Economic Opportunities and Challenges for Pharmacogenomics

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Annu. Rev. Pharmacol. Toxicol. 2010. 50:423–37

First published online as a Review in Advance on November 13, 2009

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev.pharmtox.010909.105805

0362-1642/10/0210-0423$20.00

Annu. Rev. Pharmacol. Toxicol. 2010.50:423-437.

Key Words

costs and cost analysis, public policy, health policy, outcomes assessments (health care)

Abstract

Economic evaluation provides health care decision makers with a powerful tool for resource allocation decisions because it offers a framework for comparing the costs and benefits of competing interventions or options. This paper reviews how economic analyses have been applied to the field of pharmacogenomics, both by the pharmaceutical industry to inform investment decisions and by payers to make coverage decisions. There is much anticipation that pharmacogenomic testing is likely to be cost-effective because it uses genomic information to improve drug effectiveness and reduce toxicity both in the drug development process and at the bedside. However, the demonstration of economic benefits first requires that pharmacogenomic testing show evidence of clinical effectiveness. This will only be achieved by greater participation of pharmacogenomics experts in comparative effectiveness research and additional emphasis on including costs in the determination of the relative value of pharmacogenomic testing to the health care system.

INTRODUCTION

Pharmacogenomics, the science of how genetics influences an individual's response to medication, has the potential to significantly improve both drug development and drug therapy decision making. The benefits of pharmacogenomics range from enhancing the efficiency of clinical trials of new drugs to targeting medications in clinical practice to achieve better health and economic outcomes for patients. For example, understanding how overexpression of the HER2 oncoprotein predicts the response to the monoclonal antibody trastuzumab (Herceptin®; Genentech) enables clinicians to tailor trastuzumab treatment to individual breast cancer patients and avoid the morbidity and costs associated with adverse drug reactions or lack of effectiveness to this agent (1). Although there are a growing number of promising examples of pharmacogenomic tests in clinical practice today, the majority of these tests are limited to specialty care such as oncology, with relatively limited diffusion of pharmacogenomic testing into primary care settings. The reasons for the delays in broader integration into the clinic include the complexity of the underlying science, as well as an intricate array of clinical, economic, and organizational barriers to the effective delivery of molecular medicine (2).

In the meantime, the processes of drug discovery and development have become increasingly expensive (3) and inefficient (4), with fewer new drugs being approved (5) and heightened concerns about the safety of marketed drugs (6). Clinicians and patients understand firsthand that drug response is often unpredictable and suboptimal, and there is compelling biological plausibility for the hypothesis that some of this variability in treatment outcomes might be explained by genetic differences among individuals (7). Pharmacogenomics promises to at least partially address all of these concerns through the use of genomics-based tests to better predict medication response (8). It also offers the potential for significant economic benefits, both in the immediate term through the avoidance of potentially unsafe or ineffective medications in specific patients and in the longer term because patients on targeted drug treatments are more likely to experience improved health outcomes (9).

These improvements in health care quality and efficiency are particularly important as both public and private payers struggle with the rising costs of health care. In the United States, total health care spending has risen from approximately 8% of gross domestic product in 1975 to 16% in 2006 and is projected to reach almost 20% in 2016, with the major driver of this trend identified as increases in per-enrollee spending (10). One of the major sources fueling the real growth in health care expenditures over the past several decades has been the development and diffusion of new medical technologies and interventions, not changes in population demographics or disease prevalence (11, 12). After a period of slowing, pharmaceuticals have again become one of the fastest growing components of health care spending, owing to public financing of prescription drug benefits through Medicare Part D and the growth of specialty drugs (13) that are often biotechnology based, complex to administer, indicated for serious diseases, and very expensive. Payers are particularly interested in pharmacogenomics as a science-based tool to target the use of specialty drugs to patients most likely to benefit.

ECONOMIC EVALUATIONS

Faced with a continuing surge of new products and services and limited health care resources, decision makers at all levels are interested in assessing whether they are receiving value (see sidebar) in return for their investment in health care. The framework for determining value is an assessment of the relative costs and health outcomes (benefits) associated with competing health care interventions, and economics is the discipline that provides the quantitative methods for comparing the

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VALUE

An explicit examination of the resources consumed for the outputs achieved. In health care this typically involves both health outcomes and health care costs, but these measures can be narrowly or broadly defined depending on the perspective of the decision maker. For example, the determination of value might differ from consumer to insurer to societal perspectives.

costs and benefits of different health care interventions (see **Table 1**). Cost-effectiveness analysis is a well-established framework within health care for informing decisions at numerous levels: technology assessment, insurance coverage and reimbursement, drug development, and most recently pharmacogenomics, because it examines the incremental costs and changes in health status of various health care choices, given limited resources (14).

These investigations not only answer the question, "Does it work?" (ideally by comparing the new health care technology to the standard of care), but most explicitly address the question, "Is it worth it?" and can inform a range of resource allocation decisions depending on the perspective that is adopted for the analysis (15). For example, payers and clinicians want to understand whether current evidence supports the conclusion that genomics-guided dosing of warfarin therapy produces better health outcomes than standard induction of this widely prescribed anticoagulant (16) and if the addition of pharmacogenomic testing to warfarin dosing algorithms is likely to be cost-effective (17). Developers in the pharmaceutical industry also employ economic analysis (and cost-effectiveness frameworks specifically) to evaluate the impact of pairing a pharmacogenomic

Table 1 Economic evaluations of health care interventions

Cost-identification
Estimates and compares the net costs of different strategies
Does not explicitly consider health outcomes
Cost-consequence
Computes and lists components of costs and consequences of alternative programs, without aggregating results into a single measure
Does not permit comparisons across diverse diseases or conditions
Cost-benefit
Measures and compares all costs and benefits in monetary terms
Monetary valuation of health outcomes controversial
Cost-effectiveness
Quantifies both economic and health benefits in a single ratio
Easily understandable but cannot compare interventions across disease areas
Can measure health effects in disease-specific terms, but preferred method evaluates interventions using a standard measurement (life expectancy; year of life gained)
Cost-utility
Recommended by several expert consensus groups
Measures health benefit in terms of QALYs (quality-adjusted life years)*
Incorporates values or preferences people place on different outcomes
Allows comparisons across disease areas and interventions

*QALY: A quality-adjusted life year uses utility scores between 0 (death) and 1 (perfect health) to adjust a life year in terms of its quality. For example, a year spent in poor health might have a utility score of 0.4, and thus a year of life in such a state would be equal to $1 \times 0.4 = 0.4$ QALYs.

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test with a drug to segment the market into responders and nonresponders and use this information to predict the likely effects of pharmacogenomics on incentives for innovation and the pharmaceutical industry's business model (18). This information is then used to make investment decisions regarding whether to codevelop a drug and diagnostic or use a pharmacogenomic test to rescue a drug that has an unacceptable safety profile in the general population by identifying a patient subgroup that is less likely to experience an adverse reaction to the drug while still receiving the desirable therapeutic benefit.

In this paper, we discuss both types of economic evaluations—those that focus on characterizing the long-term health benefits of pharmacogenomics at the population level and are useful for shaping research and development investment decisions, as well as those that focus on assessing the near-term health benefits of integrating pharmacogenomics into clinical practice now and are useful for coverage and reimbursement decision making. Both types of evaluations are based on a similar set of assumptions about the likely benefits and costs of pharmacogenomics, all predicated on the notion that pharmacogenomic testing will improve drug safety and effectiveness by using molecular diagnostics to either (a) identify responders versus nonresponders or (b) identify patients at increased risk for drug toxicity. This stratification of the population on the basis of pharmacogenomic testing is intended to reduce the use of ineffective or unsafe drugs, which should translate into improved health outcomes for patients and more efficient use of health care resources.

Assuming that the initial promise of pharmacogenomics is supported by the science, we also need to presuppose that pharmacogenomic testing will diffuse appropriately into clinical practice for any given disease treated with a pharmacogenomic-linked drug. For example, there are real concerns that the benefits of pharmacogenomic testing will not be realized on a large scale without first investing in extensive provider education and training in genetics, as well as a twenty-first-century information technology infrastructure capable of storing and sharing (real-time) complex medical information in a secure environment (2). When both the upstream [research and development (R&D)] and downstream (health care delivery system) economic implications of pharmacogenomics are considered, the situation becomes even more complicated, and conclusions regarding value (cost in relationship to outcome) will be most heavily influenced by the perspective of the decision maker (see **Table 2**). Nevertheless, any economic projections of the societal benefits of the technological advances in pharmacogenomics depend largely on the quality of the evidence demonstrating the clinical utility (net balance of risks and benefits of using the test in routine practice) (see sidebar) of pharmacogenomic testing. As one health economist eloquently stated, "A technology cannot be cost-effective if it is not effective" (19).

IMPACT OF PHARMACOGENOMICS ON PHARMACEUTICAL R&D

It is a basic economic principle that expected financial returns drive R&D spending and hence the rate of innovation. Pharmaceutical R&D is expensive and uncertain, and in the United States we incentivize this investment by granting temporary monopoly rights to innovators in the form

CLINICAL UTILITY

A term used to refer to the net balance of risks and benefits associated with using a pharmacogenomic test in clinical practice, including its ability to inform clinical decision making, prevent adverse health outcomes, and predict outcomes considered important to patients and their families.

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Table 2 Potential economic consequences of pharmacogenomics

	Increased Costs	Decreased Costs
Patient	Higher drug prices	Reduced likelihood of adverse events
	Pharmacogenomic test costs	Avoidance of ineffective medication
		Improved medication compliance
		Improved health outcomes
Providers/payers	Higher drug prices	Reduced health care resource utilization
	Pharmacogenomic test costs (including costs of false positive and false negative tests)	Avoidance of treatment for those who do not need it
	Expanded patient populations for drugs	Improved response rates for treatment of diseases
	Expanded patent protection for drug and test combination (potentially)	Avoidance of unsafe medications
	Genetic test training, interpretation	Decreased liability and malpractice
Pharmaceutical industry	Higher development costs in short term (development and validation of biomarkers)	Improved decision making and lower attrition
	Evolving regulatory environment (test approval process for diagnostics becoming more rigorous)	Focused discovery and development programs
	Loss of blockbuster drug business model	Earlier approval of new therapies
	Cultural differences between drug and diagnostics industries	Greater confidence in postmarketing surveillance systems
		Expanded patient populations for drugs

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of patents. Pharmacogenomics is only likely to alter this landscape if it increases the probability of successfully developing a new drug or lowers the costs. One way for this to occur is to use pharmacogenomic test information to create an enriched population of responders so that the drug development process can become more efficient. Smaller (and perhaps shorter) clinical trials are likely to reduce drug development costs to the extent that clinical trial costs vary with clinical trial sizes.

As a real-world example of this principle, consider the case of the biologic Herceptin (trastuzumab), which is approved for both adjuvant and metastatic treatment indications in patients with breast cancer. Genentech, the company that produces Herceptin, found that conducting a clinical trial using pharmacogenomic screening reduced the development costs and the time it took to bring the product to the market for patients (20). Specifically, using a diagnostic test to select and enroll patients who were HER2 positive enabled Genentech to conduct a study with only 470 enrollees, rather than the 2200 patients that would have been required without an ability to prescreen (21). Moreover, as Cook et al. note, "the time to bring the product to market was also reduced. The time for the larger study was projected to be 10 years, while the actual study took only 1.6 years. Overall, the clinical trial costs were (also) reduced by an estimated $35 million" (20).

However, development of a drug and a pharmacogenomic test in parallel has been fairly atypical to date, and it is equally plausible that the costs and risks of discovering and validating new pharmacogenomic tests will introduce additional costs and complexity to the inherently risky process of drug development. Moreover, significant differences in the business models, regulatory requirements, and company cultures between the pharmaceutical industry and the diagnostics industry complicate and potentially undermine the scientific and economic drivers for drug-diagnostic codevelopment strategies. What we have learned from case examples of anticancer drugs such as

irinotecan (Camptosar®; Pfizer) and gefitinib (Iressa®; AstraZeneca) that have become stratified based on a postapproval understanding of the molecular basis of treatment response is that pharmacogenomic testing can play a variable role in predicting the clinical adoption and market success of the drug (22). Depending on the particular clinical parameter (safety, effectiveness) predicted by the pharmacogenomic test, a unique set of complex factors will influence the investment decisions within the biopharmaceutical and diagnostics industries, leading us to conclude that future investment decisions in pharmacogenomics by the private sector will most likely be made on a case-by-case basis.

Another way pharmacogenomics may prove useful to industry is through the rescue of products that would otherwise have failed in development because of apparently idiosyncratic adverse drug reactions in a subset of the target population. However, if these adverse drug reactions can be linked to pharmacogenomic markers, then products that otherwise would have been terminated in the development process (or rejected or delayed for approval by the FDA) could potentially be made available to patients who test negative for the genetic variants associated with an increased risk for the adverse reaction. This strategy is most promising for investigational drugs because the stigma and liability concerns associated with a previously marketed drug with a known adverse event profile are likely to complicate its subsequent use despite its new pairing with a pharmacogenomic test designed to identify patients at increased risk of toxicity (23). One example of a pharmacogenomic test that has helped overcome an undesirable safety profile limiting the use of a potentially effective drug is in the setting of treatment for HIV/AIDS. Patients are tested for specific HLA haplotypes prior to receiving treatment with abacavir, a nucleoside reverse transcriptase inhibitor that has been associated with severe hypersensitivity reactions in patients with certain germline variants (HLA*B5701) (24). The economic advantages of drug rescue on a broad scale remain plausible but essentially unproven and will most likely require both postmarketing risk-management strategies and changes to the legal system to occur in parallel with advances in pharmacogenomics.

The consequence of shorter, less expensive drug development programs, when coupled with the higher drug development success rates (fewer products failing in the development process) is a lower cost of drug development. Recent estimates place the cost of drug development at more than $1 billion (inflated by the consumer price index) (25); therefore, any scientific advances such as pharmacogenomics that are likely to positively impact the economics of drug development merit careful examination in order to direct research and development spending in a manner that both maximizes return on investment and fuels future innovation.

Specifically, the net effect of pharmacogenomic testing in terms of higher probabilities of technical success, (e.g., smaller and less expensive clinical trials, shorter average development times, more products gaining FDA approval, etc.) will be to lower the expected costs of drug development. This will mean that more R&D projects will be profitable and thus undertaken by firms. Another critical factor influencing the economic profile of a new drug is the time to product launch. If a drug can reach the market earlier because pharmacogenomic testing has streamlined the drug development process, cash flows to the company will be received sooner, which as basic finance shows, increases the present value of future cash flows. Also, products reaching the market sooner will have longer periods of patent protection, which also increase expected economic returns (see sidebar).

The impacts of all of these variables on firm cash flows are illustrated in **Figure 1**, and a more detailed analysis of various economic scenarios for the industry can be found in Reference 26. For example, given that estimates of the value of a life year in the United States range from $100,000 to $175,000 (27), then any pharmacogenomic strategies that alter the clinical epidemiology of debilitating diseases such as Alzheimer's disease, cancer, diabetes, or cardiovascular disease would

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EXPECTED ECONOMIC RETURNS (OR NET PRESENT VALUES)

This is an expectation at a point in time that reflects net (costs and benefits) present values. A positive expected net present value (NPV) indicates an expected positive return, as expected present value benefits exceed expected present value costs. NPV is a commonly used method in finance (and used by firms) to assess the commercial viability of potential new products. A positive NPV represents a good investment: one where benefits exceed costs. A negative NPV represents a bad investment: one where costs exceed benefits.

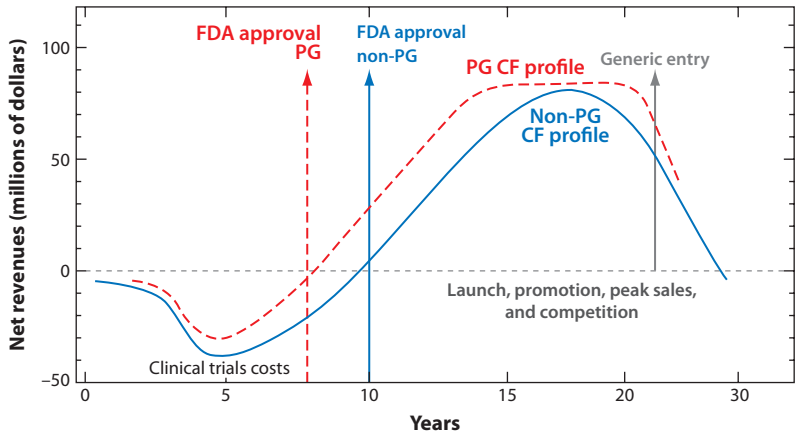

Figure 1

An economic model of the impact of pharmacogenomics (PG) on life-cycle product cash flows (CFs).

have tremendous social value. Thus, the argument can be made that the United States (and the global research enterprise more generally because the United States invests the most in medical and pharmaceutical R&D) is currently underinvesting in biomedical research owing to the size and value of the long-term health-related benefits relative to the cost of the research. From an industry perspective, that value needs to be captured in terms of premium pricing, faster adoption, or longer effective patent life for a portfolio of targeted drugs, to offset the reduction in potential revenues from market stratification (22). Economic evaluation of the potential trade-offs of pharmacogenomic-guided drug therapy is a useful tool for developers to use to model these investment opportunities and help ensure commercial success.

IMPACT OF PHARMACOGENOMICS ON CLINICAL PRACTICE

Whereas there are many theoretically promising applications for pharmacogenomic testing in clinical practice, there are significant barriers to assessing the relative contribution of pharmacogenomics for improving the management of chronic conditions such as Alzheimer's disease, cardiovascular disease, depression, and diabetes. Examples of some of the measurement challenges include the presence of multiple pathways involved in drug effects, multiple polymorphisms, gene-environment interactions, length of time between testing and clinical outcomes, and multiple determinants of clinical outcomes. In the absence of empiric evidence, economists have used mathematical modeling techniques to identify circumstances where pharmacogenomic testing is likely to be cost-effective, such as for drugs with a narrow therapeutic index whose biological

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effects are mediated by prevalent pharmacogenomic variants that can be reliably detected with high sensitivity and specificity (28). To date, few examples exist outside of oncology and HIV-AIDS, where pharmacogenomic testing has been shown to be cost-effective in clinical practice, although rapid scientific advances in the field of personalized medicine in general have alerted clinicians and payers to be prepared for an influx of new pharmacogenomic tests across a wider range of therapeutic areas. These tests may prove to be cost-effective, particularly if they are useful in guiding the use of expensive biologic agents.

Although cost-effectiveness analysis provides a rational framework for comparing the costs and outcomes of various health care interventions and numerous guidelines and recommendations exist for conducting these evaluations for health care and even for pharmacogenomic tests specifically (9, 29), there historically has been political resistance to the explicit use of cost-effectiveness analysis in the United States (30). This situation may be slowly changing as part of health care reform efforts, but ongoing efforts are also being made to link considerations of value to coverage and reimbursement decision making (value-based purchasing). As stated previously, any determination of value requires an assessment of both costs and outcomes, which is precisely the approach economists follow in cost-effectiveness analysis.

In the United States, most new medical technologies require coverage and reimbursement by a third-party payer such as a private or public health care insurer before they are accessible to patients. The trend in the payer community is to apply evidence-based approaches to the evaluation of new medical technologies to support the use of effective health care interventions and avoid payment for ineffective care. Early evidence exists that this same framework for coverage decision making and the emphasis on value-based purchasing is directly relevant to the diffusion of new pharmacogenomic tests into clinical practice, but the decision-making process is highly decentralized. For example, although the warfarin package insert has been updated to include information about the association between the inherited variation in cytochrome P450 2C9 and VKORC1 and warfarin responsiveness, and although there are numerous commercially available (including FDA-approved) pharmacogenomic tests for these genes, the payer community is divided regarding their conclusions about whether to pay for testing based on the available evidence. Whereas several algorithms have been developed to alter initial warfarin dosing based on genotype, no completed prospective studies demonstrate that genotype-guided therapy improves anticoagulation control or reduces the risks of hemorrhagic or thromboembolic complications (31). In the United States, it is commonplace that payers are put in the position of having to decide whether a new technology merits coverage or has value based on incomplete data because the published studies are typically designed for other purposes (e.g., regulatory approval, academia).

In the meantime, experts continue to call for not only prospective evidence of the clinical benefits, but also studies to evaluate the costs of implementing routine pharmacogenomic testing for warfarin dosing (32). This is probably not surprising given the conflicting estimates of the likely cost-effectiveness (ranging from very favorable to unfavorable) of using pharmacogenomic information to guide warfarin dosing based on modeling studies with varying assumptions regarding expected benefits (33, 34). Most recently, the Centers for Medicare and Medicaid Services decided not to support reimbursement for pharmacogenomic testing to guide warfarin management because they felt the available evidence did not demonstrate that pharmacogenomic tests that predict warfarin responsiveness improve health outcomes in Medicare beneficiaries. Instead, they proposed paying for warfarin pharmacogenomic testing only in the setting of "coverage with evidence development" (a clinical trial designed to answer one or more questions regarding prespecified health outcomes) (35).

This warfarin case analysis highlights that the field of pharmacogenomics needs to move beyond association studies to demonstrate that use of pharmacogenomic testing in clinical practice

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improves health outcomes for patients compared with usual care. Particularly for tests with high unit costs or tests that target high-risk patient groups, developers should anticipate additional scrutiny from payers regarding whether pharmacogenomic testing is likely to be cost-effective. The validity and reliability of the economic analyses designed to address this issue are directly linked to the quality of the underlying effectiveness data.

For a pharmacogenomic test to be useful in clinical practice, it must provide reliable, actionable, and predictive information that the clinician would otherwise not know, and an alternative drug or dosing regimen must have been studied (36). This evidence threshold is much higher than the standards required for regulatory approval of the test itself and may explain why, even for FDA-approved pharmacogenomic tests with applicability to drugs with specific pharmacogenetic information in the product label, there is highly variable payer response in the marketplace. Where there are prospective data such as for HLA-B*5701 testing and abacavir, reimbursement for the pharmacogenomic test has been consistent; where the data are lacking, such as with the cytochrome P450 genotyping test for 2D6 variants and targeting antidepressant therapy with selective serotonin reuptake inhibitors (36a), reimbursement for the test has been limited.

Payers act on the same evidence base used by clinicians and professional societies to determine whether there is sufficient evidence to support the use of the test in clinical practice. Ideally, this information would come from well-controlled trials powered to examine clinical end points, rather than relying on retrospective association data that are much weaker and therefore less likely to change clinical practice. However, from a practical perspective, it is unlikely that randomized controlled trials will be conducted for all new pharmacogenomic tests that enter the market. In the absence of prospectively collected data, economists often create mathematical models, but historically these studies in the field of pharmacogenomics have been of relatively poor quality (37, 38). More recent publications of cost-effectiveness models in the areas of oncology and HIV are examples of well-conducted studies that can provide useful information to decision makers (39, 40).

RECOMMENDATIONS

The economic challenges and opportunities for payers and providers stem from the interdependent factors (and associated costs) that result from the decision to implement a pharmacogenomic test in clinical practice, such as impacts on treatment decisions, impacts on health outcomes, impacts on adverse events, impacts on health care utilization, test accuracy, delivery system readiness, etc.—all of which must be accounted for beyond simply the cost of the pharmacogenomic test. Similarly, the economic challenges and opportunities for industry stem from balancing the requirements for the initial (and potentially risky) investments in pharmacogenomic research against the longer-term presumed benefits of drug development efficiencies and return on investment. The combination of all these factors emphasizes the significant upside that exists if the science of pharmacogenomics evolves as predicted for a range of chronic diseases. Gains in life expectancy and improvements in population health are potentially enormous when valued in economic terms and provide a strong justification for expanding our investment in pharmacogenomic research, given that we are only beginning to understand the relative contribution of genomics to predicting drug response. However, before these health benefits and corresponding cost offsets can be achieved, many steps must occur for a promising new biomarker to be integrated into clinical practice as a pharmacogenomic test with proven clinical utility and adequate reimbursement.

The only way to know whether we are achieving the intended health and economic consequences for pharmacogenomics is through the types of questions and corresponding answers that are generated at the various stages of clinical translation and implementation (see **Figure 2**). The

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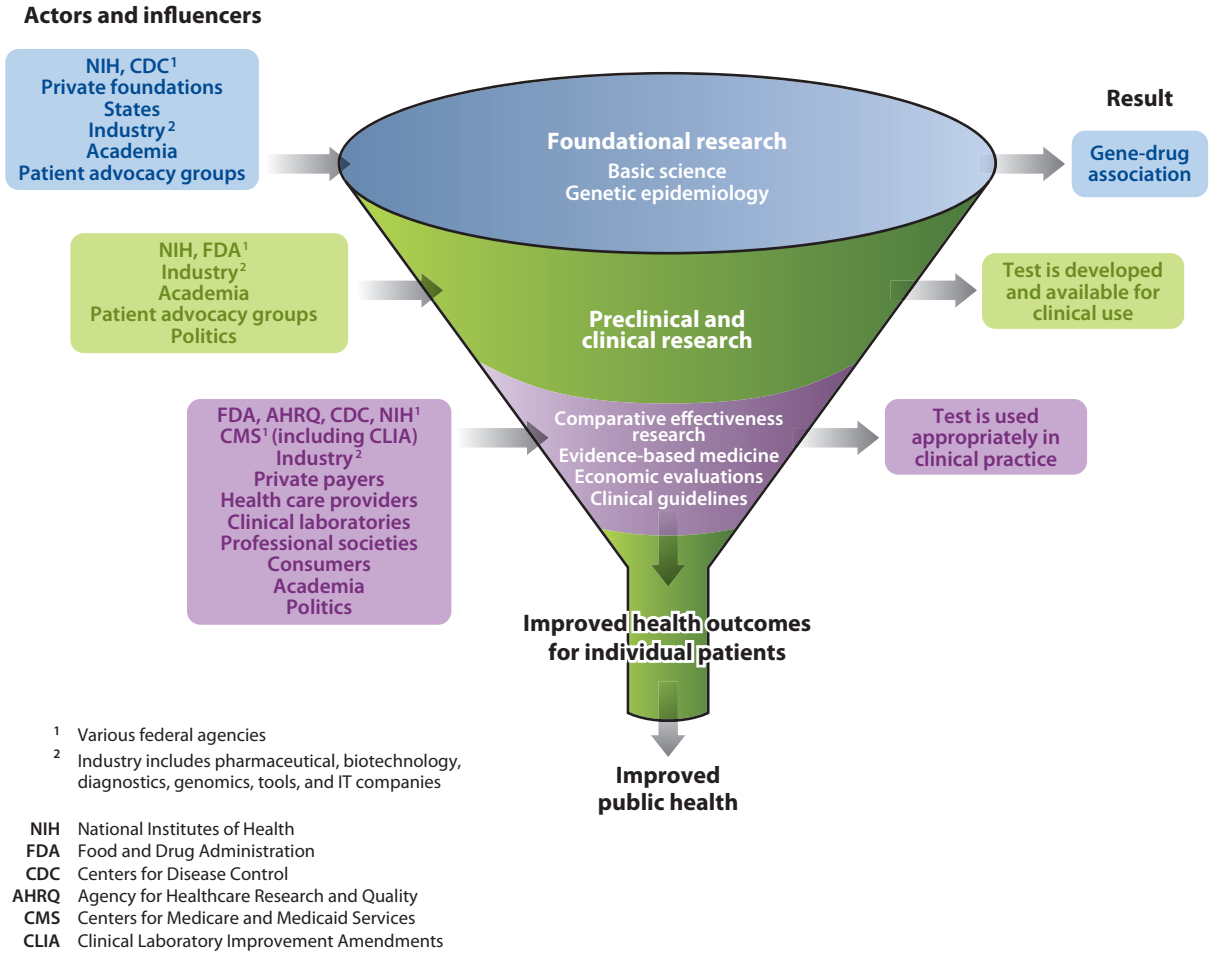

Figure 2

The translational pathway for pharmacogenomics is an information funnel.

existing translational pathway for new pharmacogenomic tests is essentially an information funnel that starts with basic research at the top of the funnel, leading to preclinical and clinical research in the middle part of the funnel, and culminating in comparative effectiveness research (see sidebar) at the bottom of the funnel. Each of the three categories of research is separated from the others by a horizontal line that essentially acts as an information filter; new evidence is required before progressing to the next lower level of the funnel. The information that flows through the funnel

COMPARATIVE EFFECTIVENESS RESEARCH

The generation and synthesis of evidence that compares the effectiveness of alternative methods to prevent, diagnose, treat, monitor, and improve delivery of care for a clinical condition. The purpose of comparative effectiveness research is to assist patients, clinicians, purchasers, and policy makers in making informed health decisions.

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should drive appropriate use in clinical practice in a way that improves health outcomes for individual patients and ultimately for public health. However, the current process of evidence generation for pharmacogenomic tests is poorly defined, with very few requirements for what evidence passes to the next level and what is discarded or used for no-go decisions.

Notably, the funnel has very steep sides—intending to show that the evidence base for pharmacogenomic tests narrows rapidly. Whereas no financial data exist regarding the amount of money spent on pharmacogenomic research specifically, it is well known that funding (both public and private) for comparative effectiveness research is dramatically lower than funding for either basic or clinical research (41). Even for branded pharmaceuticals where we have substantial amounts of clinical data at launch, we have very little data on comparative effectiveness in real-world settings (42). Therefore, it is entirely predictable that there is very little evidence to demonstrate the clinical benefit of a new pharmacogenomic test because this information is lacking for medical innovations in general. The reasons for these translational gaps are multifactorial (lack of incentives, funding, workforce training, information systems, public participation, etc.), but these deficiencies are particularly acute at the point where clinical studies are translated into medical practice and health care decision making (43). This is precisely where economic analyses have their greatest value because they can inform decision making by providing information regarding the incremental costs and benefits of competing health care interventions.

The lack of comparative effectiveness and cost-effectiveness data is not unique to pharmacogenomic tests, but clearly the bar is being raised in terms of payers and now policy makers demanding better evidence to make more informed coverage and resource allocation decisions at both the local and national levels. Wide regional variations in adoption of new health care technologies without corresponding changes in health status have been attributed in large part to an absence of information on the risks, benefits, and costs of different treatment options. An opportunity exists for pharmacogenomic experts to ride the wave of the comparative effectiveness movement (44) and capitalize on the recent federal investment in research infrastructure and methods development to conduct the appropriate prospective studies that demonstrate the clinical utility of pharmacogenomic tests. The biggest barrier to realizing the economic benefits of pharmacogenomic testing is the lack of evidence that using this test information to guide prescribing decisions improves health outcomes for patients (45). Our contention is that we need to harness the expertise of multidisciplinary teams of researchers to prove the value of pharmacogenomic testing. This will create a positive cycle of continued investment in research in both the public and private sectors while providing the evidence to guide appropriate use of the new technology in clinical practice.

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SUMMARY

Payers and clinicians see pharmacogenomic tests as a potentially significant medical advance and are interested in evidence-based recommendations for adopting this technology. Pharmacogenomic tests are most likely to be cost-effective for medications that have significant risks of serious adverse events or poor or highly variable drug response or are very expensive, such as specialty drugs. Given the rising costs of drug development, there is growing interest on the part of industry in using pharmacogenomics as a tool to improve the efficiency of drug development over time. For many common medical disorders, an opportunity exists to improve the response to current medications and to develop new targeted therapies that deliver better health outcomes and improve patients' quality of life. The public health benefit of using pharmacogenomics to improve the risk-benefit profile of new and existing drugs, while ensuring efficient use of scarce health care resources, is potentially very great.

SUMMARY POINTS

1. The economic benefits of using pharmacogenomic testing to improve drug development and drug therapy decision making are potentially very favorable from a societal perspective.
2. The biggest barrier to translating pharmacogenomic testing into clinical practice is the lack of evidence that using this test information to guide prescribing decisions improves health outcomes for patients.
3. Anticipated health care cost savings from targeting drug therapy will remain theoretical until we demonstrate the clinical benefits of using pharmacogenomic testing in real-world settings.
4. While currently there is no centralized or consistent process for conducting health technology assessments in the United States, payers are interested in evaluating the clinical utility and economic impact of pharmacogenomic testing as part of coverage and reimbursement decisions.
5. Generating better evidence for pharmacogenomics will require expanded investment in basic and clinical research activities, greater investment in comparative effectiveness research, and additional emphasis on including costs in the determination of overall value.

FUTURE ISSUES

1. Economic evaluations of pharmacogenomic opportunities will play an increasingly important role in influencing drug portfolio decision making.
2. Recent increased investment by the federal government in comparative effectiveness research will create enhanced capacity to also study the relative impact of pharmacogenomic testing on clinical and economic outcomes.
3. Payers and clinicians will continue to need additional training to take advantage of the growing body of cost-effectiveness research surrounding the use of pharmacogenomic testing in clinical practice.

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DISCLOSURE STATEMENT

Dr. McLeod participates in consulting/advisory boards for Affymetrix, Medco Health Solutions, and Myriad Genetics.

ACKNOWLEDGMENTS

This work was supported by the NIH Pharmacogenetics Research Network (U01GM63340).

LITERATURE CITED

1. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, et al. 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344:783–92

2. Deverka PA, Doksum T, Carlson RJ. 2007. Integrating molecular medicine into the US health care system: opportunities, barriers and policy challenges. *Clin. Pharmacol. Ther.* 82:427–34
3. DiMasi JA, Hansen RW, Grabowski HG. 2003. The price of innovation: new estimates of drug development costs. *J. Health Econ.* 22:151–85
4. Food and Drug Administration. 2004. *Innovation or stagnation: challenges and opportunity on the critical path to new medical products*. **http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html**
5. Kola I, Landis J. 2004. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3:711–15
6. Moore TJ, Cohen MR, Furberg CD. 2007. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. *Arch. Int. Med.* 167:1752–59
7. Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, et al. 2005. Drug-metabolizing enzymes: evidence for clinical utility of pharmacogenomic tests. *Clin. Pharmacol. Ther.* 78:559–81
8. Ginsburg GS, Konstance RP, Allsbrook JS, Schulman KA. 2005. Implications of pharmacogenomics for drug development and clinical practice. *Arch. Int. Med.* 165:2331–36
9. Phillips KA, Van Bebber SL. Measuring the value of pharmacogenomics. *Nat. Rev. Drug Discov.* 4:500–10
10. Orszag PR, Ellis P. 2007. The challenge of rising health care costs: a view from the Congressional Budget Office. *N. Engl. J. Med.* 357:1793–95
11. Newhouse JP. 1992. Medical care costs: how much welfare loss? *J. Econ. Perspect.* 6:3–21
12. Chernew ME, Jacobson PD, Hofer TP, Aaronson KD, Fendrick AM. 2004. Barriers to constraining health care cost growth. *Health Aff.* 23:122–28
13. Catlin A, Cowan C, Hartman M, Heffler S, National Health Expenditure Accounts Team. 2008. National health spending in 2006: a year of change for prescription drugs. *Health Aff.* 27:14–29
14. Phillips KA, Veenstra D, VanBebber S, Sakowski J. 2003. An introduction to cost-effectiveness and cost-benefit analysis of pharmacogenomics. *Pharmacogenomics* 4:231–39
15. Drummond MF, Schwartz JS, Jonsson B, Luce BR, Neumann PJ, et al. 2008. Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int. J. Tech. Assess. Health Care* 24:244–58
16. International Pharmacogenetics Warfarin Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N. Engl. J. Med.* 360:753–64
17. Eckman MH, Rosand J, Greenberg SM, Gage BF. 2009. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann. Int. Med.* 150:73–83
18. Vernon JA, Johnson SJ, Hughen WK, Trujillo A. 2006. Economic and developmental considerations for pharmacogenomic technology. *Pharmacogenomics* 24:335–43
19. Veenstra DL. 2007. The cost-effectiveness of warfarin pharmacogenomics. *Int. Soc. Thromb. Haemost.* 5:1974–75
20. Cook J, Hunter G, Vernon J. 2009. The future costs, risks, and rewards of drug development. *Pharmacoeconomics* 27:355–63
21. Press M, Seelig S. 2004. Lessons learned from the development of a diagnostic to predict response to Herceptin: targeted medicine—from concept to clinic. Thomson Financial Street Events, Conference Report on Targeted Medicine, November 11, pp. 10–11
22. Trusheim MR, Berndt ER, Douglas FL. 2007. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat. Rev. Drug. Discov.* 6:287–93
23. Garrison LP, Carlson RJ, Carlson JJ, Kuszler PC, Meckley LM, Veenstra DL. 2008. A review of public policy issues in promoting the development and commercialization of pharmacogenomic applications: challenges and implications. *Drug Metab. Rev.* 40:377–401
24. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, et al. 2008. HLA-B*5701 screening for hypersensitivity to avacavir. *N. Engl. J. Med.* 358:568–79
25. DiMasi JA, Hansen RW, Grabowski HG. 2003. The price of innovation: new estimates of drug development costs. *J. Health Econ.* 22:151–85
26. Vernon J, Hughen K, Trujillo A. 2008. The future of drug development: the economics of pharmacogenomics. *Exp. Rev. Clin. Pharm.* 1:49–59

Annu. Rev. Pharmacol. Toxicol. 2010.50:423-437.

27. Murphy KM, Topel RH. 2006. The value of health and longevity. *J. Polit. Econ.* 114:871–904
28. Flowers CR, Veenstra D. 2004. The role of cost-effectiveness analysis in the era of pharmacogenomics. *Pharmacogenomics* 22:481–93
29. Weinstein MC, Siegel JE, Gold MR, Damlet MS, Russell LB. 1996. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 276:1253–58
30. Neumann PJ, Rosen AB, Weinstein MC. 2005. Medicare and cost-effectiveness analysis. *N. Engl. J. Med.* 353:1516–22
31. Limdi NA, Veenstra DL. 2008. Warfarin pharmacogenetics. *Pharmacotherapy* 28:1084–97
32. Flockhart DA, O'Kane D, Williams MS, Watson MS, Gage B, et al. 2008. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet. Med.* 10:139–50
33. McWilliam A, Lutter R, Nardinelli C. 2008. Healthcare impact of personalized medicine using genetic testing: an exploratory analysis for warfarin. *Personal. Med.* 5:279–84
34. Eckman MH, Rosand J, Greenberg SM, Gage BF. 2009. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann. Intern. Med.* 150:73–83
35. Centers for Medicare & Medicaid Services. 2009. *Proposed Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N)*. **http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?from2=viewdraftdecisionmemo.asp&id=224&**
36. Flockhart DA, Skaar T, Berlin DS, Klein TE, Nguyen AT. 2009. Clinically available pharmacogenomics tests. *Clin. Pharmacol. Ther.* 86:109–13

36a. Katsanis SH, Javitt G, Hudson K. 2008. A case study of personalized medicine. *Science* 320:53–54 (erratum post 18 April 2008)

37. Phillips KA, Van Bebber SL. 2004. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. *Pharmacogenomics* 5:1139–49
38. Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, Postma MJ. 2008. Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes. *Pharmacoeconomics* 26:569–87
39. Schackman BR, Scott CA, Salensky RP, Losina E, Freedberg KA, Sax PE. 2008. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. *AIDS* 22:2025–37
40. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. 2009. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health* 12:20–27
41. Moses H, Dorsey ER, Matheson DHM, Thier SO. 2005. Financial anatomy of biomedical research. *JAMA* 294:1333–42
42. Garrison LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. 2007. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 10:326–35
43. Sung NS, Crowley WF, Genel M, Salber P, Sandy L, et al. 2003. Central challenges facing the national clinical research enterprise. *JAMA* 289:1278–87
44. Wilensky GR. 2006. Developing a center for comparative effectiveness information. *Health Aff.* 25:2572–85
45. Garber AM, Tunis SR. 2009. Does comparative-effectiveness research threaten personalized medicine? *N. Eng. J. Med.* 360:1525–27

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Department of Health and Human Services. Report of the Secretary's Advisory Committee on Genetics, Health and Society 2008. *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges.* **http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_report.pdf**

Annu. Rev. Pharmacol. Toxicol. 2010.50:423-437.

Department of Health and Human Services. Report of the Secretary's Advisory Committee on Genetics, Health and Society 2006. *Coverage and Reimbursement of Genetic Tests and Services*. **http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf**

Neumann PJ. 2005. *Using Cost-Effectiveness Analysis to Improve Health Care. Opportunities and Barriers*. New York: Oxford University Press

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