SYMPOSIUM

Implications of Pharmacogenomics for Drug Development

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The use of pharmacogenomics (PGx) today is almost ubiquitous in drug development and is advancing into the practice of medicine as an increasing number of drugs come to market with indications that are related to the presence or absence of a specific genetic biomarker. The authors review the history of PGx and its tools in research, in clinical trials and in clinical medicine. The economic, regulatory, and technological driving forces for adoption of PGx are then considered. Current impediments to a more robust proliferation of the benefits of these technologies are discussed—pharmaceutical companies, clinical education, required statistical methods, and intellectual property landscape. Exp Biol Med 233:1484–1497, 2008

Key words: pharmacogenomics; drug development; clinical trials; metabolizers; biomarkers

Introduction

Pharmacogenomics (PGx) is a term which embraces both the use of genetic information of populations in drug research, design, and development; and the use of a patient's genetic information in the clinical management of pharmacotherapy, including drug selection, dosing, and analysis of drug toxicities. The use of PGx today is almost ubiquitous in drug development and is advancing into the practice of medicine ('clinical PGx') as an increasing number of drugs come to market with indications that are related to the presence or absence of a specific genetic biomarker. Far from warranting the appellation "personalized medicine," the technology is actually a continuation of a long tradition of rationally based, casuistic medicine as articulated by Galen. Medically, PGx is yet another step in the refinement of our understanding of a patient; technologically, the correlation between drug response and genetic variation is widely accepted, and can be thought of as a functional expansion of classical Structure Activity Relationship (SAR), which has historically focused exclusively on the elucidation of the structure and function of both drug and receptor (1). PGx can be thought of as an extension of traditional SAR through classification of possible variations in the drug target, but more importantly, by the prophylactic identification of interindividual variability in the ability to metabolize a drug, transport it or otherwise benefit from it. The promise of PGx is considerable: improved patient outcomes, lower drug development cost, faster drug development timelines, and lower drug spending are all reasonably foreseeable consequences of these technologies.

In this article, the authors review the history of PGx and its tools in research, in clinical trials, and in clinical medicine. The driving forces—economic, regulatory, and technological—for adoption of PGx are then considered. Finally, current impediments to a more robust proliferation of the benefits of these technologies are summarized.[1]

History of Pharmacogenomics

It is well established that drug therapies have variable results among patients in both efficacy and side effects. Numerous efforts have focused on identifying the mecha-

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DOI: 10.3181/0805-S-150
1535-3702/08/23312-1484$15.00

[1]We employ the term 'drug' in the broadest sense so as to include 'biological' species. Further, we link PGx in drug development to clinical PGx throughout based on the following logic: If a PGx package in drug development does other than to rule out the possibility of narrowing the drug's indication through a genetic test, the result should be a drug with an associated biomarker, the utility of which will necessarily require the use of PGx in the clinic of a practicing physician.

nisms which cause variability of drug response. Initially, various potential causes were noted such as disease heterogeneity, age, gender, diet, co-administration of drugs, renal function, and hepatic function. In addition, genetic factors involved in drug disposition or drug action were identified as being able to modify drug response. These genetic factors are reported to account for 20 to 95 percent of the variability seen in drug therapies (2, 3).

The first report of a pharmacogenetic study was the 1932 link between the inability to taste phenylthiocarbamide (PTC) and an autosomal recessive trait, demonstrating that certain chemicals react differently based on genetic differences (4). This was one of the first known examples of genetic polymorphism, described formally by Ford in 1965 (5). One of the first examples of genetic differences in drug metabolism was the varied response of patients to succinylcholine, which was described by Kalow in the 1950s (6). A deficiency in plasma cholinesterase activity—an inherited abnormality of succinylcholine metabolism—results in prolonged paralysis for approximately 0.03 percent of the population. The term pharmacogenetics was coined in 1959 by Friedrich Vogel to describe the scientific practice of examining inherited differences in the response to drugs (7). The term pharmacogenomics (PGx) has been used in recognition that the genome is more than the aggregate of genes, and that genomic technologies are used to identify disease susceptibility, drug discovery, pharmacological function, drug disposition, and therapeutic response (8).

Evolution of Research Tools. DNA microarrays and microfluidic devices allow for efficient high-throughput screening and gene mapping. DNA microarrays are based on methods developed by Southern in the 1970s, and microcapillary electrophoresis devices developed in the last two decades have essentially replaced traditional gel electrophoresis (4). To better handle the massive amounts of sequence data, improvements have been and will continue to be made in genome-based research strategy, informatics and analytical methods, and automated instruments.

New gene targets and the association between biomarkers and drug response are being identified with genomic techniques. Numerous research tools are available for use by multiple groups, who share the vision of leading to new methods for preventing, diagnosing, and treating disease. Large-scale collaborations include the Pharmacogenetics Research Network (PGRN), The SNP Consortium (TSC), and the International HapMap Project. Efforts from the PGRN contribute to the Pharmacogenomics Knowledge Base (PharmGKB), developed by and based at Stanford University with funding from the National Institute of General Medical Science at NIH. This database evaluates the functions of proteins, identifies polymorphisms, and assesses the relationship of genetic variants to clinical drug responses. The database, made up of patient information such as medical history, drug responses, and DNA sequences, currently contains information on 608 genes, 540 drugs, 523 diseases, and 27 annotated PGx genes (9, 10).

TSC, a nonprofit partnership formed in 1999 among major pharmaceutical companies, technological companies, and academic research centers, sought to identify 300,000 single nucleotide polymorphisms (SNPs) of biomedical interest. Ultimately, the initial phase of the project resulted in the identification of 1.8 million SNPs. These SNPs have contributed to dbSNP, a public library of variations maintained by the National Cancer for Biotechnology Information. This library contains information on SNPs for 44 organisms, with 6.3 million validated human SNPs (11).

The HapMap Project, started in 2002, is a multi-country initiative to identify common genetic variants in humans (12). HapMap is expected to be a useful tool when conducting association studies, allowing researchers to link variations to the risk for specific illnesses. Instead of testing all 10 million common SNPs in a patient, HapMap will afford researchers an understanding of how SNPs and other variants are organized on chromosomes.

Use in Clinical Trials and Clinical Medicine. Pharmacogenomics has changed the way many clinical trials are conducted, such as genotyping all patients in a given study or specifying inclusion criteria for study groups based on biomarkers. In fact, pharmacogenomics is useful for each part of the clinical trial path. In pre-clinical trials, unevaluated biomarkers can be used in the internal process of deciding whether to conduct subsequent trials. During Phase I and Phase II trials, biomarkers that have been validated by a regulatory agency can be used as a surrogate endpoint to measure toxicity and efficacy. In Phase III trials, the validated biomarkers are useful for patient stratification (13). Since the largest costs of clinical development are in Phase III, the chance of loss of investment can be reduced if biomarkers are integrated as early as possible in the drug discovery process.

Polymorphic genes have been considered as markers for the optimization of clinical medicine, particularly in oncology. A genetic predisposition to drug efficacy and adverse drug reactions have already been shown by candidate gene association studies investigating polymorphic drug metabolizing enzymes, including CYP2D6, CYP2C9, CYP2C19, N-acetyltransferase (NAT2), thiopurine S-methyltransferase (TPMT), UDP-glucoronosyltransferases (UGTs), and dihydropyrimidine dehydrongenase (DPD). These markers are highly meaningful across a broad swath of drugs. For example, CYP2D6 is responsible for the metabolism of over 60 drugs, including antiarrhythmics, β-adrenoreceptor antagonists, antihypertensives, antianginals, neuroleptics, antidepressants, and analgesics (8). The Very Important Pharmacogenes (VIP) project, an initiative of the PGRN, has identified 27 genes they feel are of particular relevance for PGx. This first set of genes, shown in Table 1, is being further examined by PGRN.

Table 1. Genes of Particular Interest for Pharmacogenomics by the Pharmacogenomics Research Network

Gene symbol	Gene name
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
ACE	Angiotensin I converting enzyme
ADRB1	Adrenergic, beta-1-, receptor
ADRB2	Adrenergic, beta-2-, receptor, surface
AHR	Aryl hydrocarbon receptor
ALOX5	Arachidonate 5-lipoxygenase
BRCA1	Breast cancer 1, early onset
COMT	Catechol-O-methyltransferase
CYP2A6	Cytochrome P450, family 2, subfamily A, polypeptide 6
CYP2C9	Cytochrome P450, family 2, subfamily C, polypeptide 9
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
CYP3A5	Cytochrome P450, family 3, subfamily A, polypeptide 4
DPYD	Dihydropyrimidine dehydrogenase
DRD2	Dopamine receptor D2
F5	Coagulation factor V
HMGCR	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
KCNJ11	Potassium inwardly-rectifying channel, subfamily J, member 11
MTHFR	5,10-methylenetetrahydrofolate reductase (NADPH)
SCN5A	Sodium channel, voltage-gated, type V, alpha (long QT syndrome 3)
SLC19A1	Solute carrier family 19 (folate transporter), member 1
SLCO1B1	Solute carrier organic anion transporter family, member 1B1
SULT1A1	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1
TPMT	Thiopurine S-methyltransferase
VDR	Vitamin D (1,25-dihydroxyvitamin D3) receptor
VKORC1	Vitamin K epoxide reductase complex, subunit 1

Substantial amounts of research continue to be conducted for predicting the likelihood that a patient will respond to a therapy for a particular condition. Identifying genes associated with heart attacks is a prime example. Scientists have tried for years to link genes to heart attacks, since coronary heart disease causes one in five deaths in the U.S. (14). Despite the identification of multiple genetic links by the scientific community, deCODE Genetics' 9p21 gene variant—for which the company offers a $200 diagnostic test—has been the only one to hold up. Additional genetic associations for heart attacks are being investigated. Researchers at Celera recently published results from a study of 35 SNPs in 30,000 patients, reporting that a variant of the KIF6 gene makes people more responsive to certain statins, such as Pravachol (pravastin) and Lipitor (atorvastatin) (15).

Over half a dozen products are currently approved in the U.S. with either mandatory or recommended genetic testing associated with use of the drug, illustrating the growing use of PGx in clinical medicine:

Herceptin (trastuzumab), a humanized monoclonal antibody that acts on the HER2/neu receptor, is used as a therapy for breast cancer in patients with HER2 overexpression. Identification of overexpression, required by the drug label, is conducted by methods such as immunohistochemistry or fluorescent in situ hybridization. Herceptin, which received FDA approval in 1998, was jointly developed by Genentech and the Jonsson Cancer Center at UCLA.

Gleevec (imatinib), a targeted cancer drug that inhibits specific tyrosine kinase enzymes, is used to treat multiple cancers including chronic myelogenous leukemia and gastrointestinal stromal tumors. Imatinib mesylate is a small molecule protein-kinase inhibitor that inhibits BCR-ABL tyrosine kinase. This abnormal tyrosine kinase is created by the Philadelphia chromosome, a translocation between chromosome 9 and 22. Quantification of p210 expression levels is a method to monitor response to the drug. Gleevec, which received FDA approval in 2001, was developed by Novartis.

Iressa (gefitinib) selectively targets epidermal growth factor receptor's (EGFR, also known as Her1, ErbB-1) tyrosine kinase domain. The current indication of the drug is for locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have previously undergone chemotherapy. Tests for EGFR expression, such as Genzyme's EGFR Mutation Assay, help predict which patients may respond to Iressa. The therapy, approved by the FDA in 2003, was developed by AstraZeneca.

Tarceva (erlotinib), a drug developed by Genentech which also targets the EGFR tyrosine kinase domain, is used to treat cancers such as NSCLC and pancreatic cancer. In 2005, the FDA approved Tarceva in combination with Eli Lilly's Gemzar (gemcitabine) to treat locally advanced, unresectable, or metastatic pancreatic cancer. Genzyme's

EGFR Mutation Assay can be used to predict patient response to Tarceva.

Erbitux (cetuximab) is an EGFR inhibitor for treating metastatic colorectal cancer and head and neck cancer. EGFR immunostain performed on tumor tissue is used to predict patient response to Erbitux. The drug was discovered by ImClone, and its U.S. distribution is conducted by ImClone and Bristol-Myers Squibb while ex-U.S. distribution is done by Merck KGaA. It was approved by the FDA in 2004. The drug label requires the EGFR test.

Vectibix (panitumumab) is designed to treat EGFR-expressing metastatic colorectal cancer in patients who have received prior treatment. The drug, manufactured by Amgen, was approved by the FDA in 2006. Vectibix differs from Erbitux in its isotype (IgG2 for Vectibix and IgG1 for Erbitux) and potentially in its mechanism of action.

Camptosar (irinotecan), a topoisomerase 1 inhibitor chemotherapy agent, is a semisynthetic analogue of camptothecin used to treat colon cancer. It was first introduced in Japan by Yakult Honsha as Campto and is now marketed by Pfizer in the U.S. as Camptosar after receiving FDA approval in 1994. In 2005, the FDA changed the labeling to add recommendations that patients with polymorphisms in UGT1A1 gene, particularly the TA_7/*28 variant, should receive lower doses (16). Patients with this variant express fewer UGT1A1 enzymes in their liver and are not able to clear the drug during chemotherapy as effectively as others, thus resulting in a larger dose. Camptosar is the first chemotherapy agent to be dosed according to a patient's genotype.

With genomic information, we are better able to achieve optimal therapeutic response by predicting an individual's response to a drug. There are multiple clinical trials using biomarker enrichment. The following are some examples:

Biogen Idec recently completed two Phase I trials of **CNF1010**—a heat shock protein (HSP90) inhibitor 17-allyamino-17-demethoxygeldanamycin (17-AAG) obtained through the acquisition of Conforma Therapeutics—in patients with solid tumors and chronic myelogenous leukemia (17). The effects of the drug on multiple biomarkers were examined. Inhibition of HSP90 results in tumor growth suppression by the degradation of client proteins.

Introgen's **Advexin** is a p53 tumor suppressor therapy in a Phase III trial for head and neck cancer. The company is using its p53 molecular biomarker in the analysis of clinical data to predict efficacy of its cancer therapy.

Avalon's lead candidate **AVN944** targets Inosine Monophosphate Dehydrogenase (IMPDH). It is currently in Phase I for hematologic malignancies and Phase II in combination with gemcitabine for pancreatic cancer. Through the use of AvalonRx, which integrates defined biomarkers and molecular profiling in their trial design, the company is hoping to identify biomarkers that may help stratify responsive patient populations.

Clinical Data's **Vilazodone**, a dual serotonergic antidepressant compound for the treatment of depression, is in a Phase III trial of 400 adult patients which will include the examination of certain potential biomarkers, identified by the company in a previous Phase III study, for each clinical subject (18).

In recent years, there has been a strong focus on pharmacogenomics in drug development. Despite increased screening of new chemical entities with high throughput technology, new drug applications have been declining. Ninety percent of preclinical phase candidates fail during clinical development. Poor response or side effects are reported as the reason for terminating development in eighty percent of those that enter clinical trials (8). Identifying potential responders and non-responders on the basis of genetic testing before inclusion into a clinical trial is believed to increase the success rate and reduce the number of patients required to demonstrate efficacy, resulting in shortened development time and reduced costs. These issues of safety, weak efficacy, and drug development cost—key drivers for the use of PGx in drug development—are discussed in the following section.

Drivers for the Use of PGx in Drug Development

The advent of PGx in research and development is driven largely by the need to improve Return On Investment (ROI) from such programs. The *one size fits all* approach utilized in the therapeutic development efforts that produced most of the currently marketed therapeutics may not be sustainable, as evidenced by the multi-year decline in ROI from the R&D budgets of the major pharmaceutical and biotech companies, generally (19). Improvements to ROI may be obtainable from PGx due to improved technology and the availability of useful databases; reduction of toxicity effects (through identification of genotypes that are more likely to have them or genotypes that should receive a dose that differs from normal); reduction of size and expense of clinical trials; use of polymorphic metabolizing enzyme genotyping in dose ranging studies; and, *arguendo*, increased pricing per dose. Each of these factors, except the last, improves ROI by removing cost from the health care system, either directly or indirectly.

PGx Technology—Faster, Better, Cheaper. Pharmaogenomics serves to provide a more tailored approach to the development of new therapies by directly associating drug response to genomic data, and is facilitated by the extensive sequence information yielded by the Human Genome and International Haplotype Mapping Project projects (20, 21). The first generation of genome sequencing, a widely accepted technique developed by Sanger in 1977, is highly manual with throughput of 100 base pairs (bp) per day. ABI developed the second generation sequencers capable of 1,000 bp/day throughput. Third generation fully automated multicapillary DNA sequencers were capable of 600,000 bp/day. Today,

complete system solutions, such as those from Illumina and 454 Life Sciences, allow for the amplification and sequencing of over 20 million bases in a few hours. With each generation, an exponential increase in throughput has been made possible, while the costs have dropped dramatically—DNA sequencing costs have fallen more than 99 percent over the past decade (22).

Reducing Drug Toxicity. Toxicity effects and overall drug safety are paramount to the drug development process, and are ultimately responsible for the preclusion of a majority of potential pharmaceutical candidates from entering the market. The recent debacle involving the safety profiles of non-steroidal anti-inflammatory agents including Bextra, Vioxx, and Celebrex exemplifies the need for additional safety measures (23). The increased risk of serious cardiovascular events, mainly heart attack and stroke, and the fact that these adverse events were not recognized prior to drug launch have drawn harsh criticism from members of the U.S. Congress, physicians, and even from within the FDA itself (24). While adverse cardiac events (ACEs) were the major contributor to the removal of Vioxx from the market, many currently approved pharmaceuticals, while not explicitly causing ACEs themselves, can contribute to cardiac issues in individuals with congenital susceptibility for cardiac channelopathies.

Long QT Syndrome is a heart condition associated with prolongation of the QT interval, or the recovery and excitation of the ventricular anatomy, and can contribute to fainting and sudden death in certain individuals (25). Many individuals with Long QT Syndrome (LQTS) are of the LQT1/LQT2 genotype, and represent ~60 percent of all cases, with at least 1/3 of these being asymptomatic (26). Many currently approved pharmaceuticals are well known to aggravate LQTS, thus increasing the overall potential for an adverse cardiac event. Over 120 drugs including antibiotics such as Clarithromycin, Ciprofloxacin, and Gemifloxacin, and antidepressants such as Paxil, Sarafem, and Sinequan come with recommendations to avoid if one is diagnosed with LQTS (27). Therefore, the pharmacogenomic identification and sequestration of asymptomatic individuals who possess the LQT1/LQT2 phenotype could serve to prevent ACEs in both clinical development and therapeutic capacities.

The use of pharmacogenomic information in the drug prescribing process has been gaining traction, most notably with the commonly used anticoagulant Warfarin. Warfarin is a commonly used anticoagulant drug with fine therapeutic index and a high interindividual variability in metabolic processing. Typically administered in racemic form, *S*-warfarin is metabolized mainly by polymorphic cytochrome *P*450 (CYP2C9), as shown in Figure 1 (28). Genotypic variability in the metabolic processing enzymes affects drug clearance rates, and ultimately drug toxicity, thus requiring a genotypic analysis to establish safe dosing ranges. Prior studies have shown that maintenance dosing of Warfarin is significantly related to the number of functional CYP2C9 genes, and Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1), and other factors (29). The FDA has approved updated labeling information for Warfarin to include the recommended use of pharmacogenetic testing to determine an individual's sensitivity to the drug (30). Approximately one-third of patients prescribed Warfarin exhibit unexpected metabolic variation which is directly attributable to the patient's variants of the genes CYP2C9 and VKORC1, and it has been estimated that by identifying people who carry genes for compromised Warfarin-metabolizing enzymes, serious bleeding events could be reduced from 27.6 percent to 12.6 percent among this population (31). Additionally, it has been estimated that a pharmacogenomic influenced dosing regimen could reduce warfarin-related strokes by half (31). The costs associated with treating a bleeding event average $13,500 and a stroke is $39,000, suggesting that an annual net health care savings of as much as $1 billion per year could be realized by integrating genetic testing in the administration of Warfarin therapy (31).

Downsizing Clinical Trials. Candidate therapies traditionally take multiple years to go through the clinical trials process. In the end, thousands of patients may be needed to complete clinical development of a therapy. Still, 90 percent of compounds fail during clinical development. Of the drug failures in clinical development, 41 percent is attributed to poor absorption, distribution, metabolism, and excretion (ADME), while 30 percent is attributed to lack of efficacy. The remaining 29 percent of drug failures are attributed to toxicity, market and commercialization rationale, and other reasons (13).

Non-response and varying metabolism of drugs are issues associated with efficacy. The following sections explain these two issues, quantify the costs of drug development through approval, and discuss the benefits of data enrichment through the analysis of biomarkers.

Relationship Between Non-Response and Trial Size. A clear way of illustrating how weak efficacy can affect a trial is by describing the relationship between non-response and trial size. The following sample size calculations show how an increase in clinical benefit (i.e., a reduction in non-response) can significantly reduce the sample size required to successfully conduct a trial.

The size of a trial necessary to demonstrate a significant difference between the control and intervention groups is related to the response rates for the groups. The sample size required to detect true differences between events for two independent samples is given by

$$2N = \frac{2\{Z_\alpha\sqrt{2\bar{p}(1-\bar{p})} + Z_\beta\sqrt{p_c(1-p_c)+p_i(1-p_i)}\}^2}{(p_c-p_i)^2}$$

where 2N is the total sample size (N per group), the average event rate $\bar{p} = (p_c + p_i)/2$ since $N_i = N_c$, Z_α is the critical value for significance level α, and Z_β corresponds to the power 1-β (32). If we define event rates p_c and p_i as the rate

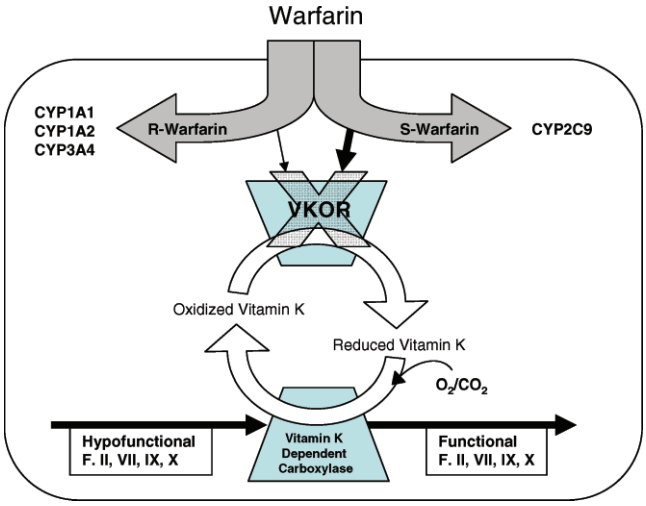

Figure 1. Metabolism of warfarin, which is typically administered in racemic form. *S*-warfarin is metabolized mainly by polymorphic cytochrome *P*450 (CYP2C9). Regeneration of reduced vitamin K is prevented by the S-enantiomer by blocking vitamin K epoxide reductase (VKOR). *Modified from Gage BF and Eby CS, 2004 (reference 52).*

of having a positive outcome, the percentage difference between the true proportions is the clinical benefit. The relationship between non-response (1-clinical benefit) and sample size needed for a trial is then given by the following general pattern that is shown in Figure 2.

While the sample size required for a particular trial depends on a variety of factors—such as baseline response of the control group, significance level, and power—this curve illustrates how the sample size can be dramatically decreased with reductions in non-response. A 2006 benchmarking publication reported that the cost per patient of clinical trials for new drugs on average costs $15,700 for Phase I, $19,300 for Phase II, and $26,000 for Phase III (33).

The following example clarifies the point that even reductions in sample sizes by dozens of patients would be beneficial with regards to trial costs. For a hypothetical drug, let the placebo response be 30 percent, general population drug response 60 percent, and biomarker positive population drug response 90 percent. The sample size needed to detect the difference between the placebo control group and general population intervention group would be 120 (60 per group, using $\alpha = 0.05$ and power $=$ 0.90). However, the sample size needed to detect the difference between the placebo control group and the biomarker positive intervention group would be 30 patients (15 per group, using the same values for α and power). Assuming an average cost per patient of $20,000 (based on the average cost from the aforementioned benchmarking publication), the use of biomarkers would result in a savings of $1.8 million, or a 75 percent reduction in cost. PGx offers the potential to reduce sample sizes and trial costs by investigators pre-selecting subpopulations for which a therapy is known to elicit greater response, such as through the identification of biomarkers in patients.

Metabolizers Affecting Dose Ranging Studies. Various drug metabolizing enzymes exhibit genetic polymorphisms, including CYP2D6, CYP2C9, CYP2C19, N-acetyltransferase (NAT2), thiopurine S-methyltransferase (TPMT), UDP-glucoronosyltransferases (UGTs), and dihydropyrimidine dehydrogenase (DPD) (8). Often, there are poor metabolizers (PMs), intermediate metabolizers (IMs), and ultrarapid metabolizers (UMs), as is the case for CYP2D6-dependent hydroxylation of the antihypertensive drug debrisoquine. UMs possess multiple copies of the gene for normal metabolism, resulting in very low concentrations of the drug and high concentrations of metabolites. IMs are heterozygous and display a modest impairment in drug metabolism.

CYP2D6 is responsible for the metabolism of over 60 approved drugs. One of the first reports of an association between CYP2D6 polymorphism and toxicity is with antianginal agent perhexiline. Although the initial standard dose was 100 mg three times a day, a subsequent study

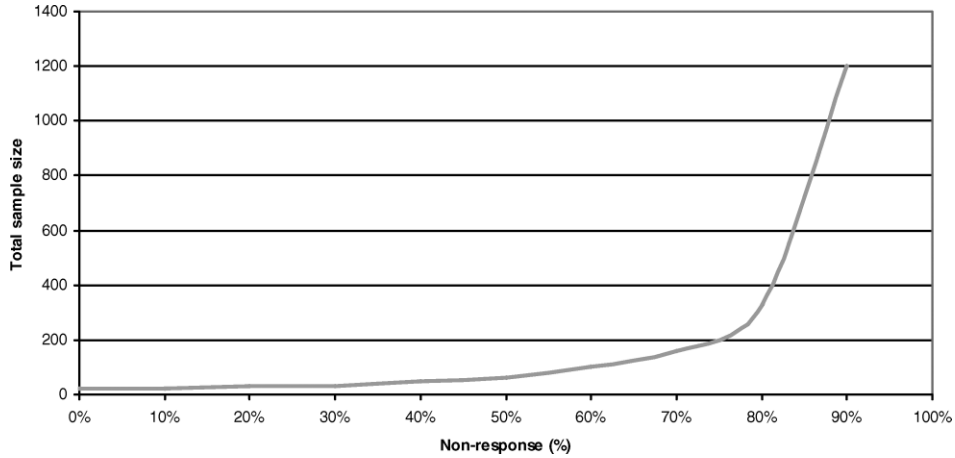

Figure 2. Relationship between total sample size and non-response for control group event rate 0.8, with two-sided significance level of 0.05 and power of 0.90.

Table 2. Costs per Approved New Molecule for Biotech and Pharma (in Millions of Dollars)[a]

	Pre-approval cash outlay		Pre-approval capitalized cost	
Stage	Biotech	Pharma	Biotech	Pharma
Preclinical	$198	$150	$615	$439
Clinical	$361	$522	$626	$879
Total	**$559**	**$672**	**$1241**	**$1318**

[a] Source: DiMasi JA and Grabowski HG, 2007 (reference 41).

revealed that PMs required 10–25 mg/day, EMs required 100–250 mg/day, and UMs required 300–500 mg/day (34). However, it is difficult to distinguish IMs from UMs based on phenotyping alone. Data can appear multimodal and skewed in a particular direction. The authors of the perhexiline study noted that patients could be separated into three groups by the quotient of perhexiline plasma clearance and bioavailability, by the metabolic ratio for the metabolite *cis*-OH-perhexiline, or by the daily dose required to attain steady-state perhexiline concentrations within the therapeutic range.

Depending on the pharmacokinetics of a particular drug, there may be extremely high interindividual variability. This can result in a large coefficient of variation. Improper conclusions drawn from dosing studies based on such data will likely increase the probability of an unsuccessful later-stage trial. PGx can improve safety and efficacy by identifying these groups, as UMs may require excessive doses of drugs because they do not respond to standard doses, and PMs may not respond at all. Recognition of varying metabolism of drugs as early as possible in clinical development will allow for optimal results.

Drug responsiveness and drug metabolism are thought to be the reason that 40 to 60 percent of patients do not benefit from prescribed blockbuster drugs. These individuals may even suffer adverse effects. Nearly three million prescriptions are written annually that are incorrect or ineffective, and according to the FDA more than 100,000 patients die in the U.S. from adverse drug reactions (ADRs) (35). In 2001, 2.2 million people were affected by ADRs (36). The costs of ADRs—the leading cause of market withdrawals of drugs—are estimated to exceed $177 billion annually (36). PGx has the potential to increase safety and effectiveness by identifying those at risk for ADRs and in helping physicians select drugs and dosages to fit individual patient responses. Reductions in the rate of ADRs can substantially reduce costs and improve outcomes in patients.

Cost Trends for Drug Development Through Approval. The absolute cost to bring a drug through the approval process has been examined in numerous studies. Development estimates range from $800 million to $1,700 million for a period of up to 15 years (13, 37–40). In 2007, DiMasi and Grabowski found that although out-of-pocket costs per approved biopharmaceutical were lower than for pharmaceuticals, the estimated total capitalized cost (which includes time cost) per approved new molecule was nearly the same (41). A comparison of the out-of-pocket and capitalized costs for biotech and pharmaceutical companies are given in the following table. The costs for pharmaceuticals are time-adjusted, since DiMasi *et al*. originally estimated those costs five years earlier (Table 2).

Biotech was more costly during the preclinical period in both out-of-pocket cash outlay and capitalized cost. This seems reasonable considering that biotech companies spent 52 months in the preclinical stage before advancing to Phase I trials (Table 3). However, despite slightly longer approval times for biopharmaceuticals, clinical stages are more costly for pharmaceuticals.

Drug development costs can be reduced with PGx by pre-selecting candidates for clinical trials. BCG argued that with today's genomics technologies, an average of nearly $300 million and two years could be saved per drug, equivalent to a reduction of 35 percent cost and 15 percent time by their estimates (40). DiMasi and Grabowski detailed transition probabilities, as shown in Table 4, for clinical development of pharmaceuticals and biopharmaceuticals.

With PGx, an increase in the probability of response to treatment can be achieved if targeted populations are selected earlier, especially prior to clinical stages. The transition probabilities for clinical phases should increase and, as a result, the cost per approved drug should decrease. In November 2007, RTI International prepared a planning report for the National Institute of Standards & Technology with economic analyses of various technologies for the biopharmaceutical industry. RTI determined that biomarkers will reduce DiMasi and Grabowski's estimated $559 million cost per approved drug by 38 percent to $347.9 million. In

Table 3. Approval Times (Months) for Clinical Development[a]

	Biotech	Pharma
Preclinical	52.0	
Phase I	19.5	12.3
Phase II	29.3	26.0
Phase III	32.9	33.8
Regulatory review	16.0	18.2
Total	**97.7**	**90.3**

[a] Source: DiMasi JA and Grabowski HG, 2007 (reference 41).

Table 4. Transition Probabilities for Clinical Phases[a]

	Biotech	Pharma
Phase I–II	83.70%	71.00%
Phase II–III	56.30%	44.20%
Phase III–approval	64.20%	68.50%
Total	**30.25%**	**21.50%**

[a] Source: DiMasi JA and Grabowski HG, 2007 (reference 41).

terms of capitalized cost, they reported that biomarkers would reduce costs by 45 percent, from DiMasi and Grabowski's estimated $1241 million to $676.9 million. In total, development time would decrease 19 percent from 133.7 months to 108.2 months. Meanwhile, RTI calculates that IND approval probability would be 11 percent higher (42). Table 5 summarizes the benefits expected by incorporating biomarkers into the development of a drug.

In addition to increasing response to treatment, PGx can improve safety. PGx tests that address varying metabolism of drugs would offer the ability to reduce the frequency of adverse events in patients.

Through the Critical Path Initiative, the FDA is exploring how methods can be established to lower development costs. The initiative kicked off in March 2004 with the release of a white paper, calling for efforts to modernize scientific tools—such as qualified biomarkers—and make use of bioinformation to evaluate and predict safety and efficacy of potential medical products (43).

The difficulty facing PGx will be finding relevant genes. In order to increase the probability of response for those in a trial, the nonresponder genotype needs to be identified before the trials are designed. A Phase I trial would be too small for this to occur before Phase II, and streamlining before Phase III would be difficult. In 2006, Amgen gained approval by the FDA for Vectibix despite weak efficacy and high toxicities. Retrospective analysis of K-Ras data showed no responders in patients with mutated K-Ras, compared to a response rate of 17 percent in wild-type (wt) patients. The FDA was reluctant to accept retrospective data and determined that a prospectively designed study would have to be submitted before the biomarker could be included on the U.S. label. Based on the same retrospective data shown to the FDA, however, the EMEA approved the drug for use in patients with wt K-Ras marker for whom efficacy was considerably more robust. Approving biomarker use with retrospective data would help address the difficulty of finding relevant genes and conducting the necessary analyses to confirm their utility.

Data Enrichment Through Analysis of Biomarkers. The following method has been proposed for prospective PGx studies (44). All patients are tested for a particular marker, and those who are positive for that marker are then randomized to receive drug or placebo. However, a PGx test must be available if the group who is negative for the marker is not studied, since safety must be considered. Otherwise, if pre-treatment selection is not possible, those who test negative must also be randomized to receive drug or placebo. Including the group who tested negative will also allow for any difference in effect size to be determined. This method is summarized in Figure 3.

Although the gold standard for studies is the randomized clinical trial, these trials are not conducted on a random sample of the population. There are entry criteria and lead-in periods, among other requirements, which all help to enrich the trial and optimize the outcome. Study power can be increased by reducing heterogeneity, finding a population with many outcome events, and identifying a population capable of responding to the treatment (45).

An example of enrichment is Tarceva (erlotinb). A randomized, double-blind, placebo-controlled trial of 150 mg Tarceva was conducted in 731 patients with locally advanced or metastatic non-small cell lung carcinoma after failure of at least one prior regimen. This 2:1 randomized (488 Tarceva, 243 placebo) study showed survival effect, as described by Table 6 and Figure 4.

EGFR expression, defined as at least 10 percent staining using DAKO EGFR pharmDx kit, was examined in tumors of 238 patients. A difference in survival was seen among patients with and without EGFR expression. In the placebo group, survival was higher in those without EGFR expression. However, in the group taking Tarceva, survival

Table 5. Estimated New Biopharmaceutical Drug Approval Rates, Failure Rates, and Reductions in Cost and Development Time[a]

		Baseline	Biomarkers	Percentage change from baseline
IND approval probability		30.2%	41.0%	
For INDs failing in clinical trials, percentage failing by phase	Phase I	23.4%	39.2%	
	Phase II	52.4%	37.0%	
	Phase III	24.2%	23.8%	
Probability of recall		0.40%	0.30%	
Estimated actual cost per approved drug (millions)		$559.60	$347.90	−38%
Estimated capitalized cost per approved drug (millions)		$1240.90	$676.90	−45%
Development time (months)		133.7	108.2	−19%

[a] Source: NIST, 2007 (reference 42).

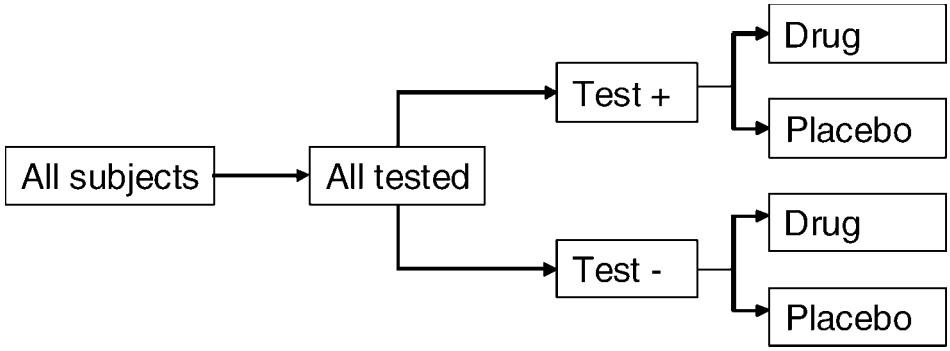

Figure 3. Design for stratified, prospective PGx study when pretreatment selection is not possible. *Modified from Temple RJ, 2005 (reference 44).*

time was about double for those with EGFR expression. By targeting those who have positive EGFR expression, the efficacy of Tarceva can be strengthened (see Table 7 and Fig. 5).

Another example that clearly illustrates the benefit of PGx to clinical trial size is Herceptin. Press and Selig, in a 2004 conference, presented the data in Table 8 for Herceptin.

With the inclusion of the HER2 neu biomarker in the trial, investigators were able to reduce the number of patients needed by almost 80 percent as well as reduce the number of years of follow-up required.

In addition to reducing trial size, PGx is in a strong position to help reduce costs of clinical trials through the use of pre-selection. Using quantitative models, scientists have demonstrated that genetically-guided dose adjustment strategies can increase efficacy and reduce toxicity in clinical trials (46). The above example of Herceptin confirms this theory, as investigators were able to save $35 million in clinical trial costs with the use of HER2 neu. In addition, income from eight-year acceleration of the product totaled $2.5 billion. The benefit was not limited to Genentech: due to acceleration, an additional 120,000 patients had access to Herceptin.

Increasing Price Per Dose. Today, patented therapeutics account for the vast majority of total drug expenditure, while comprising a minority of the unit volume (47). This is another way of saying that patented drugs cost a great deal more than generic drugs. It is not uncommon for the market price of a drug to decline by 80 percent or more from the time of patent expiry to the market entry of the second or third generic entrant. From a consumer perspective, this is permitted and even desirable because the temporary patent monopoly provides incentives for the massive investment in research and development that is required to bring promising new therapies—and other novel and nonobvious innovations—to market, while the benefits of the drug may be enjoyed long after the patent has expired. Although drug manufacturers, during the life of a patent, may theoretically charge any price they desire for a new patented drug, the actual prices charged tend to be very similar to other patented drugs of the same class or that treat the same condition, especially where the differentiation among the competing drugs is modest. When a new drug is first in a class or otherwise offers significant and advantageous differentiation to the other drugs that are prescribed for its indication, however, pharmaceutical companies usually commission 'pricing studies'. These studies examine the attitudes of various constituents—physicians, payers, patients, managed care organizations—to a variety of pricing scenarios in order to determine the price that produces the best overall result to the seller. In classical microeconomics, "the best overall result" means the price at which total revenue (price $\times$ doses sold in market, in the case of a drug) is maximized. In particular and ideally, this optimum price is the price at which if one more cent were charged, consumers would reduce their quantity demanded by more than a proportional amount. Symmetrically, this also means that if one cent less were charged, consumers would not purchase an additional quantity so as to compensate the seller for the price concession.[2]

In an efficient and rational market, PGx may also positively impact drug revenue. If a PGx therapy is more effective for a given patient than the current standard, then a price premium would seem sustainable. Hypothetically, if a cancer therapeutic is 30 percent effective in the general population and the competing agents for the same indication are of approximately equal efficacy, but the new therapy using a biomarker could promise 90 percent effectiveness for a subpopulation, the increased effect size for those patients may warrant a price premium that is more than proportional to the decline in the number of doses attendant to the loss of sales to the marker negative population. Indeed, considering the reduction in developmental cost detailed elsewhere in this paper, the price premium of a PGx therapeutic would not have to be even proportional to the

[2]The authors apologize to those of their readers who know elementary microeconomics well enough. Our defense is two-fold: (1) We have observed that issues of drug pricing (or the pricing of anything else in healthcare) seem to produce a collective forgetfulness concerning the operation of efficient markets; and (2) We recognize that inducing investment in PGx must be made attractive to the capital that is needed in order for society to benefit from its promise.

Table 6. Efficacy Results for Tarceva Among Patients Receiving Drug or Placebo[a]

	Tarceva	Placebo	Hazard ratio	95% CI
Median survival (months)	6.7	4.7	0.73	0.61–0.86, $P < 0.001$
1-year survival	31.2%	21.5%		

[a] Source: Tarceva package insert (reference 54).

unit sales decline for this proposition to produce a greater ROI than the *one size fits all* blockbuster model. We leave aside the potential for reduction in sales and marketing costs that may be realized in connection with genuinely superior therapies (as compared with therapies that the pharmaceutical industry refers to as 'promotionally sensitive', i.e., poorly differentiated).

Impediments to the Adoption of Clinical PGx

As is true for many new technologies, PGx has not encountered a friction-free universe on its road to ascendancy. While it seems almost axiomatically true that removing patients from consideration for a therapy that would do them positive harm and administering therapies only to those patients who are very likely to benefit from them, all while realizing total net savings to the health care system, should be highly desirable, clinical PGx has lagged the use of PGx in drug development by a quite considerable amount: ubiquity in development; obscurity in the clinic. Indeed, outside the realm of cancer treatment (where all the constituents are more versed in molecular biology), this darkness is almost total. We here identify a number of observable challenges to large-scale adoption of clinical PGx in particular.

Pharmaceutical Companies. The best explanation for the resistance of pharmaceutical companies to embrace clinical PGx is aptly expressed in an aphorism that has come to be known as Upton Sinclair's Law: "If a man's paycheck depends on his not understanding something, you can rely upon his not understanding it." While the many benefits of pharmacogenomic testing may seem obvious from other perspectives, certain attributes of this technology and its adoption could be perceived by some to be threatening to the course of business. These tests are slated to improve safety and efficacy of pharmaceuticals; however, in doing so, the treatable patient population for a given therapy will likely be reduced in number. For pharmaceutical companies, this assumedly translates into lost revenues, and without alternative revenue models, could inhibit widespread implementation. The pursuit of multiple targeted (read smaller) markets with multiple pharmaceutical agents supported by biomarkers and pharmacogenomic testing does indeed represent an attractive alternative; however, this multi-product "micro-blockbuster" (or 'blockbuster catalog') strategy has yet to be adopted by big pharma.

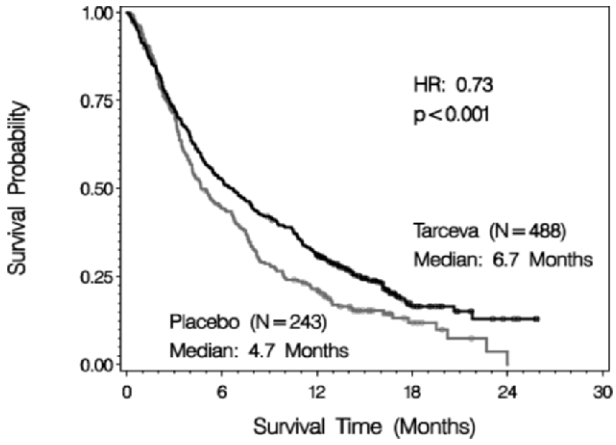

Figure 4. Kaplan-Meier curve for Tarceva study. *Source: Tarceva package insert (reference 54).*

Clinical Education. Considering the importance of the polymorphic drug metabolizing enzymes that already are well understood to inform the advisability and/or the dosing of vast numbers of currently marketed (and often prescribed) therapeutics, why are the vast majority of primary care physicians prescribing these drugs without any knowledge of their patients' CYP2D6 profile, for example? Cost? Such a test is commonly available from the same reference labs with which these physicians do business today for approximately $500. And specialty labs that focus on such CLIA tests charge approximately $120 to $130. Considering the total cost to the health care system of a serious adverse event, leaving aside the cost of not treating the underlying malady quickly and successfully, medical economics research has concluded that such testing would be a paying proposition (31). Our private and admittedly anecdotal quizzing of primary care physicians reveals a quite consistent lack of familiarity with PGx and its potential. On the other hand, each such practicing physician displayed an intense level of curiosity to learn more about the subject. Moreover, the authors are familiar with a small pharmaceutical company that markets a rather poorly differentiated drug in a very crowded class that was able to increase its 'average time with the doctor' several-fold on the average detail simply by talking about a PGx technology that is not even useful in connection with their marketed therapeutic. Their increased drug sales have been spectacular. Physicians want to know more about PGx.

The need for physician education, however, represents an additional challenge that is likely to stymie the use of PGx testing. Genetic testing and its results bear little relation to the types of diagnostic testing with which most physicians are familiar. Because of the complex nature of

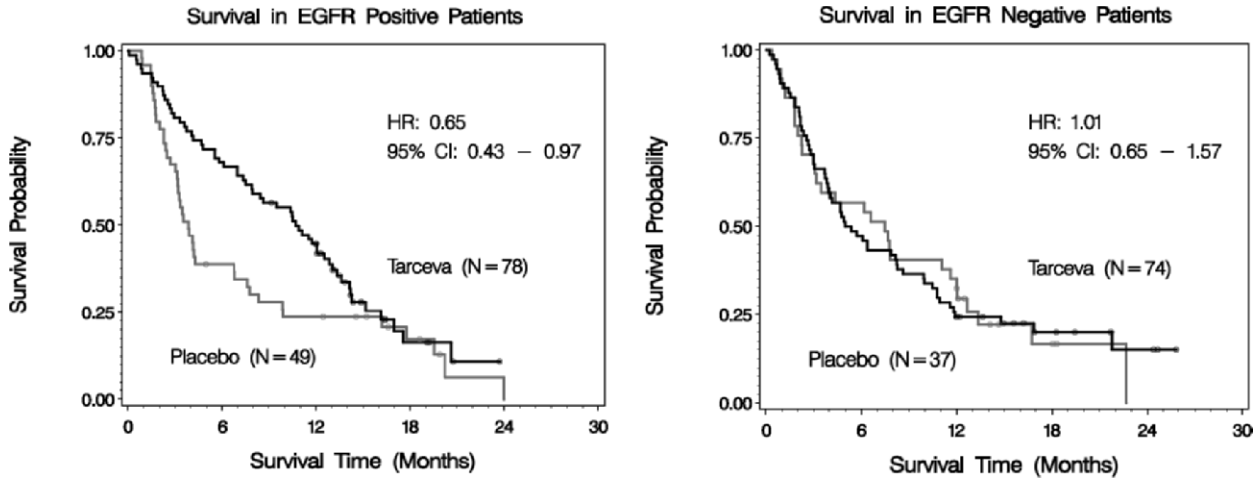

Figure 5. Kaplan-Meier curve for Tarceva study, stratified by EGFR expression. *Source: Tarceva package insert (reference 54).*

drug metabolism, test specificity will likely be very high for a given SNP while yielding markedly reduced sensitivity (most diagnostic tests today offer high specificity and high sensitivity—an unlikely possibility for a PGx test). Such is the case for clozapine testing where a positive test can be used to preclude individuals from receiving the drug; however, due to the multigenic nature of drug metabolism, the contrapositive diagnosis does not hold true, and could have a disastrous treatment outcome should such results be used to guide drug administration. Thus, clear test labeling and physician education as to the diagnostic limitations of such testing is critical. Organizations like The National Coalition for Health Professional Education in Genetics (NCHPEG) have undertaken efforts to educate health care professionals and have developed a core competency framework to assist the development of educational initiatives in genetics and genetically based health care (48, 49). As physician adoption will drive the future of PGx testing, initiatives such as this are critical for widespread implementation (36).

Required Statistical Methods. Although the U.S. FDA has been a strong proponent of the use of PGx,[3] there are a number of areas in which the Agency could better implement its mission and further stimulate the use of these technologies. The type of statistical analysis that the Agency is prepared to recognize generally and the extent to which retrospective analysis of PGx data may replace or supplement prospective PGx studies are worthy of consideration.

Classic frequentist statistical approaches have long been favored in clinical trials. This is primarily because the Agency does not wish to allow drug sponsors the opportunity of 'cherry picking' clinical endpoints after the data is known. But with almost 90 percent of all drug candidates failing in the clinic and the accumulation of biomarker data of significant power only being achievable, as a practical matter, in Phase III, any methods that may potentially advance the insight into valid biomarker relationships to efficacy or safety should be utilized. In recent years, Bayesian statistics have garnered more attention in clinical trials. While a frequentist approach utilizes a sequential monitoring of data and determines the probability that an outcome is arrived at by chance, Bayesian trials allow for continuous monitoring of data and provide the probability that a drug is effective. Bayesian methods compare the probability to prior probabilities and updated posterior probabilities. The drawback to implementing these methods, however, is that they are logistically and computationally more complex. Logistical capability and the availability of computing power have advanced quite considerably in recent years, however.

Pfizer published results in 2003 from their Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN) trial. This full-scale Bayesian trial offered adaptive allocation of patients to different dose groups. In the event of strong efficacy, a seamless transition to Phase III was possible. In addition to the logistical challenges of conducting the study in 100 centers worldwide, the authors of the study estimated that more patients were ultimately recruited than would have been required under traditional designs (50). Despite these drawbacks, the trial did accomplish its goal, as the drug was terminated promptly with Pfizer feeling that they had a complete answer. Although modern computing has made calculations more feasible, a significant amount of work remains for implementing Bayesian statistics in clinical trials.

Strict adherence to prospective study designs also hinder widespread use of PGx. The approval process for Amgen's Vectibix clearly illustrates this hurdle. The metastatic colorectal cancer drug was approved by the EMEA on retrospective data, while the FDA determined that a prospectively designed study must be submitted before the K-Ras biomarker could be added to the U.S.

[3]Indeed, several parts of this paper have referenced, in particular, the work of Dr. Robert Temple, Director of the Office of Drug Evaluation I at the FDA's Center for Drug Evaluation and Research.

Table 7. Survival Among Patients Receiving Tarceva or Placebo, Stratified by EGFR Expression[a]

	Tarceva	Placebo	Hazard ratio	95% CI
EGFR + (127) survival (months)	10.71 ($n = 78$)	3.84 ($n = 49$)	0.65	0.43–0.97 ($P = 0.033$)
EGFR − (111) survival	5.35 ($n = 74$)	7.49 ($n = 37$)	1.01	0.65–1.57 ($P = 0.958$)

[a] Sources: Temple RJ, 2007 and Tarceva package insert (references 45 and 54).

label. The FDA previously granted accelerated approval in 2006 based on a prolongation in progression-free survival from 60 to 96 days in a Phase III open-label trial of 436 patients. However, the overall response rate to Vectibix was 8 percent. Furthermore, the U.S. label warns of various toxic effects, such as a 89 percent incidence of dermatologic toxicity, 12 percent incidence of severe dermatologic toxicity, and a 1 percent incidence of severe infusion reactions.

Amgen's retrospective examination of their Phase III results showed that patients with wild-type (WT) K-Ras were more likely to respond to Vectibix than those with mutated versions of the oncogene. In fact, no response was seen in patients with mutated K-Ras, while 17 percent of patients with WT K-Ras responded. The FDA sees the retrospective analysis as hypothesis-generating since the realization that the marker may have significance came late. However, Amgen argues that they addressed concerns of sampling bias and cherry picking endpoints, the biggest sources of bias for retrospective analyses of biomarkers (51).

In March 2008, the FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee debated a preference for collecting DNA samples from all patients in clinical trials. Such steps may ultimately lead to improving conditions for PGx discovery that may otherwise be too difficult to implement in earlier phase trials. Wider acceptance of novel statistical methods and the potential to attain biomarker approval with retrospective data may help expedite broader implementation of PGx.

Intellectual Property Landscape. Patent law represents a delicate threshold for promoting innovative and life-saving discoveries. Regrettably, ever-increasing hurdles to patentability imposed by the courts, Congress and the USPTO are signaling a weakening of the patent system and have a disproportionately negative effect on pharmaceutical and genomic innovator companies.[4] If the trend continues it will have a significant impact on innovator health care companies and erode the U.S. leadership role for health care.

Changes in subject matter patentability analysis have already increased the considerable burden for all innovations particularly those directed to human genetic material and biotechnology.[5] Nevertheless, outdated and misguided intentions have driven bills such as H.R. 977—a bill designed to outlaw the patenting of the human genetic material—into public debate.

Public debate aside, once an invention crosses the initial threshold of utility it is subject to the rigors of novelty, non-obviousness, written description, and enablement. These criteria have been increasingly tightened, for example, through the expansion of the doctrine of inherency by the Federal Circuit and a heightened standard for obviousness articulated by the Supreme Court in its ruling in *KSR v. Teleflex*.[6] In *KSR* the Court ruled that the person of ordinary skill in the art would utilize "common sense" in finding a motivation to combine references and that there did not need to be a direct teaching in the references themselves to render an invention obvious. Finally, the proposed stricter continuation practice rules currently enjoined by the Eastern District of Virginia and pending changes in the Patent Reform Act of 2007 may prove to be harbingers of further decline in U.S. patent protection.[7]

Any further degradation of patent rights available to innovator companies in the area of genetic therapy and diagnostics could prove fatal to groundbreaking research in cancer therapy, diabetes, depression, schizophrenia, and numerous other economic and socially costly diseases. Research, development, and funding of new genetic tests based on the dynamics of isolated genetic materials promises to decisively position therapeutics in the world of personalized medicine—but only if these findings of genetic variation to drug response are eligible for the necessary patent protection to promote investment.[8] Without patent protection there will be little if any impetus to

[4]Similar trends are also being seen in Europe and Australia, two traditionally strong backers of intellectual property.

[5]To address concerns related to the patenting of human genetic material the U.S.P.T.O issued revised guidelines in 2001, clarifying its position that all inventions under the current statute required a "specific and substantial utility." (Fed. Reg. Vol. 66, No. 4; Jan. 5, 2001)

[6]127 S. Ct. 1727 (2007).

[7]Innovators are again placed in a state of uncertainty as the U.S.P.T.O determines if it will appeal the current injunction. Likewise, while passage of the Patent Reform Act of 2007 is unlikely at this stage, a coalition is already being formed to promote similar legislation in 2008.

[8]Unlike other industries, other forms of intellectual property do not provide adequate protections for the substantial investment required to bring a new drug or test to market. For instance, trade secret protection is largely impractical for biotechnology and genetic material due to the stringent regulatory environment which demands transparency and the ease with which these products can be reverse engineered.

Table 8. Reduction of Trial Size for Herceptin with Use of HER2 Neu[a]

Trial design	With HER2 neu (actual)	Without (calculated)
Number of patients	470	2200
Response rate	50%	10%
Years of follow-up	1.6	10

[a] Source: Press M and Selig SA, 2004 (reference 53).

make the necessary investment for forward-thinking approaches to these challenging diseases.

Conclusions

Recent advents in instrumentation and the acceleration of genomic knowledge have provided the ability to deduce associations between genomic variation and likely drug response. In consequence, an individual's genetic information can be used *a priori* to predict with greater precision the efficacy and safety of a given therapeutic when administered to that patient. As the present *one size fits all* pharmaceutical development paradigm begins to shift toward evidence-based efficacy models, the improved efficiency and reduced economic burden afforded by PGx will ultimately be passed on to the consumer. Through the implementation of PGx technologies, improved patient outcomes, lower drug development cost, faster drug development timelines and lower drug development spending are all achievable goals.

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