose them to respond in certain ways to certain medicines. If physicians can use this information to quickly and reliably choose the appropriate drug at the most effective dose for each patient, they may produce better patient outcomes and save health care dollars. An understanding of the genetic variables that influence drug response could also help pharmaceutical companies design new, more effective therapies. Although it is early in the development of pharmacogenomics, there are indications that this promising new technology has begun to challenge public policies to keep pace. Issues surrounding the safety, access, cost, and ethical dimensions of new clinical genetic tests and targeted drug therapies will need to be addressed if pharmacogenomics is to fulfill its potential. Conceptually, few of the issues raised by pharmacogenomics are unique to the field—or even to genetics—but all will have to be considered explicitly in the context of this new technology.

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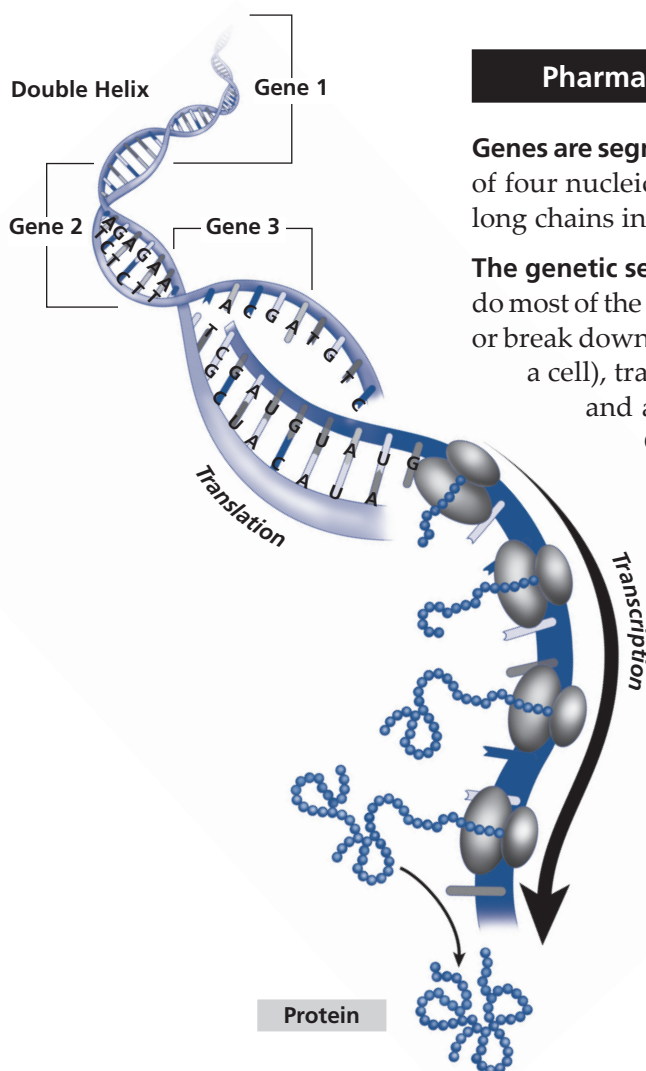
Americans and their health insurers—both private and public—spend more than \$250 billion per year on pharmaceuticals, and for most of the past 15 years that spending has been the fastest growing component of health care costs.¹ According to some estimates, it can cost nearly \$1 billion to bring one drug to market.² A large share of that amount underwrites clinical trials that drug manufacturers carry out in order to prove a drug's safety and effectiveness. Yet many currently approved drugs are effective in less than 50 percent of the people treated with them,³ and adverse drug reactions are the sixth leading cause of hospitalization and death in the United States.

Building on the tools and knowledge generated by the Human Genome Project, pharmacogenomics is a rapidly growing field that explores the contribution of genetics to drug safety and efficacy—specifically, how genetic variations affect individuals' responses to drugs. Genes determine the make-up of human proteins, including enzymes, receptors, transporters, and other molecules involved in drug and disease pathways (see illustration, next page). Pharmacogenomics uses genetic tests to classify patients and diseases according to variants in these genes. This information can help predict who will or will not benefit from a particular drug, at what dose, and which patients may be at risk for adverse reactions. Eventually, pharmacogenomics may be used to design new drugs and to identify candidates for preventive drug regimens long before disease symptoms are apparent.

Although headlines have proclaimed a coming genetic “revolution” in health care, most of the anticipated advances in pharmacogenomics are still in the early research stage. Massive, multi-institutional studies are just beginning to unravel the genetic basis of today's most important diseases, and to identify the environmental, behavioral, and dietary factors that interact with gene variation to affect drug response. So far only a handful of drugs “tailored” to specific genotypes have been developed and approved.

Bringing pharmacogenomics from the realm of basic exploratory genetics research to safe, effective applications in the doctor's office will require enormous investment, collaboration, and innovation across the biomedical enterprise. Like all new medical technologies, pharmacogenomics will have to prove that its tools and discoveries produce real added value in treatment decisions and outcomes before it is widely embraced. It will also require new regulatory standards, safeguards, and educational initiatives to guide its path from bench to bedside. Finally, it will cost will money. This paper describes the opportunities and challenges embodied in this new technology, current federal efforts to advance the field, and outstanding policy issues related to safety, quality, access, cost, and ethical implications.

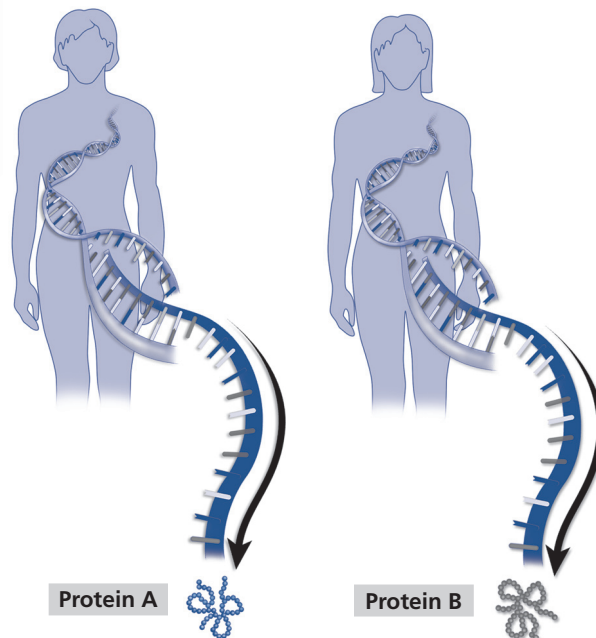
Pharmacogenomics Basics: Genes, Proteins, and Drugs



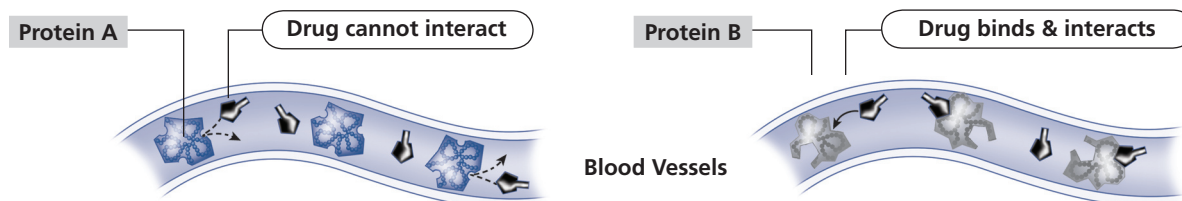
Genes are segments of DNA. DNA is composed of different combinations of four nucleic acids, or “bases,” abbreviated **A, T, C** and **G**, arranged in long chains in a double helix.

The genetic sequence encodes instructions for making proteins, which do most of the work in living cells. Proteins include enzymes (which build or break down substances), receptors (which serve as signal receivers for a cell), transporters (which move molecules across cell membranes and around the body), and many other important molecules. Genetic instructions for making proteins are “read” or translated through a process called transcription.

The nucleic acid sequence of specific genes can vary from person to person, even within immediate family. This natural variation means that at least some of the proteins made by each person will be different from others.



Drugs are designed to interact with substances in the body, most often proteins. Sometimes, genetic differences can affect how well a particular drug serves its intended function by influencing how that drug is activated, broken down, transported, or eliminated by the body, as well as the fit between the drug and its protein target.



Pharmacogenomic technologies try to detect genetic variations in a patient, or among patient populations, to help doctors select the drug compounds and doses that are most likely to work.

CURRENT APPLICATIONS

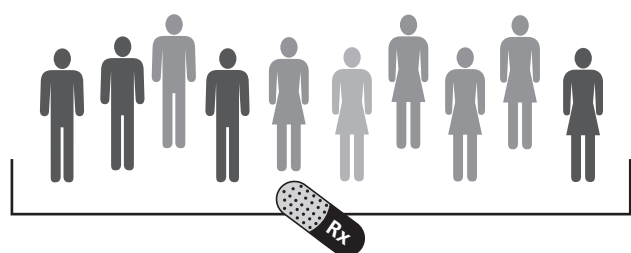
Some genes control *pharmacodynamics*: how the drug affects the body. Others control *pharmacokinetics*: how the body absorbs and disposes of a drug (that is, how the drug is metabolized). Pharmacogenomic techniques work with both processes. Examples include:

- **Subtyping common diseases to help physicians choose the right drug therapy** — What appears to be one disease in a clinical setting can turn out to be several different diseases at the molecular level, each requiring a different therapy. Cancers, for example, are a particularly promising area for pharmacogenomics because genetic “glitches” direct tumors to grow and spread in different ways and their response to treatment often depends on these unique characteristics.⁴ The classic example of a pharmacogenomic drug, Herceptin, is a highly effective therapy in the 15 to 25 percent of breast cancers that have a particular genetic variant that causes marked overexpression of the HER2 protein (a cell growth promoter) and is useless against breast tumors without that variant.⁵ This variety in the genetic underpinning of disease is true for many other diseases as well. For example, heart attacks are associated with at least 20 different genetic variations (many of which also have roles in inflammation or immunity),⁶ suggesting that there are multiple types of heart disease that are potentially treatable in different ways.
- **Subtyping patients to help guide drug dosing regimens (see illustration below)** — Drugs are broken down (metabolized) in the body by enzymes. One family of enzymes called cytochrome P (CYP) 450 is responsible for

Genetic Characteristics and Medication Dosing

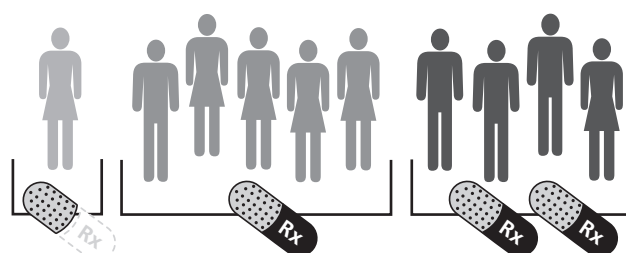
Without pharmacogenomics, recommended dosages are based on how drugs work in random samples of the population. Adjustments to dosing involve a process of trial and error to reach the desired effect for an individual patient.

All patients receive
same dose



With pharmacogenomics, doctors could potentially test patients' genetic characteristics in advance and use that information when needed to individually select medications and set dosage amounts.

Genetic characteristics of individuals
help drive dosing decisions



Source: Adapted from Felix W. Frueh, U.S. Food and Drug Administration, “Personalized Medicine, What Is It? How Will It Affect Healthcare?” slides from the 11th Annual FDA Science Forum, April 26, 2005; available at www.fda.gov/Cder/genomics/scienceForum2005.pdf.

breaking down more than 30 different classes of drugs, including anti-depressants, antipsychotics, beta blockers, and some chemotherapeutic agents. Individual variations in the genes that produce these enzymes can cause different people to metabolize the same drug differently: less active or inactive forms of CYP enzymes that are unable to break down and efficiently eliminate a drug from the body (“slow metabolizers”) can cause the drug to build up and lead to severe overdose in patients, whereas very active forms (“ultrarapid metabolizers”) can cause the body to clear itself of a drug before it has had a chance to work. Identifying which variant(s) a patient has could help physicians determine the appropriate dose of some medications to achieve therapeutic effects more quickly and avoid potential drug reactions. For example, every year in the United States, 2 million surgical and cardiac patients take the blood thinner warfarin (Coumadin®) to prevent blood clotting, but finding the correct dose for each person is notoriously difficult and mistakes can be deadly. Researchers found that differences in a gene called VKORC1, in tandem with specific CYP enzymes, influence how much warfarin is optimal for each person, a discovery that led the U.S. Food and Drug Administration (FDA) for the first time to recommend genetic testing on the label of a popular drug. A few clinically important variations in other metabolic enzymes also have been identified. For example, one version of the enzyme thiopurine methyltransferase (TPMT) prevents patients from metabolizing the anticancer drug 6-mercaptopurine (6MP), used to treat one form of childhood leukemia. Patients who have a specific mutation in the gene that codes for the enzyme may need less than one-tenth of the regular dose, and they can die if they receive a full dose.

- **Identifying individuals who could benefit from prophylactic drug therapy** — Many advocates are hopeful that pharmacogenomics will enable tailored pharmaceutical interventions to prevent disease. For example, a risk assessment that takes into account a patient’s genetic susceptibility to coronary artery disease could result in a lower threshold for prescribing anticholesterol medication than is recommended for the population at large.⁷ Pharmacogenomics can also support targeted primary chemoprevention, for example, by identifying women with BRCA1 and BRCA2 gene mutations who may benefit from using the drug tamoxifen to prevent breast cancer. The value of pharmacogenomics for disease prevention is currently limited by the fact that gene variants discovered so far explain only a small proportion of overall risk; however, ongoing discovery and characterization of disease “susceptibility” genes may improve risk prediction.⁸

In addition to its clinical applications, pharmacogenomics has some potential to help drug companies and the FDA bring drugs to market more quickly. When drugs fail clinical trials, it is often because they cannot show a statistically significant therapeutic effect in a diverse population; other drugs fail because of safety issues in a small number of trial participants. Pharmacogenomics could potentially reduce the risk of these expensive failures by enabling companies to identify and recruit clinical trial participants

who are likely to respond favorably to the drug and to eliminate subsets of patients whose genotypes make them likely to suffer adverse reactions, thus reducing the time and number of subjects necessary to prove safety and efficacy. For drugs that have failed trials or been recalled from the market

CYP Enzymes and Psychotropic Drugs

Psychiatric drugs have long been a priority for pharmacogenomics research because of the economic and social burden of mental illness and because it is very difficult for physicians to predict who will respond best to which of the many available drugs. Selective serotonin reuptake inhibitors (SSRIs) have become the first-line drugs in the treatment of depression, but physicians must choose among more than two-dozen branded products in this drug class with little definitive clinical evidence to determine which is most likely to work for which patient. In addition, finding the correct dose usually involves a process of trial and error, which can lengthen the time until treatment begins to help a patient. One-third of people treated with antidepressants do not respond to any medication or suffer such intolerable side effects that they cannot continue with the drugs.*

Researchers know that SSRIs are metabolized by the CYP 450 family of enzymes, and genetic tests recently have become commercially available that can identify whether an individual has the “slow,” “rapid,” or “ultrarapid” metabolizer version of the genes that code for these enzymes. Researchers are now trying to uncover the specific associations between genetic variants in the CYP system and the effectiveness and side effects of specific SSRIs along with other antidepressants. To succeed,

researchers will have to isolate the effects of CYP 450 differences from the effects of other known and suspected genetic variants that could influence response to SSRIs, as well as differences in diet, exercise, the presence of other health conditions, other drugs the patient may be taking, and so on. The task is so complicated that government agencies in both the United States and Europe have established research networks to divide the work and share data.†

Even if the specific effects of CYP 450 status become known, it is unclear how much or how soon such information will be available to assist physician decisions about selecting specific SSRIs and their doses for individual patients. Physicians will look for evidence that prescribing based on CYP status improves patient outcomes—evidence that, according to a recent AHRQ report, does not yet exist.‡ Many will also look to professional practice guidelines to inform genetic testing criteria and to help translate genetic test lab results into useful prescribing information; however such guidelines will require even more detailed levels of evidence that will take more time and resources to develop.§ Ultimately, a physician may decide that the combined influence of other variables in depressed or anxious patients may outweigh the predictive value (and expense) of a genetic test to look only at CYP status.

* Arline Kaplan, “Advances in Pharmacogenomics Reduce Side Effects and Save Lives,” *Psychiatric Times*, XXII, no. 7 (June 1, 2005); and J. Kirchheiner et al., “Pharmacogenetics of antidepressants and the antipsychotics: the contribution of allelic variations to the phenotype of drug response,” *Molecular Psychiatry*, 9, no. 5 (May 2004): pp. 442–473.

† These include centers within the Pharmacogenetics Research Network (PGRN), supported by the U.S. National Institutes of Health (NIH) and the Genes and Depression study (GENDEP), supported by the European Union and involving scientists and clinicians from ten countries.

‡ D. B. Matchar et al., *Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs)*, Evidence Report/Technology Assessment No. 146, AHRQ Publication No. 07-E002, Agency for Healthcare Research and Quality, November 2006; available at www.ahrq.gov/downloads/pub/evidence/pdf/cyp450/cyp450.pdf.

§ Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, “Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors,” *Genetics in Medicine*, 9, no. 12 (December 2007): pp. 819–825.

for safety reasons, pharmacogenomics could potentially lead to relabeling and approval of these products for populations whose genotypes indicate they would benefit from, or not be harmed by, the drug. Finally, a better understanding of how genetic variations affect specific disease processes and drug responses may help identify new targets for drug development. Many see this as the ultimate promise of pharmacogenomics.

CHALLENGES

Pharmacogenomics carries great promise; however, the degree to which that promise is realized will depend on effective implementation of myriad steps and policy decisions that must be made by a variety of organizations in both the public and private sectors.

Basic Research

The most obvious hurdle for pharmacogenomics is the complexity of the underlying science. The sequencing of the human genome, completed in 2001, and the HapMap (see text box), completed in 2007, has given scientists a “parts list” and a companion catalogue of variations for the workings of the genome. However, the key to fully exploiting the potential of pharmacogenomics is understanding how the relationships among genes, disease processes, drugs, and environmental factors work at the molecular level, and that understanding is still very rudimentary. Some genes (or their products) and the drugs that affect them are relatively well understood, but they are the exception, not the norm. Indeed, many believe that the handful of genetically targeted drugs already on the market are the “low-hanging fruit”; most involve single genes (“mongenic”) whose influence was discovered (sometimes by accident) after the drug was already in use. In contrast, most important biological processes are

Deciphering Genetic Variation

There are roughly 22,000 genes amidst the 3 billion DNA “bases” (designated by the letters A, T, C and G) that make up the human genome (see illustration, page 4). While more than 99 percent of those DNA bases are identical from person to person, there are still an estimated 10 million single-letter variations—called single nucleotide polymorphisms (SNPs, pronounced “snips”)—in the human genetic sequence. Most of these variations are believed to be biologically insignificant, but a small fraction of them are known to alter the function of a gene—often only slightly, but sometimes significantly. The effect of many slightly altered genes interacting with each other, combined with environmental factors, may lead to increased risk for a particular disease or shift a biochemical pathway normally targeted by a drug. Scientists have mapped (the “HapMap”) where SNPs tend to occur in the genome.* However, the arduous process of deciphering which variations (and combinations) account for what biological effects, including drug effects, is immensely complex and has only just begun.†

* David A. Hinds et al., “Whole-Genome Patterns of Common DNA Variation in Three Human Populations,” *Science*, 307, no. 5712 (February 18, 2005): pp. 1072–1079; and International HapMap Consortium, “A second generation human haplotype map of over 3.1 million SNPs,” *Nature*, 449 (October 18, 2007): pp. 851–861.

† Genome-wide association studies (GWAS) represent a powerful approach to detecting associations between genetic variants and common diseases, however, such studies are not designed to discover the specific mechanisms involved. If an association is confirmed, its effect generally must be elucidated using different techniques. For information on NIH-supported GWAS, see www.genome.gov/20019523.

governed by several genes (“polygenic”) and are often the result of variations in those genes interacting with each other and with something in the environment. How a person responds to a particular drug, for example, can be influenced by variables such as diet, other medications, and other underlying conditions, in addition to his or her particular set of genes.

The cost and technical challenges of putting together the infrastructure needed to support research on the scale required to discover and characterize genetic influences within complex interactions are enormous. Given so many variables, association studies and clinical trials need to enroll large numbers of participants and be supported by robust information management systems that can adapt to upgrades in the methods of genomic analysis.⁹ Moreover, while investment in genomic technologies has driven costs down significantly over the last decade,¹⁰ it is still expensive to sequence and analyze the amount of genetic material needed to pinpoint gene-drug-disease interactions. Once a specific genetic influence is determined, additional work is needed to explain the molecular pathways and mechanisms of action. Few individual institutions have the resources to mount such studies, so collaborations are a must.¹¹

Co-Development of Pharmaceuticals and Genetic Tests

One major challenge for both industry and regulators will be integrating genetic testing into drug development, approval, and marketing. The development of a genetically targeted drug will require the development of an associated genetic test, first to locate the gene target for drug development and then to identify patients who possess the targeted gene variant and therefore are candidates for the new therapy. As a practical matter, few pharmaceutical companies have expertise in the diagnostics business. The two industries have evolved separately, with distinct cultures, regulatory mechanisms, product lifecycles, and commercialization pathways. Therefore, drug companies that wish to pursue pharmacogenomics as part of their drug development strategies will have to either learn diagnostics or partner with companies that already know the field. In addition, regulators and third-party payers will need to develop policies to ensure that clinically validated genetic tests needed to inform prescribing of approved pharmacogenomic drugs are appropriately promoted with the drug and are accessible to physicians and their patients.

Translating Research into Treatment

Research to discover associations between genes, disease, and drugs will be of little practical value without an understanding of how those findings should translate into actual treatment decisions. For example, as noted above, doctors now know that an individual’s response to warfarin therapy is partially but significantly influenced by two genes, and a test is available to detect whether a patient has slow or fast metabolizer variants of these genes. However, knowing which genetic variants a patient

has does not tell the physician *how* to adjust the warfarin dose. Should doses be smaller? Should there be more time between them? Or should a different anticoagulant therapy be used? Further complicating matters, these genes explain less than half of the observed variability in patients' responses to standard warfarin dosing.¹² What other factors—genetic or otherwise—should be considered in making a dosing decision? In fact, gene-based dosing guidelines have not been developed for warfarin¹³ or any other CYP-metabolized drug because there is, as yet, no clear understanding of the optimal doses for slow or rapid metabolizers. Moreover, the rate at which the body clears a drug, and thus the likely corresponding adjustment to dose, varies by drug. This variability also applies to predicting side effects and drug interactions. Finally, the effects of the same genetic variant may be quite different in different populations, again reflecting the interplay of many variables. Thus, each drug must be studied individually across multiple groups,¹⁴ which is a massive undertaking.

Health Information Technology

Basic, translational, and clinical research and applications in pharmacogenomics will require the sharing, storage, and management of massive amounts of information across multiple organizations and institutions, from the U.S. National Institutes of Health (NIH) and industry gene databases to point-of-care decision support tools.¹⁵ Information technology systems will need operating rules and a common nomenclature that can accommodate the types and level of detail of pharmacogenomic-related data collected in different settings (the research center, the lab, the clinic, the surveillance registry, etc). Computational and analytic methods also will need to embrace bioinformatics (from the genomic testing) and clinical informatics (clinical trials and health care data).

Pharma Buy-In

Until recently, most large pharmaceutical companies, which control the lion's share of capital for pharmaceutical research and development, have been ambivalent about making significant investments in pharmacogenomics. Some pharmaceutical executives worry that by segmenting diseases and patient populations, pharmacogenomics could shrink the market for "blockbuster drugs" that are the bedrock of the industry.¹⁶ In addition, because the traditional pharmaceutical business model generally depends on mass advertising and billion dollar sales, many experts believe these companies simply could not be successful developing drugs that serve only a small portion of the population.

However, the number of profitable drugs coming off patent, shrinking drug pipelines, and persistent (and expensive) consumer and regulatory concerns over drug safety are forcing many pharmaceutical makers to reassess their current research methods and business portfolios. Most pharmaceutical companies now routinely collect pharmacogenomic data from their clinical

Until recently, most large pharmaceutical companies have been ambivalent about making significant investments in pharmacogenomics.

trial participants for exploratory in-house analysis, and many have begun to invest in building capacity for pharmacogenomics to support at least a portion of their future drug development work. However, a sustained industry commitment to pharmacogenomics research and development will hinge on many variables, including the economics of “mini-buster” drugs and well-aligned regulatory pathways for each stage.

Cost

New pharmacogenomic therapies are likely to be expensive. Many of the drugs will be biologics (drugs made from human or animal proteins), the fastest-growing and most expensive group of drugs on the market. Moreover, both biologics and traditional “small molecule” drugs that are developed or approved for a genetically defined subpopulation or subcategory of disease are likely to occupy the high end of the pricing spectrum. A treatment course of Herceptin, for example, can cost upward of \$60,000. Manufacturers argue that premium prices are justified in exchange for the lower risk and higher certainty that these drugs will work in their target populations, and that less wasted drug use—that is, less use of drugs on patients for whom the drug has no effect or serious side effects—would help offset higher prices. Manufacturers also point out that a drug created for a limited market still needs to generate enough revenue to offset its development costs.

Genetic tests also are expensive (between \$200 and \$3,500) and could become more so even though the cost of the technology is expected to decline. Genetic test manufacturers are beginning to challenge the practice of “cross walking” new tests to old tests in order to establish fees, arguing that new diagnostics should be reimbursed based on the value of the information provided by the test. There are no standards or mechanisms to determine the “value” of new tests (though some have been proposed).¹⁷ However, the maker of a new prognostic test for early-stage breast cancer reasons that the \$3,500 price tag is just one-quarter of the cost of chemotherapy for that condition, and that it will detect and avoid unnecessary chemo for the estimated 85 percent of patients whose breast cancer will not recur after surgery.¹⁸ Tests such as microarrays or “gene chips” that detect variations in multiple genes or gene products at one time are also potential cost drivers. Although the tests themselves may not be very expensive, like all tests, they will produce some false positives that will then take additional testing and resources to rule out. And the opportunity for false positive findings is amplified when many genes are tested simultaneously. One group of researchers dubbed this phenomenon the problem of the “incidentalome.”¹⁹ There is also the possibility that these tests could find true positives or turn up other information—for example, a genetic predisposition to a particular form of heart disease—that were not part of the original reason for seeking the test but could lead to expensive medical interventions or prophylactic drug regimens. These costs may be warranted, but they are added costs nonetheless.

Demonstrating Value

Pharmacogenomic technology will only move forward if developers are confident that the market is robust enough to justify the investment. The market for pharmacogenomic (and most other) therapies is mediated by third-party payers who will want proof that these therapies add value to health care by holding or reducing costs and improving outcomes—proof that is currently missing and that will take time and resources to develop. A widely cited literature review turned up just 11 cost-benefit analyses of pharmacogenomic interventions, covering a limited range of conditions with mixed results.²⁰ Today a few of the largest health care organizations, such as Kaiser Permanente, Aetna, and Partners Health Care, are studying whether and how they should incorporate pharmacogenomics into their clinical processes. They are examining parameters like the cost of a pharmacogenomic test, mortality due to adverse drug reactions, prevalence of the particular genotype being targeted by the test, and whether test results would change providers' clinical decisions in ways that improve patient outcomes—all key to establishing the value of a pharmacogenomic approach to prescribing a particular drug. These early assessments, in turn, will help determine how much incentive developers have to invest in this arena and where their energies would be best directed.

Third-party payers will want proof that these therapies add value to health care by holding or reducing costs and improving outcomes.

FEDERAL INITIATIVES

Federal health agencies have undertaken a number of initiatives to facilitate the progress of pharmacogenomics. These include significant funding and organizational support for public-private sector research networks designed to broadly share data and research tools, a consultative approach to evolving new regulations, and efforts to create evaluation methods for the clinical applications of this developing technology.

The **NIH**, the nation's primary driver of basic biomedical and genetics research, has launched several major projects specifically to help genetics researchers find meaningful associations between genetic variations and drug response among the 10 million common variations in the human genome. The Pharmacogenetics Research Network (PGRN) is a nationwide collaboration of scientists created specifically to study the effects of genes on individuals' responses to medications, including drugs for asthma, depression, cancer, and heart disease.²¹ The Genetic Association Information Network (GAIN) is a public-private partnership that provides industry and academic researchers access to tissue samples from NIH clinical trial participants for genetic association studies. A primary objective of the NIH is to place as much genomic data and research technology as possible in the public domain, making it accessible to the global research community.

The **FDA** sees pharmacogenomics as both a tool to help achieve its mission of ensuring that drugs are safe and effective and as an opportunity to advance its Critical Path Initiative, which aims to help drug (and other medical product) development keep pace with advances in biomedical research.²² The

agency has been spearheading discussions with industry about all aspects of pharmacogenomics and the research and regulatory approaches that can best promote it.²³ FDA and the Arizona-based C-Path Institute,²⁴ a new private foundation with which FDA collaborates, are coordinating research consortia that include some of the nation's largest drug manufacturers as well as academic researchers to develop new targets (biomarkers) and research tools for pharmacogenomics and to share preclinical and clinical research methods and data that may be relevant to assessing drug safety. The FDA has also developed a Voluntary Genomic Data Submission process to encourage companies to share data on exploratory genetic biomarkers they are collecting from clinical trial participants without fear that these data will be used to delay approval or make it conditional.²⁵ New rules for "adaptive" clinical trials permit genetic "enrichment" of the study population as a trial proceeds in order to reduce the time needed to demonstrate a new drug's safety and effectiveness.²⁶ For companies that want to market a drug specifically to a genetic subset of patients, the FDA is refining a process and standards for coordinated review and approval of the drugs and their associated genetic tests, which currently are regulated differently by separate Centers within the agency.²⁷ Finally, the FDA is negotiating what pharmacogenomic information must be included on specific drug labels where evidence of gene-drug interactions is conclusive.

The **Centers for Disease Control and Prevention (CDC)** and the **Agency for Health Care Research and Quality (AHRQ)** support a number of programs that potentially could answer questions about the value of pharmacogenomics that clinicians, health plan administrators, policymakers, and patients will be asking as more applications become available. The CDC created the Evaluating Genomic Applications in Practice and Prevention (EGAPP)²⁸ initiative to develop an evidence-based method for judging the usefulness of specific genetic and pharmacogenomic tests as they transition from research into clinical practice. So far, EGAPP has completed four of six planned evidence reviews, three of which remarked on the lack of high-quality clinical studies to determine whether the tests affect patient management decisions in ways that improve outcomes (some tests were still investigational at the time of EGAPP's review, so such studies may be forthcoming). AHRQ spearheads a network of Evidence-Based Practice Centers that conduct assessments of health care services and technologies, including the specific pharmacogenomic applications of interest to EGAPP. In addition, AHRQ conducts research "to advance the optimal use of drugs, medical devices and biological products" through its Centers for Education and Research in Therapeutics (CERTs),²⁹ which the agency operates with the FDA. CERTs could incorporate pharmacogenomic tests into their analyses of factors that influence the effectiveness of specific drug therapies. Finally, AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program taps electronic health information databases to conduct rapid turn-around studies on health services outcomes and comparative effectiveness; such studies could be instrumental in identifying priorities for pharmacogenomics clinical research.

POLICY ISSUES

How quickly pharmacogenomics develops into a useful clinical toolkit will depend greatly on how policymakers respond to policy issues associated with both genetic testing and targeted drug development, including concerns about safety, access, cost, and potential ethical and social implications.

Safety and Quality

Pharmacogenomics depends on the availability and reliability of genetic tests to accurately detect selected genetic markers that are important to drug therapy decisions as well as the ability of providers to interpret test results in order to make safe and appropriate use of targeted therapeutics. There is considerable debate over whether current resources and regulatory requirements are adequate to ensure the safety and quality of genetic testing.³⁰

Genetic tests — Regulatory oversight of genetic testing is spread across the FDA, the Centers for Medicare & Medicaid Services (CMS), and the CDC. FDA regulates “test kits” (that is, stand-alone tests that are produced, packaged, and sold with all ingredients and instructions necessary to conduct the test) as in vitro diagnostic devices (IVDs) that must be approved for safety and effectiveness before they can be marketed. Today, however, most genetic tests are not sold as test kits. They are created more or less from scratch by the clinical laboratories that offer them and have been considered to be medical services provided by the lab rather than commercial products. Historically, these so-called “home brew” tests have not been reviewed by FDA. As a result, of the more than 1,200 genetic tests clinically available,³¹ fewer than a dozen have been developed as IVDs and approved by the FDA, leaving the majority of genetic tests without any independent external review of their analytic or clinical validity before they are offered to the public.³² As genetic testing technologies grow more complex, many argue that FDA oversight should extend to laboratory-developed genetic tests in order to validate the proprietary testing methods, ensure test accuracy and appropriate labeling, provide a means of postmarket monitoring, and level the regulatory burden for manufacturers who do go through the effort of developing FDA-approved test kits.³³ Indeed, FDA has recently issued draft regulatory guidance for one new type of laboratory-developed genetic test called a Multivariate Index Assay (MIA),³⁴ which uses complex proprietary formulas to calculate the odds of a particular health outcome based on an individual’s genetic profile. The FDA is assessing whether it has the resources to actively oversee other categories of lab-developed tests; however, opponents argue that FDA review of home-brew type tests would be an intrusion into the practice of laboratory medicine and would add costs and delays to bringing new tests to market.³⁵

Genetic testing laboratories — CMS and the CDC share responsibility for ensuring the quality of testing laboratories under the Clinical Laboratory

Pharmacogenomics depends on the availability and reliability of genetic tests to accurately detect selected genetic markers that are important to drug therapy decisions.

Improvement Amendments of 1988 (CLIA). CLIA specifies standards for laboratory quality assurance and mandates specialty certification and proficiency testing for laboratories that perform certain highly complex tests. Proficiency testing measures a laboratory's actual performance on test procedures and is a key element in determining laboratory competence. Under CLIA, genetic tests are considered highly complex, but CLIA regulations—written when genetic testing was still in its infancy—have not been updated to mandate proficiency testing standards for genetic testing.³⁶ Currently, most labs performing genetic testing participate in some level of proficiency testing through programs offered by private organizations, but such participation is voluntary and not universal. To address the gaps, the CDC's Clinical Laboratory Improvement Advisory Committee announced plans in 2000 to create a genetic testing specialty under CLIA,³⁷ and a proposed rule was placed on the regulatory agenda of the U.S. Department of Health and Human Services (HHS) for late 2006.³⁸ Before the rule was issued, however, CMS reversed course, stating that it believes genetic testing is adequately covered by existing CLIA standards. Several influential genetics policy and patient advocacy organizations objected to CMS's reasoning and filed a "citizen's petition," insisting that the agency create standards for and mandate participation in proficiency testing programs for genetics.³⁹ A draft report by the Secretary's Committee on Genetics, Health and Society (SACGHS) likewise recommended that the HHS take specific steps to increase the use of proficiency testing for genetic tests.⁴⁰

Provider capacity — To use pharmacogenomics appropriately in patient care, clinicians must understand exactly what information a given test can and cannot provide, how to interpret positive and negative test results, and what medical management options are available. Studies show that many health care providers are not prepared to make appropriate use of genetic tests. In one survey, 72 percent

Direct-to-Consumer Genetic Tests

Some genetic tests are now being sold over the Internet, prompting widespread debate about the appropriateness of marketing genetic tests directly to consumers.

Though some believe that direct-to-consumer (DTC) marketing of scientifically validated genetic tests can empower consumers and encourage patients to engage their physicians in a dialogue about their health care, others argue that without the help of a qualified health care provider to interpret test results, DTC genetic tests can be difficult to understand at best and useless or harmful at worst.* In addition, a recent U.S. Government Accountability Office (GAO) investigation found evidence that some companies are capitalizing on consumer interest in genetics by selling less-than-trustworthy tests. The genetic tests in GAO's study were designed to get consumers to buy expensive food supplements "personalized" to their DNA,[†] but there is nothing to stop a company from offering genetic tests for more "serious" health-related conditions directly to consumers,[‡] whether or not the test has been reviewed by the FDA or is performed in a CLIA-certified laboratory. For that reason, the Federal Trade Commission and the FDA together issued a consumer alert about DTC genetic tests, while the GAO echoed calls for more thorough regulatory oversight of genetic tests to ensure that consumers "have reliable information in order to determine which tests are accurate and useful."

* American College of Medicine Genetics Board of Directors, "ACMG Policy Statement on Direct-to-Consumer Genetic Testing," *Genetics in Medicine*, 6, no. 1 (January/February 2004): p. 60; available at: www.acmg.net/resources/policies/Direct_Consumer_Testing.pdf.

† Gregory Kutz, U.S. Government Accountability Office (GAO), "Nutrigenetic Testing: Tests Purchased from Four Web Sites Mislead Consumers," GAO-06-977T, testimony before the Special Committee on Aging, U.S. Senate, July 27, 2006; available at <http://www.gao.gov/new.items/d06977t.pdf>. The GAO investigation found that companies purporting to analyze an individual's genetic information for personalized nutritional and lifestyle recommendations generally provide the same advice—such as adopting a healthy diet and avoiding smoking—available from many other sources, but that some go on to recommend the same "tailored" dietary supplement, costing as much \$2,000 per year, to all customers which contains vitamins obtainable at a drug store for around \$35.

‡ Stephen Barrett and Harriet Hall, "Dubious Genetic Testing," *Quack Watch*, April 9, 2002; available at www.quackwatch.org/01QuackeryRelatedTopics/Tests/genomics.html.

of nongeneticist physicians rated their own knowledge of genetics as fair to poor.⁴¹ In another study, physicians misinterpreted genetic test results in nearly one-third of colon cancer cases.⁴² Such statistics have prompted calls to revamp provider educational curricula at all levels to emphasize genetic medicine. However, many doubt that individual providers, particularly busy primary care physicians, will have the interest or the capacity to become well-schooled in genetics. Rather, they suggest, this is where professionally developed clinical guidelines—developed by appropriate specialists or specialty societies and independently reviewed—could prove valuable to practicing clinicians. Several groups have called on the federal government to create a mechanism for prioritizing and funding clinical genetic guideline development. Genetic testing laboratories may also have a role in ensuring that physicians are able to request and interpret pharmacogenomic tests appropriately. The National Academy of Clinical Biochemistry has drafted guidelines recommending that laboratories that conduct pharmacogenetic testing either have a consultation component available to provide physicians with a complete interpretation of test results, or work with an organization that can provide such services.⁴³

A complementary approach to ensuring provider competence with pharmacogenomics calls for strengthening the dedicated genetics work force. Medical geneticists and genetic counselors in particular can serve as bridging professions for nongeneticist physicians, laboratories, and pharmacists. However, there are only about 3,100 professionals in the United States who are specifically trained and certified to provide genetic counseling and clinical genetic services (and the counselors themselves would need special training in pharmacogenomics), prompting calls to grow the field with reimbursement or other practice incentives.⁴⁴

Drug trials, “off-label” prescribing, and postmarket surveillance — The very precision that characterizes pharmacogenomics could raise new concerns about drug safety. Pharmacogenomics makes it possible to “enrich” clinical trials with individuals whose genotype suggests that they will respond well to the drug under study, thereby more quickly demonstrating a drug’s efficacy and reducing the potential for adverse reactions during the trial. However, enriched clinical trials weighted with “good responders” may not reveal potentially harmful or toxic effects of the drug in other populations. FDA requires drugs that have been tested in defined populations or for specific conditions to be labeled for use only in those circumstances, but it is well-known that doctors very often prescribe drugs off label—that is, in doses or situations for which the drug has not been formally approved.

Physicians prescribe drugs off label for a number of reasons. New off-label treatments can be grounded in top-notch research that is comparable to the rigorous studies that the FDA would demand, but they can also be suggested by poorly designed studies, anecdotally by a physician colleague, or even by a pharmaceutical company representative.⁴⁵ Sometimes, a physician’s impetus for off-label prescribing is simply professional hunch

that may lead to important new indications for a drug; at other times, it is in response to patient demand for a highly touted therapy, particularly when there are few acceptable alternatives. Herceptin, one of the first pharmacogenomic drugs, is effective (and labeled) only for patients whose breast cancer tumors overexpress the HER2 gene, but doctors have prescribed it for patients without that mutation. In this case, the patient is unlikely to receive any benefit from this very expensive drug.⁴⁶ More worrisome is the potential that drugs developed to treat or avoid toxicities and/or adverse reactions in people with a specific genotype could be problematic and possibly even dangerous when prescribed off label to someone with a different genotype.

Given these concerns, some have suggested the need for a firmer approach to managing off-label prescribing, including restrictions on the clinical use of targeted therapies and tests, enhanced state requirements for physician compliance with product labeling, or the required involvement of licensed pharmacogenomics counselors in certain types of prescribing decisions.⁴⁷ The FDA was given expanded authority under the Food and Drug Administration Amendments Act of 2007 to impose Risk Evaluation and Mitigation Strategies (REMS) that could include such provisions if the agency can show that they are necessary to ensure that the benefits of a product outweigh the risks. However, mustering the level of evidence needed to support such a determination is fraught with challenges. In addition, monitoring compliance by health care providers and patients with any REMS safe-use provisions that FDA might require falls to the drug manufacturer, who may or may not be well-equipped for the role.

Such safety concerns may also amplify the need for a comprehensive system of postmarket surveillance. The current Adverse Event Reporting System (AERS), through which clinicians and companies are supposed to report serious and unexpected events that occur once a drug is marketed, receives no more than 10 to 25 percent of actual adverse events,⁴⁸ making it difficult to identify patterns in a timely manner. A recent report by the Institute of Medicine on drug safety and public health⁴⁹ recommends that the FDA strengthen its postmarket surveillance activities by making better use of existing data sources, such as Medicare claims and large health maintenance organizations (HMOs) that have computerized systems for tracking such events. The FDA Amendments Act implements this recommendation and also gives the FDA more authority to require new studies or clinical trials of drugs flagged by the surveillance system. Greater use of electronic health records (EHRs), which would provide important clinical context for adverse drug events, along with the collection and genetic testing of DNA samples as part of adverse event reporting (with the samples to be deposited in a national registry accessible for pharmacogenomic association studies) are other possible approaches to bolster postmarket drug safety. The success of any approach, however, will depend on whether the FDA is provided sufficient resources to support active surveillance and timely response.⁵⁰

Drugs developed to treat or avoid toxicities and/or adverse reactions in people with a specific genotype could be problematic and possibly even dangerous when prescribed off label.

Making current drugs safer — Most of the attention on pharmacogenomics has focused on its role in bringing future drugs to market, but the technology could also be used to identify genetic risk factors for adverse drug reactions associated with drugs that have long been staples in American medicine cabinets.⁵¹ One study found that all but 3 of the 27 most commonly identified drugs in adverse drug reaction studies were among the top 200 selling drugs in the United States at the time.⁵² Reducing adverse reactions in just these drugs could have a large impact. However, manufacturers struggling to fill their pipelines have little incentive to invest in costly pharmacogenomic research to identify potential genetic contraindications for popular drugs already on the market. The FDA Amendments Act provides a mechanism for the agency to compel postapproval studies by the drug sponsor under specific circumstances⁵³ but only if the agency becomes aware of a new safety problem with the drug. As a result, much of the research needed to illuminate pharmacogenomic properties of familiar, widely prescribed drugs may fall to federal agencies and academic institutions.

Access

Third-party coverage and payment decisions can speed adoption and use of new technologies or can create serious barriers to access. Health insurers, including Medicare, will need to consider coverage and reimbursement policies for genetic tests that are performed to guide prescribing decisions and for the drugs that are prescribed on the basis of those tests. Access to pharmacogenomic technology will also be influenced by incentives for companies to develop tests and therapies for smaller populations and for providers to integrate the technology into their clinical practices.

Coverage of pharmacogenomic tests — Insurers, including Medicare, make coverage decisions for new diagnostic tests on a case-by-case basis. Private health plans generally will cover pharmacogenomic tests when they are required or strongly recommended on an FDA-approved drug label, such as the HER2 test for Herceptin.⁵⁴ Coverage of pharmacogenomic tests that are not required by a label varies, depending mostly on the plan's assessment of whether the test is "medically necessary."⁵⁵ Medical necessity criteria usually include high-quality scientific evidence, preferably from clinical trials, that a given test or service is safe and effective in improving the diagnosis or management of disease at least as much as established alternatives.⁵⁶ However, most pharmacogenomic tests are still too new to have been subjected to the kind of rigorous comparative effectiveness analysis that would meet the medical necessity threshold. Until they do, many pharmacogenomic tests are likely to be regarded as experimental and therefore not covered by private health plans. Notably, CMS and its local contractors have flexibility to extend conditional coverage to such tests under Medicare's "Coverage with Evidence" policy (see text box, next page).

Medicare and Coverage with Evidence

Medicare has adopted a coverage policy for promising new technologies called Coverage with Evidence Development (CED), under which CMS may opt to cover specific medical innovations—such as pharmacogenomic drugs and diagnostics—that are too “young” to have accumulated the amount of clinical evidence required to meet the usual standard for coverage, which typically includes published results from several high-quality controlled clinical trials. CED can actually help develop that evidence base by linking Medicare coverage to a requirement that patients participate in a registry or clinical trial, which in turn could support a future decision about unconditional coverage.* A second element of CED, called “coverage with appropriateness determination,” allows CMS to approve coverage and reimbursement for an “experimental” new drug or service based on whether a patient has “appropriate” indications (potentially including genetic test results indicating that the patient would respond well to a particular therapy), similar to private insurers’ use of prior authorizations.† Both of these options give CMS the flexibility to cover some pharmacogenomic therapies, potentially even before other payers, and in the process generate data on the clinical usefulness and cost-effectiveness of specific pharmacogenomic applications that could be mined by other researchers.

* Some policymakers and patient groups have challenged the ethics of linking insurance coverage to a requirement for participation in registries, saying such a requirement could be considered coercive.

† Sean R. Tunis and Steven D. Pearson, “Coverage Options for Promising Technologies: Medicare’s ‘Coverage With Evidence Development,’” *Health Affairs*, 25, no. 5 (September/October 2006): pp. 1218–1230.

In contrast to its flexibility to cover new diagnostic tests, Medicare’s medical necessity clause does not permit coverage of tests—genetic or otherwise—for preventive screening purposes (unless coverage of a specific test is mandated by Congress). Thus, genetic testing to identify a predisposition to a disease for which the patient has no signs, symptoms, or family history, would not be covered by Medicare.⁵⁷ Private insurers generally cover screening tests, including some genetic tests that have been shown cost-effective in reducing disease burden on their population mix; however, pharmacogenomic tests are not yet able to prove value on a population basis.⁵⁸

Coverage of pharmacogenomic drugs — Current drug coverage and cost control mechanisms may not work well for pharmacogenomics. For example, formulary placement is key to any health plan’s ability to negotiate drug prices, guide drug use, and control spending. Formularies are built on the concept of “therapeutic equivalence” within drug classes, thus allowing the selection of a preferred drug and exclusion or penalties for substitution. Drug makers typically prefer formularies that are broken down into more classes or categories to increase the number of listed products, but payers prefer formularies that feature fewer drug classes and disease categories because they provide more negotiating leverage with manufacturers and distributors. Pharmacogenomics, however, is specifically intended to uncover clinically important therapeutic differences within drug classes and to identify new subcategories of disease based on genetic information. It is conceivable that, over time, pharmacogenomics could overwhelm efforts to contain the number of formulary disease categories and could create real pressure to expand preferred drug listings for genetic subpopulations.

One frequently asked question is whether payers could limit coverage of certain drugs to patients whose genetic profiles indicate that they are likely to benefit from those drugs.⁵⁹ Pharmacy coverage decisions generally follow any relevant FDA policies or label indications. Roughly ten percent of currently marketed drugs have some pharmacogenomic information on the label,⁶⁰ but only a handful go so far as to require genetic testing prior to prescribing the drug. Unless there is a very clear connection between test findings and prescribing decisions, the FDA is less likely to require the test on the label. Where the linkage appears clear, as in the case of Herceptin, the FDA has required labeling and testing, and coverage policies have followed suit. Again, physicians can always opt to prescribe drugs off label (in this case, in the absence of the genetic test), if in their professional judgment the patient would benefit from the drug. However, unless a specific off-label use has become part of accepted medical practice or has been shown effective in high-quality studies, there is a good chance that a payer could deny reimbursement.

Reimbursement rates — Genetic tests generally are reimbursed under the same pathology CPT (current procedural technology) coding system and laboratory fee schedule as other laboratory tests. Payment amounts for new tests are linked to payment levels for existing tests based on the level of effort required to perform the test.⁶¹ (That is, whether a new test diagnoses a common virus or a complex pattern of genetic variations does not matter; if the two tests use the same laboratory technique, then they are reimbursed roughly the same amount.) When a test uses a breakthrough technology that has no precedent on the fee schedule, payers will conduct technology assessments to set reimbursement rates as they do for any other service. Currently, the Medicare laboratory fee schedule serves as the basis for many private insurers' laboratory reimbursement schedules. However, the Medicare schedule was designed almost 20 years ago, and laboratory testing technology has evolved so much since then that most experts agree that the fee schedule amounts have little logical relationship to the services they cover. In other words, labs are undercompensated for some tests and may be overcompensated for others. The Medicare Modernization Act of 2003 froze the Medicare laboratory fee schedule until 2009; many hope it will be comprehensively revised at that time.

Intellectual property — The pharmaceutical industry depends on intellectual property law to protect its investment in innovation, but many are concerned that current gene patenting and licensing practices could raise the costs and slow the development of pharmacogenomic therapies.⁶² By patenting genetic sequences⁶³ or methods to detect them, patent holders gain enormous control over all “downstream” commercial applications, including the right to keep others from developing a drug to target or a test to detect that gene.⁶⁴ Multiple genes or regions of genes are usually involved in regulating drug response; if competing entities hold patents on any of those genes or regions, they could “block” each other from developing a pharmacogenetic test unless they are willing to enter into

a cross-licensing agreement. A report by the National Research Council found evidence that licensing and royalty fees are already deterring laboratories from offering certain genetic tests.⁶⁵ Laboratory directors have testified that up-front flat fees and per-test royalties typically demanded by licensing agreements add 15 percent or more to the cost of tests and that such costs are not factored into existing laboratory fee schedules.⁶⁶ As pharmacogenomic tests become more complex and include more genes, the need to negotiate multiple patents and cross-licensing agreements could eventually make some tests too expensive or cumbersome for any but the biggest laboratories to offer. It has been suggested that new intellectual property concepts similar to patent pooling adopted in other industries may be needed to keep tests affordable and accessible.⁶⁷

Orphan Drugs

As an incentive to drug companies not to overlook small markets, the federal Orphan Drug Act provides manufacturers who develop therapies for rare diseases (those that affect fewer than 200,000 people) significant financial and marketing subsidies, including grants for research and development, "fast-track" approval, tax credits, non-negotiated pricing privileges, and a period of marketing exclusivity against competing products. The Act has been very successful, resulting in new drugs for over 200 rare diseases, and the FDA is actively encouraging drug companies to pursue pharmacogenomic approaches to more of the 6,000 remaining orphan diseases identified by NIH.* However, from a regulatory standpoint, pharmacogenomics could upend disease classification schemes and basic assumptions about what constitutes a rare disease.[†] Many relatively common diseases, like breast cancers, can now be subdivided on the basis of genomics into distinct and sometimes rare subtypes that require different drug therapies. It is just as possible that diverse rare diseases may turn out to share molecular genetic disease process that are amenable to the same drug.[‡] For example,

Novartis was able to secure orphan status for Gleevec on the grounds that the drug was indicated for a population of approximately 40,000 chronic myeloid leukemia patients with a particular chromosomal abnormality. However, Gleevec has since been shown useful in treating a rare gastrointestinal tumor that has a mutation in a different but related gene, and in October 2006 it was approved to treat yet another type of tumor as well as four rare blood diseases.[§] Additional indications for the drug likely will be found that are driven by a common set of genes. Given the significant incentives conferred by the Act, drug developers may find it attractive to submit drugs whose initial application would qualify for orphan drug status even before formally testing the drug for different indications that may share the same underlying mechanism. At some point, understanding these mechanisms could lead to a redefinition of rare disease; in the meantime the FDA will need to strike a careful balance between encouraging orphan drug applications to stimulate risky pharmacogenomics research and ensuring that those applications remain consistent with the intent of the Act.

* The Office of Rare Diseases at the NIH maintains a list of rare diseases and conditions at <http://rarediseases.info.nih.gov/asp/diseases/diseases.asp>.

† Paul D. Maher and Marlene Haffner, "Orphan Drug Designation and Pharmacogenomics: Options and Opportunities," *BioDrugs*, 20, no. 2 (2006): pp. 71–79.

‡ Jai Shah, "Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare," *Nature Biotechnology*, 21, no. 7 (July 2003): pp. 747–753.

§ "Novartis Drug Wins Expanded FDA Approval," *Associated Press*, October 19, 2006.

Physician uptake — Despite its apparent advantages over trial-and-error prescribing, pharmacogenomics will probably not be embraced by physicians in the absence of significant incentives to compensate for the extra time and education that will be needed to integrate this technology into their practices. Many physicians consider their diagnostic skills and prescribing decisions part of the “art” of medicine and will demand convincing evidence that information from genetic test results adds clinical value and leads to better outcomes for their patients. From a physicians’ perspective, pharmacogenomics may only complicate prescribing and drug dispensing by requiring an extra diagnostic step that includes additional paperwork, delays in care while waiting for the laboratory report, and longer patient visits to explain the complex results. Past experience in trying to change physician practice patterns, for example, to improve rates of preventive services and encourage adoption of electronic medical records, has demonstrated the need to provide strong incentives through reimbursement and performance feedback. However, creating appropriate practice incentives for pharmacogenomics could be very challenging given already daunting budgetary issues in Medicare Part B and competing priorities in quality and performance measurement systems.

Cost

It is often asserted that pharmacogenomics will produce cost savings to the health care system through better patient care and reduced drug development costs. These claims are difficult to evaluate at this early stage of the technology’s development. It is also possible that pharmacogenomics could contribute to increasing health care costs.

Important sources of potential cost savings include a reduction in the number of adverse drug reactions that not only place patients in danger but often result in emergency room visits and expensive rehabilitative care,⁶⁸ as well as the development of more effective therapies that require fewer return visits to physicians (and free up health care resources). For example, a recent effort to model savings from integrating genetic testing into routine warfarin therapy concluded that warfarin users in the United States would avoid 85,000 serious bleeding events and 17,000 strokes annually and save \$1.1 billion each year.⁶⁹ If pharmacogenomics enables doctors to prescribe more accurately and results in faster, more effective therapy with fewer side effects, it could indeed deliver savings throughout the health care system.

Supporters also anticipate cost savings from streamlining drug development. The Boston Consulting Group estimates that targeted drug development techniques could shave up to \$335 million and two years off the cost of bringing a new drug to market, mostly through shortening the time needed for clinical trials.⁷⁰

On the other hand, there are reasons to be skeptical that pharmacogenomics will be able to reduce health care costs overall. First, in order to significantly reduce the number of ineffective therapies and adverse

drug reactions, genetic testing and targeted prescribing would have to be widely deployed, and as noted earlier, there is little incentive for drug manufacturers to undertake the expense of developing or promoting pharmacogenomic tests for drugs that are already on the market. Public sector efforts, such as the PGRN and EGAPP have stepped in to develop and synthesize the scientific and clinical research base for some of the most often implicated drugs, but these efforts will take time. Getting specific findings, including pharmacogenomic testing and prescribing guidance, into the hands of receptive physicians and other health care professionals remains a challenge.

Second, most experts anticipate that companies will demand higher prices per unit of pharmacogenomically tailored drugs to make up for the smaller potential market. Indeed, companies already have demonstrated that they are willing to set and hold premium prices for pharmacogenomic tests and targeted therapeutics, even under intense public criticism.⁷¹ Moreover, new pharmacogenomic drugs will be patent-protected from generic competition for many years. Some suggest that the very biological precision that enables the new targeted drugs to command high prices will enable would-be competitors to “invent around” patented products by targeting different molecules in the same disease pathway, or by targeting the same molecule using a different mode of action.⁷² So far, however, there is little evidence from today’s drug marketplace that inventing around will put any significant downward pressure on price.

Third, whether pharmacogenomics will reduce the cost of clinical trials is still an open question. Currently, clinical trials in which subjects’ genetic variations are taken into consideration may be more expensive to operate than those trials where no genetic data are used.⁷³ According to a trade publication, “There is no question that applying pharmacogenomics to clinical trials increases the cost. There is added cost in the preclinical stages, where biomarkers must be identified and validated. Then there is extra cost in the clinic, where study design needs to take genetics into consideration....Using a pharmacogenomic approach could even slow down clinical trials if you must seek out a patient population that is enriched for your trial.”⁷⁴ Over the longer term, as technologies for identifying biomarkers and managing patient information evolve, it is possible that some of these costs may come down,⁷⁵ and it is possible that such trials will indeed be shorter, enabling the hoped-for savings in comparison to traditional trials. Whether overall savings are achieved will likely depend on the relative proportion of targeted (versus blockbuster) drug candidates for whom streamlined trials are appropriate.

Fourth, although pharmacogenomics may create opportunities to “rescue” failed drugs, it remains to be seen whether and under what circumstances pharmaceutical companies will find that option economically viable. Because intellectual property claims are filed long before regulatory approval, there will likely be limited life remaining on the original drug, compounded by

Whether pharmacogenomics will reduce the cost of clinical trials is still an open question.

the additional time involved for further testing that the FDA likely would require.⁷⁶ One possible scenario is illustrated by the multiple sclerosis drug Tysabri, which was pulled from the market in 2004 after concerns about a potentially dangerous side effect. The drug was reintroduced a year later with a label for a smaller population, a controlled distribution system to ensure that it is only given to patients for whom the risk is justified, and a price increase of 21 percent (to \$28,400 per year).⁷⁷

Fifth, it is possible that this technology can be used to exploit incentives in the current drug approval and reimbursement systems in ways that raise costs for consumers and the health care system overall. For example, as noted previously, health plans pay for drugs according to formularies that attempt to control costs by including a limited number of therapeutically equivalent drugs and negotiating pricing on the basis of formulary placement and tiering. However, if a drug maker can show, using pharmacogenomics techniques, that a particular drug produces a statistically better result (even if only marginally so) for a genetically defined group of patients, it may be able to differentiate a “me too” product into a “me only” drug, creating pressure to include it on the formulary at least for that group of patients.⁷⁸ As one pharmaceutical company executive has noted, “Even average drugs can become ‘superdrugs’ in the right population.”⁷⁹

Finally, some worry that pharmacogenomics will add costs without adding value. For example, very expensive drugs could be used in populations or for indications beyond those for whom they are designed, as has happened with Herceptin. Test-drug combinations may not produce clinically meaningful improvements in patient outcomes over current therapies. Or genetic testing could turn up lots of potentially “abnormal” results that are not clinically relevant but that would require massive additional resources to rule out. In the absence of comparative effectiveness and cost-benefit data that can assess the value of this technology as it evolves, such developments could be very challenging for policymakers and health care institutions to manage.

In addition, pharmacogenomics will certainly add direct service costs for genetic testing, data collection and analysis, and counseling. One expert summarized the issue this way: “It will be more cost effective, but it will not be cost saving. So you’ll pay more and you’ll get more, but you will not save money.”⁸⁰

Ethical Considerations

The ethical, legal, and social implications of pharmacogenomics have been widely acknowledged. In particular, issues associated with personal genetic data collection, use, and interpretation will require careful handling by policymakers.

Patient privacy — Many believe that statutory protection against discrimination on the basis of genetic information is an essential condition for pharmacogenomics to succeed. It is well documented that people will

hesitate or even refuse to participate in genetics research, take advantage of potentially helpful genetic tests, or disclose medical history information if they fear their data could be misused or their privacy violated. In a 2003 study on hereditary colon cancer, 39 percent of patients identified the potential effect on their health insurance as the most important reason not to undergo genetic testing to find out if they carried one of several known predisposing genes for the disease.⁸¹ Other observers have argued that it is unreasonable to single out genetic information for special protection given all the other biological sources of potential stigma, such as HIV status.

Guidelines for sample collection and storage — To be ethically valid, requests for patient consent to use identifiable biological samples in research must be clear about the purpose of the research, how the samples will be used, and who will have access to them. If these parameters change, patient consent must often be obtained again. What are the appropriate standards for security, access, and informed consent when patient DNA samples are being gathered as a routine part of clinical trials and stored for future exploratory analysis?

Collateral information — While pharmacogenomic tests to inform prescribing decisions may not be as sensitive per se as other types of genetic tests, it is possible that testing will turn up additional information about disease predisposition or progression that may be more information than people want. For example, the known association of the gene ApoE with Alzheimer's disease was identified during research on the polymorphisms of familial hyperlipoproteinemia (a form of cardiovascular disease).⁸² Procedures to gather the patient's preferences for handling such collateral information—to tell or not to tell—will need to be developed and implemented.⁸³

Race and pharmacogenomics — Many gene variants vary with geographic ancestry, including variants that are associated with drug response,⁸⁴ and indeed physicians have long recognized that race can be an important variable in predicting how individuals will respond to certain medications. Researchers are now exploring the contribution of racial genetics to drug safety and efficacy. For example, researchers at the University of California at Los Angeles are looking for genetic factors that specifically influence how Mexican Americans, African Americans, and whites respond to several different antidepressants. FDA recently has required manufacturers of carbamazepine (used to treat epilepsy, bipolar disorder, and neuropathic pain) to warn on the label that patients of Asian ancestry are at risk for a rare but severe skin reaction from the drug and should have a genetic test before starting treatment. However, there are many social and scientific arguments both for and against the use of race and ethnicity to categorize subjects in pharmacogenomic research and practice. The FDA's decision to approve the drug Bi-Dil for treatment of heart failure only in self-identified African Americans—the only subpopulation in which the clinical trial showed benefit—helped to crystallize the debate. Critics warned that drug research, development and approval based on the genetics of particular population groups could lead to new forms of social or medical stigmatization.⁸⁵ They also pointed out that the correlation between

It is well documented that people will hesitate or even refuse to participate in genetics research...if they fear their data could be misused or their privacy violated.

self-identified race and genetic ancestry is highly imperfect, particularly as multi-racial backgrounds become more common, and that a higher prevalence of a genetic variant in a racial or ethnic population does not predict whether any given individual member of that racial or ethnic group will have the variant. In addition, critics worry that distinctions based on race, rather than pathophysiology, might be trumped up for commercial advantage.⁸⁶ Supporters of FDA's decision argued that in the absence of more precise categories to identify responders versus non responders to the drug, self-identified race was the best available proxy to determine who will benefit (and who not) from a medication shown to be effective against a disease with high morbidity and mortality. Choosing to ignore the distinctions or waiting for different criteria to be developed would deny access to this useful drug to those who could benefit from it.⁸⁷ Ultimately, pharmacogenomic research may provide its own key to this dilemma, by developing more accurate and specific descriptions of relevant genetic variations that could replace imprecise racial and/or ethnic categories in predicting drug response.

CONCLUSION

Many believe that pharmacogenomics offers enormous potential for improving drug safety and effectiveness as well as the productivity of the drug development pipeline. Indeed it is possible that some day each individual will carry his or her unique genetic profile on a chip that physicians will consult before prescribing. Today, however, only a small number of drugs are associated with a genetic test to determine whether that drug is appropriate for a given patient.

Bringing pharmacogenomics from the realm of basic exploratory genetics research to safe, effective applications in the doctor's office will not be easy or inexpensive. It will require enormous investment and collaboration among a multitude of players, including the pharmaceutical, biotechnology, and diagnostics industries; their federal regulators; third-party payers; health professionals and the institutions that train them; health information technology planners; and many others. The science is immensely challenging, and the cost of research needed to translate scientific findings into clinically useful tools is high. Significant issues arise from the current business models of the pharmaceutical, biotechnology, and diagnostics industries, overlaid with the need to update the regulatory framework to address potential safety issues while supporting the development of pharmacogenomic products. There are additional challenges that accompany the integration of any new technology into modern health care, including the need to prove value to the health care system, to manage uptake through appropriate coverage and reimbursement policies and provider education, and to anticipate potentially significant ethical and social implications. Few of these issues are unique to pharmacogenomics, but all will need to be explicitly considered in the context of this technology.

ENDNOTES

1. Drug spending growth slowed in 2005, partially in response to public concerns about drug safety in the wake of highly publicized drug recalls. However, spending growth has picked up again in 2006. See Paul Ginsburg *et al.*, "Tracking Health Care Costs: Continued Stability But At High Rate in 2005," *Health Affairs*, 25 (October 3, 2006): pp. w486–w495.
2. Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The Price of Innovation: new estimates of drug development costs," *Journal of Health Economics*, 22 (2003): pp. 151–185. As noted by Arthur A. Daemmrich in *Pharmacopolitics: Drug Regulation in the United States and Germany* (University of North Carolina Press, 2004), DiMasi *et al.*'s estimates are not without controversy: their original 2001 analysis found that it costs an average outlay of \$402 million over the course of 10 to 15 years to develop a new drug, to which he added an "opportunity cost of capital" of \$400 million to arrive at the more than \$800 million estimate that pharmaceutical companies use to defend drug prices. In contrast, the Public Citizen's Health Research Group argues that once NIH research support and federal tax breaks are taken into account, it costs closer to \$150 million to bring a new chemical entity to market.
3. Brian Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Application of Pharmacogenomics," *TRENDS in Molecular Medicine*, 7, no 5 (May 2001): pp. 201–203.
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5. Two recent studies that women who did not test positive for the HER2 variant nevertheless responded to the drug have called into question the accuracy of certain laboratory tests used to determine HER2 status as well as the cutoff values used to determine whether a woman is HER2-positive. See this paper's discussion of genetic testing safety and quality.
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28. See EGAPP's Web site, available at www.egappreviews.org/default.htm.
29. For a list of current projects at CERTS, see www.certs.hhs.gov/projects/ongoing.html.
30. Gail H. Javitt and Kathy Hudson "Federal Neglect: Regulation of Genetic Testing," *Issues in Science and Technology*, 12 (Spring 2006): pp. 59–66. For a case in point, see the recent controversy surrounding the quality of genetic testing for Herceptin, as summarized by Andrew Pollack, "Cancer Drug May Elude Many Women Who Need It," *The New York Times*, June 12, 2007. In response to concerns about the current oversight of genetic testing, HHS Secretary Michael Levitt asked the Secretary's Advisory Committee on Genetics, Health, and Society (SAGHS) to "develop a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests." The November 5, 2007 draft SAGHS report, "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of HHS," is available at www4.od.nih.gov/oba/SACGHS/public_comments.htm.

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45. Some have suggested that academic detailing by pharmaceutical companies may be the most effective avenue to educate physicians about specific pharmacogenomic tests that are recommended on drug labels to guide prescribing; however, few companies actively discourage off-label prescribing because it generates additional sales. Off-label prescribing can also identify potential new indications that, if validated through formal studies and approved by the FDA, could extend a drug's patent protection.

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