Assessing the Cost-Effectiveness of Pharmacogenomics

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David L. Veenstra and Mitchell K. Higashi

Pharmaceutical Outcomes Research and Policy Program and Public Health Genetics Program, University of Washington, Department of Pharmacy, Seattle, WA, USA

Kathryn A. Phillips

Department of Clinical Pharmacy and Institute for Health Policy Studies, University of California-San Francisco, San Francisco, CA, USA

ABSTRACT The use of pharmacogenomics to individualize drug therapy offers the potential to improve drug effectiveness, reduce adverse side effects, and provide cost-effective pharmaceutical care. However, the combinations of disease, drug, and genetic test characteristics that will provide clinically useful and economically feasible therapeutic interventions have not been clearly elucidated. The purpose of this paper was to develop a framework for evaluating the potential cost-effectiveness of pharmacogenomic strategies that will help scientists better understand the strategic implications of their research, assist in the design of clinical trials, and provide a guide for health care providers making reimbursement decisions. We reviewed concepts of cost-effectiveness analysis and pharmacogenomics and identified 5 primary characteristics that will enhance the cost-effectiveness of pharmacogenomics: 1) there are severe clinical or economic consequence that are avoided through the use of pharmacogenomics, 2) monitoring drug response using current methods is difficult, 3) a well-established association between genotype and clinical phenotype exists, 4) there is a rapid and relatively inexpensive genetic test, and 5) the variant gene is relatively common. We used this framework to evaluate several examples of pharmacogenomics. We found that pharmacogenomics offers great potential to improve patients' health in a cost-effective manner. However, pharmacogenomics will not be applied to all currently marketed drugs, and careful evaluations are needed on a case-by-case basis before investing resources in research and development of pharmacogenomic-based therapeutics and making reimbursement decisions.

INTRODUCTION

The rapid advance of the Human Genome Project and the development of technologies such as gene chips, automated gene-sequencers, and bioinformatics software promise to bring a new era of genomics to medicine (1,2). Among the goals of integrating the large volumes of genomic information with the practice of medicine are 1) detection of patients with hereditary predisposition to disease, 2) development of gene-based drug therapies, and 3) the individualization of drug therapy based on an individual's genetic information. The third application is generally referred to as pharmacogenomics, and it will likely be one of the first tangible benefits resulting from the Human Genome Project (3).

The concept underlying pharmacogenomics is that response to drug therapy is variable, in part because of genetic variation. Genetic variations that are common (occurring in at least 1% of the population) are known as polymorphisms, and mutations of a single nucleotide are known as single nucleotide polymorphisms (SNPs) (4). More than one-third of human genes have been found to be polymorphic (5). A change in the nucleotide sequence of a gene can lead to a change in the amino acid sequence of the protein and altered enzymatic activity, protein stability, and binding affinities (6,7). Genetic variation can thus affect drug efficacy and safety when the mutations occur in proteins that are drug targets (e.g., receptors), are involved in drug transport mechanisms (e.g., ion channels), or are drug-metabolizing enzymes (3).

The term "pharmacogenetics" refers to the interaction of one gene (typically one involved in drug metabolism) with a drug, while

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Corresponding Author: David L. Veenstra, Pharmaceutical Outcomes Research and Policy Program, University of Washington, Department of Pharmacy, Box 357630, Health Sciences Bldg., Room H-375A, Seattle, WA 98195; telephone: 206-221-5684; fax: 206-543-3835; e-mail: veenstra@u.washington.edu

"pharmacogenomics" is a more general term that refers to the interaction between a drug and any gene, or multiple sites throughout the genome (3,8). Borrowing well-established terminology from pharmaceuticals, we separate pharmacogenomic therapies into those based on variation in drug targets (pharmacodynamic) and those based on variation in metabolic enzymes (pharmacokinetic).

Several recent publications have reviewed the implications of pharmacogenomics. These articles have focused on the impact of pharmacogenomics on the drug development process (9,10), regulatory aspects (11), or business implications (12,13), while others have been broader reviews (3,8). Many of these articles have suggested that the use of pharmacogenomics will be widespread and lead to cost savings for the health care system. We believe this issue deserves a more critical analysis and that the potential societal benefits of pharmacogenomics can best be assessed using a formal cost-effectiveness analysis framework.

The objective of this paper was to develop a framework for prospectively evaluating the incremental cost-effectiveness of pharmacogenomic-based therapies versus standard clinical practice. We then assessed several pharmacogenomic examples using this framework and highlighted future areas of research where we foresee the successful and cost-effective development of pharmacogenomic applications.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis provides a quantitative framework for evaluating the complex and often conflicting factors involved in the evaluation of health care technologies. It helps ensure that all costs and effects resulting from a health care intervention have been properly evaluated. The application of cost-effectiveness studies has increased dramatically in the past decade as a result of increasing health care costs and the desire to deliver the greatest health care value for the money. Recently, the United States Panel on Cost-Effectiveness in Health and Medicine provided general recommendations for performing such studies (14,15). Similar recommendations have recently been made in other countries (16,17) and in the U.S. managed care market (18).

Several types of economic evaluation are used in health care: cost-minimization, cost-consequences, cost-benefit, cost-effectiveness, and cost-utility analyses (Table 1). These methods vary primarily in the way they measure health outcomes, such as in monetary terms, number and severity of medical events, or quality of life-adjusted life expectancy. Although cost-effectiveness analysis is a specific type of economic evaluation, the term is commonly used (sometimes mistakenly) to refer to all types of economic evaluation in health care. Cost-utility analysis has been more accepted in health care than other types of economic evaluation because it measures benefit in patient-oriented terms (quality of life) and permits comparison between different interventions by standardizing the denominator (15). In a formal cost-utility analysis, the costs of clinician time required to provide the medical care, patient time away from work, and downstream medical care years or decades after the intervention as well as the quality of life of the patient and their family need to be considered. It is also important that the intervention be compared with current medical practice in an incremental analysis. The incremental cost-effectiveness ratio (ICER) is defined as

$$\text{ICER} = C_2 - C_1 / E_2 - E_1$$

where C_2 and E_2 are the cost and effectiveness of the new intervention being evaluated and C_1 and E_1 are the cost and effectiveness of the standard therapy.

Medical interventions are considered to be cost-effective when they produce health benefits at a cost comparable to that of other commonly accepted treatments. A general guide is that interventions that produce 1 quality-adjusted life-year (QALY, equivalent to 1 year of perfect health) for under \$50,000 are considered cost-effective, those that cost \$50,000 to \$100,000 per QALY are of questionable cost-effectiveness, and those above \$100,000 per QALY are not considered cost-effective (14).

The cost-effectiveness of health care technologies is driven by several primary factors: the cost and efficacy of the intervention, the morbidity and mortality of the disease, and the cost of treating the disease and its sequelae. Below, we review these factors in relation to pharmacogenomics.

Table 1. Types of economic evaluations in health care

Study design	Costs measured?	Effects measured?	Strengths	Weaknesses
Cost-minimization	yes	no	• easy to perform	• useful only if effectiveness assumed to be the same
Cost-consequences	yes	yes, typically in clinical terms	• data presented in straightforward fashion	• a ratio is not calculated, thus making comparisons of health interventions difficult
Cost-benefit	yes	yes, in economic terms	• good theoretical foundation • can be used within health care and across sectors of the economy	• less commonly accepted by health care decisionmakers. • evaluation of benefits methodologically challenging
Cost-effectiveness	yes	yes, in clinical terms	• relevant for clinicians • easily understandable	• cannot compare interventions across disease areas
Cost-utility	yes	yes, in quality-adjusted life-years (QALYs)	• incorporates quality of life • comparable across disease areas and interventions	• requires evaluation of patient preferences can be difficult to interpret

The cost of a genetic testing strategy includes more than just the cost of the test itself. Induced costs such as additional clinic visits, genetic counseling, and further diagnostics are potentially of greater magnitude and should be evaluated. Tests that have direct implications for patient care will be more efficient than those requiring additional follow-up. In general, interventions with a one-time cost that offer long-term benefits, such as immunizations, are often cost saving or cost-effective. Pharmacogenomics will sometimes fall in this category. Indeed, one of the benefits of genetic testing to predict drug response is that the information can be used throughout the lifetime of the patient. Thus, other potential uses of the genetic information obtained from a test may further offset the cost of the test. This is most likely to occur when the genetic variation affects more than one drug as with the P450 metabolic enzymes, for example.

Time costs are also relevant; if the test results are not available at the point of care, particularly for chronic medications prescribed by primary care providers, the additional clinical, administrative, and patient

time required to respond to the test results may negate any efficiency gained by providing the test. For conditions such as acute infectious processes, a delay in obtaining test results may have serious clinical consequences. In contrast, for disease areas like oncology, the availability of test results within a week's time frame may have only a minimal impact on overall treatment costs.

The effectiveness of pharmacogenomic tests in clinical practice will be determined by several factors in addition to the accuracy of the test. Genetic tests for detection of variant genes are typically quite accurate, with sensitivities and specificities near 99% when direct sequencing or restriction site assays are used. However, the degree of association between genotype and clinical phenotype will be equally as important. For example, if 50% of patients with a certain gene variant experience a severe adverse side effect from a drug, avoiding the use of the drug in all patients with the polymorphism would unnecessarily deprive half of the patients (the "false positives") of medication. The issue of "false-positives" will be important for almost all applications of pharmacogenomics, and the consequence of labeling

patients as having a genetic variation despite the fact that not all of them will have clinically relevant effects must be considered. The degree of phenotypic expression of genetic variation is known as gene penetrance. Thus, genes with high penetrance will be better candidates for cost-effective pharmacogenomic strategies. Note that the term "false positives" does not refer to patients who were falsely identified as having a variant gene, but rather to patients *with* a variant gene who do not express the clinical phenotype.

Several clinical and economic outcomes may drive the cost-effectiveness of pharmacogenomics. In the case of pharmacokinetic strategies, avoiding adverse drug effects may offset the cost of genetic testing and provide patient benefit. Thus, drugs that have a narrow therapeutic index, cause severe or expensive adverse side effects, and have significant interpatient variability will likely be better candidates for pharmacokinetic-based testing strategies. Testing costs for pharmacodynamic strategies, on the other hand, will be offset by avoiding unnecessary drug expenditures or by providing beneficial treatment to patients who would otherwise not have been treated. Thus, using pharmacodynamic-based testing will likely be more cost-effective for expensive or chronic medications or for drug therapies that are developed for genetically identifiable subpopulations.

The incremental cost-effectiveness of using pharmacogenomics to better predict toxicity or efficacy will depend on the current ability to accurately monitor patients for toxic effects and drug response and to individualize their therapy accordingly. Plasma drug levels are often used to monitor toxic drugs, while surrogate markers such as blood pressure for hypertension, lipid levels for hypercholesteremia, and blood glucose for diabetes are used to measure drug response for chronic diseases. When readily available, inexpensive, and validated means of monitoring drug response exist, pharmacogenomics may offer little incremental benefit. Pharmacogenomics will likely be most cost-effective for diseases in which monitoring disease progression and drug response is difficult.

Finally, the cost-effectiveness of preventative

screening strategies, such as pharmacogenomics, is highly dependent on the underlying prevalence of disease. In the case of pharmacogenomics, the frequency of the variant allele in the population being tested will be a critical factor. For example, if the frequency of a variant allele is 0.5%, only 1 patient with that variant allele would be detected for every 200 patients tested, on average. Thus, testing for variant alleles that occur infrequently will be cost-effective only in instances when the clinical and economic benefits of identifying patients with variant alleles are significant.

A COST-EFFECTIVENESS FRAMEWORK

We have defined a set of cost-effectiveness criteria for evaluating the potential cost-effectiveness of pharmacogenomics: severity of clinical outcome, ability to monitor drug response, genotype-phenotype association, assay characteristics, and variant allele frequency (Table 2). Before conducting a formal cost-effectiveness analysis, these criteria can be useful indicators as to which interventions warrant a full cost-effectiveness analysis. These criteria can also assist scientists in designing basic research strategies that will be more likely to result in clinically useful and economically viable improvements in patient care. Below we review several examples of pharmacogenomics and evaluate their potential cost-effectiveness using the framework outlined above.

Table 2. Framework for evaluating the potential cost-effectiveness of pharmacogenomic-based therapies

Factors	Characteristics favoring cost-effectiveness
Severity of outcome avoided	Severe outcome, including high mortality, significant impact on quality of life, or expensive medical care costs
Drug monitoring	Monitoring of drug response currently not practiced or difficult
Genotype-phenotype association	Strong association between gene variant and clinically relevant outcomes
Assay	A rapid and relatively inexpensive assay is available
Polymorphism	Variant allele frequency is relatively high

PHARMACODYNAMIC-BASED STRATEGIES***Cardiovascular disease***

A recent example of pharmacogenomics in the literature is the association of a variant allele of an enzyme (cholesteryl ester transfer protein [CETP]) involved in cholesterol metabolism with clinical response to pravastatin (19). Interestingly, drug response as measured by coronary vessel intraluminal diameter was correlated with CETP genotype but not with lipid levels. The implication of this study is that drug response may be predictable based on CETP genotype but not on lipid levels, the typically used surrogate marker.

Referring to our framework, we see that this application has several potential strengths. Although the outcome of administering pravastatin to a nonresponder in the short term may simply be hyperlipidemia for a month or two, a relatively low risk, the most important characteristic of this gene-drug interaction is that the outcome was not associated with lipid levels. Thus, using traditional monitoring methods would be problematic, and the

potential long-term outcomes (eg, myocardial infarction or death) would be not only clinically severe but also expensive (Table 3). The prevalence of the nonresponder genotype, 16%, is reasonably high, but further studies are needed to characterize this association and evaluate associations with clinical endpoints (eg, myocardial infarction or death).

Infectious disease

The use of genetic testing to identify viral genotype in the treatment of hepatitis C with interferon and ribivirin (combination therapy) provides an excellent case study in pharmacodynamic-based testing strategies. Although the viral genome, not the patient's genome, is tested, many of the clinical and economic implications are similar. In brief, patients with the more virulent viral genotype (genotype 1) respond significantly better to 48 weeks of treatment versus 24 weeks of treatment, while patients with non-genotype 1 respond similarly to 24 or 48 weeks of therapy (20).

Table 3. Assessment of the potential cost-effectiveness of pharmacogenomic interventions

Example	Outcome	Monitoring	Association	Assay	Prevalence	Overall assessment
CETP and pravastatin response	Short-term: minor Long-term: severe	Surrogate readily available, but not ideal	One report using surrogate outcome	Not readily available	Intermediate: 49% heterozygous, 16% homozygous	Unclear potential
HCV genotype and duration of combination therapy	Clinically severe and expensive	Difficult to predict sustained response	Very good	Commercially available, \$250	High: 60%	Appropriate application
CYP2C9 and warfarin metabolism	Rare, but clinically severe and expensive	Currently practiced	Some evidence, more studies needed	Available from research labs	Low/Intermediate: 30% heterozygous, <1% homozygous	Intermediate potential
TPMT and 6-MP metabolism	Clinically severe and expensive	Phenotypic assays available, but problematic	Good association with clinical phenotype	Commercially available soon	Low/Intermediate: 10% heterozygous, 0.3% homozygous	High potential

Abbreviations used: CETP, cholesteryl ester transfer protein; HCV, hepatitis C virus; 6-MP, 6-mercaptopurine; TPMT, thiopurine methyl transferase

Is it cost-effective to evaluate a patient's viral genotype and adjust the duration of therapy accordingly? Recent studies suggest that it is. Younossi and colleagues reported that genotyping was the most cost-effective strategy among a variety of treatment options (21). In a separate study, we estimated that genotyping saved \$750 per patient with no loss in efficacy compared with empiric 12-month therapy and added 0.33 QALYs per patient compared with empiric 6-month therapy (with an incremental cost-effectiveness ratio of \$3,500/QALY) (22). Thus, pharmacogenomics results in treating some patients for an extended duration but in a cost-effective manner. This application of genetic testing to guide drug therapy is cost-effective for several reasons: administering 6 months of unnecessary therapy is expensive; failing to achieve optimal sustained response rates leads to significant future morbidity, mortality, and costs; predicting sustained response is otherwise difficult; and the prevalence of genotype 1 is high, 60%.

The evaluation of viral genotype may also be clinically useful for individualizing HIV treatment cocktails. Several preliminary studies have suggested that HIV genotyping for resistance to protease inhibitors after treatment failure is relatively cost-effective (23,24). On the basis of the evidence to date, it appears that the genetic diagnosis of infectious disease in general will be a cost-effective application of pharmacogenomics. This paradigm can also be extended to genetic evaluation of tumor cells in oncology and customized chemotherapeutic regimens (25).

PHARMACOKINETIC-BASED STRATEGIES

Many of the examples of pharmacodynamic-based strategies are preliminary, and implementation in clinical practice may be years, even decades, in the future. In contrast, there has been extensive research on the genetic variation of enzymes involved in drug metabolism. Many of the first applications of pharmacogenomics will likely be in this area because of the extensive basic research conducted over the past several decades (26). We present several examples of pharmacokinetic-based pharmacogenomic strategies below.

Warfarin

The anticoagulant warfarin exhibits great variability in drug response, primarily because of disease, diet, and drug interactions. However, part of the variability has been attributed to polymorphisms of the enzyme that metabolizes warfarin, the cytochrome P450 enzyme CYP2C9 (27). Individuals who are deficient in CYP2C9 activity may be at higher risk for severe bleeding episodes and require lower starting doses or more frequent monitoring (28). The use of genetic information may thus assist clinicians in initiating and monitoring warfarin dosing.

The prevalence of heterozygotes is relatively high, approximately 30%, but patients with a null genotype are rare (<1%). In addition, serious bleeding episodes are rare in patients followed in anticoagulation clinics because warfarin therapy is closely monitored and individualized. Genetic testing will have to facilitate this process in a cost-effective manner. Whether evaluating warfarin patients for their CYP2C9 genotype will be cost-effective is not clear, and additional epidemiologic studies are needed to assess the association between CYP2C9 genotype and the risk for bleeding events.

Childhood leukemia

Polymorphisms of the thiopurine S-methyltransferase (TPMT) enzyme play an important role in metabolism of the antileukemic agent 6-mercaptopurine (6-MP), which is used for treatment of acute lymphoblastic leukemia (ALL) in children (29-32). TPMT is responsible for the inactivation of 6-MP, and TPMT deficiency is associated with severe hematopoietic toxicity when deficient patients are treated with standard doses of 6-MP.

Because the implications of overdosing 6-MP are serious, and because of the significant costs involved in treatment of ALL, testing children to establish their TPMT genotype before initiating therapy may be one of the best examples of pharmacogenomics that is not only clinically useful but also cost-effective.

As an illustrative example, we developed a simplified decision analytic model to evaluate the

potential cost-effectiveness of genotyping children before administering 6-MP (Figure 1). Decision analysis provides a quantitative method for evaluating decisions and can incorporate information from a variety of sources (33). As shown in Figure 1, children are either genotyped and their 6-MP dose modified accordingly, or they are given empiric therapy with standard dosing. They may develop severe hematopoietic toxicity, which can lead to death. Their likelihood of developing hematopoietic toxicity depends on their genotype and whether their genotype was known and dosing adjusted appropriately. By weighting the clinical events and their costs by their likelihood of occurrence, we can determine the strategy that provides the most value for the money.

We assumed the following in the base-case analysis: patients not dying from myelosuppression had a quality-adjusted life expectancy of 10 years (10 QALYs), the cost of treating myelosuppression was \$5,000, and the probability of severe myelosuppression for a patient deficient in TPMT was 90% without testing and 10% with testing (Table 4). The costs and probabilities used in the model are for illustrative purposes only. The following parameters were varied in a series of sensitivity analyses: cost of the test (\$5 to \$250), mortality due to severe myelosuppression (5% to 25%), and prevalence of patients with a TPMT-deficient genotype (0.3%, 0.5%, and 1.0%) (Figure 2). These 3 parameters are representative of 3 of the dimensions that affect the cost-effectiveness of pharmacogenomics: economic (cost of test), genetic (allele frequency), and clinical (mortality of myelosuppression).

As can be seen in Figure 2, it is immediately apparent that the variant allele frequency has a significant impact on the cost-effectiveness. At a null allele genotype frequency of 1.0%, the incremental cost-effectiveness of genetic testing falls below the commonly cited \$50,000/QALY cutoff for essentially all of the parameter combinations tested. By halving the frequency to 0.5%, there is a greater chance that testing would not be cost-effective. Finally, for a frequency of 0.3%, the actual frequency of the null allele genotype for TPMT, the cost-effectiveness of genetic testing is not clear. In

Figure 1. Decision model evaluating the hypothetical cost-effectiveness of thiopurine S-methyltransferase (TPMT) genotyping with 6-mercaptopurine (6-MP) therapy in children with acute lymphoblastic leukemia (ALL)

Table 4. Parameters used in decision model

Parameters	Base-case	Range
<u>Probabilities</u>		
Thiopurine S-methyltransferase (TPMT) deficient	0.5%	0.3%, 0.5%, 1.0%
Mortality with myelosuppression	25%	15% – 35%
Mortality without myelosuppression	10%	--
Myelosuppression without testing, TPMT deficient patients	90%	--
Myelosuppression with testing, TPMT deficient patients	10%	--
Myelosuppression with or without testing, TPMT normal patients	10%	--
<u>Outcome</u>		
Discounted quality-adjusted life expectancy (years)	10	--
<u>Costs</u>		
Genetic test	\$100	\$5 – \$250
Myelosuppression	\$5,000	--

Figure 2a: Influence of cost of genetic test and severity of clinical outcome on the hypothetical cost-effectiveness of TPMT genotyping with a deficient genotype prevalence of 0.3%.

Abbreviations used: QALY, quality-adjusted life-year; TPMT, thiopurine S-methyltransferase

Figure 2b: Influence of cost of genetic test and severity of clinical outcome on the hypothetical cost-effectiveness of TPMT genotyping with a deficient genotype prevalence of 0.5%.

Figure 2c: Influence of cost of genetic test and severity of clinical outcome on the hypothetical cost-effectiveness of TPMT genotyping with a deficient genotype prevalence of 1.0%.

this scenario, the cost of the test has a significant impact on the cost-effectiveness ratio because approximately 300 children must be tested, on average, to identify one that is TPMT deficient. Furthermore, with a high attributable mortality of severe myelosuppression (eg, >20%), genetic testing is cost-effective for all scenarios. This preliminary analysis suggests that genotyping children with ALL before administering 6-MP has the potential to be cost-effective, but a formal cost-effectiveness analysis is required.

DISCUSSION

Clearly, using pharmacogenomics to individualize drug therapy will have clinical and economic benefits. However, these benefits must be weighed against the additional cost of genotyping all patients to adjust therapy in a few. Our analysis suggests pharmacogenomics likely will be cost-effective only for certain combinations of disease, drug, gene, and test characteristics, and that the cost-effectiveness of pharmacogenomic-based therapies needs to be evaluated on a case-by-case basis. The framework we have developed can assist scientists, clinicians, and policymakers to evaluate the implications of pharmacogenomic strategies and identify when formal cost-effectiveness analysis should be conducted to quantitatively evaluate the added value of pharmacogenomic-based therapeutics.

We foresee pharmacogenomic applications being particularly relevant for drugs with a narrow therapeutic index and a high variability in response, for drugs for which measuring response is difficult, and for molecular diagnosis of disease, particularly in the area of genetically subtyping infectious diseases (Table 5). Oncology will be one of the most appropriate disease areas for the application of pharmacogenomics because of the high toxicity of chemotherapeutic agents and the severity of clinical outcomes in cancer.

The cost-effective application of pharmacodynamic-based strategies to chronic diseases such as hypertension, diabetes, and hypercholesterolemia may depend on one critical aspect—the validity of the surrogate markers that are commonly used to

Table 5. Examples of disease areas where pharmacogenomic applications may be cost-effective

Disease Area	Disease	Drug
Oncology	Breast cancer	Herceptin (25)
	FAP colon cancer	COX-2 inhibitors (34)
	ALL	6-MP (29–32)
Infectious disease	Hepatitis C	Interferon/Ribivirin (20–22)
	HIV	Protease inhibitors (23,24,35,36)
Respiratory disease	Asthma	B2-adrenergic receptor agonists (37,38)
Cardiovascular disease	Hyperlipidemia	Statins (19)
Mental health	Alzheimer's disease	Tacrine (39,40)
	Depression	SSRIs (41)

Abbreviations used: FAP, familial adenomatous polyposis; ALL, acute lymphoblastic leukemia; COX-2, cyclo-oxygenase 2; 6-MP, 6-mercaptopurine; SSRIs, selective serotonin reuptake inhibitors

measure disease progression and drug response (42). Pharmacogenomics may not be as cost-effective for diseases such as hypertension where drug individualization is essentially already practiced, in this case through the use of blood pressure monitoring to adjust dosing and modify drug selection. On the other hand, pharmacogenomics may be cost-effective for disease states such as asthma, where outcomes are acute and expensive (eg, emergency room visits) and attaining control of symptoms can be a trial-and-error process. Diseases such as Alzheimer's and depression are also good candidates because monitoring drug response is difficult and time consuming. As more therapeutic alternatives become available for many disease states, pharmacogenomics will become increasingly important to assist in drug selection.

There is significant opportunity to develop pharmaceuticals targeted to patients based on

genotype. Such drugs may not have passed regulatory scrutiny using a population-wide approach because of adverse drug effects in some patients, but they could prove to be quite cost-effective if targeted appropriately to specific patients. A key business issue will be the market incentives for pharmaceutical and biotechnology companies to develop such targeted drugs. Decreased market sizes may be offset by better market penetration, added value of the drug, decreased development costs resulting from streamlined clinical trials, and regulatory incentives to develop pharmacogenomic strategies. Cost-effectiveness analysis can be used to assist such policy decisions.

Other authors have also evaluated the potential impact of pharmacogenomics on health care. Lichter and Kurth concluded that pharmacogenomics will be cost-effective "sometimes," but suggested pharmacogenomics would be cost-effective primarily for chronic disease states where many years of unnecessary drug therapy could be avoided (43). We believe pharmacogenomics will be cost-effective for chronic diseases only if there is no validated means of measuring drug response. The authors also suggested acute illnesses might not be amenable to pharmacogenomic therapies because the drug cost offsets will be low. In contrast, we think that acute diseases may be amenable to pharmacogenomics if the disease outcomes or adverse drug reactions are severe. Lichter and Kurth also raise the important point about willingness to pay for individualized drug therapy. Society, particularly in the United States, may be willing to pay more for individualized drug therapy than the generally accepted \$50,000 per QALY.

Rioux, in an analysis of genetic factors important for drug development, reached conclusions similar to ours (44). He concluded that pharmacogenomics would be best applied for life-threatening or chronic diseases, especially for chronic diseases for which treatment response is difficult to evaluate. Rioux also elucidated the importance of variant allele frequency on the usefulness of pharmacogenomics.

An important limitation of our analysis is that the demand for genetic tests may not be highly correlated with cost-effectiveness. In addition,

pricing of genetic tests and drugs developed specifically for genetic subpopulations will not necessarily be based on cost-effectiveness. Cost-effectiveness analysis should be used for informing resource allocation decisions at the population-based level. Decisions about individual patient care should incorporate individual patient preferences for genetic testing. There are also potentially significant concerns about the ethics of genetic testing that cost-effectiveness analysis is not able to address. In pharmacogenomics, drug response often may not be linked to a polymorphism that is associated with disease risk; thus, ethical issues, and privacy concerns with regard to life insurance and employment, may be different than those for genetic markers that are linked to disease risk.

Pharmacogenomics has great potential to improve the effectiveness and safety of pharmaceutical care. However, pharmacogenomic strategies will be cost-effective only for certain combinations of disease, gene, drug, and test characteristics. Pharmacogenomic-based therapeutics should thus be evaluated in light of their potential cost-effectiveness before investments in research, development, and health care resources are made.

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