Pharmacogenomics: Bench to Bedside

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Pharmacogenetics is the study of the role of inheritance in inter-individual variation in drug response. Since its origins in the mid-twentieth century, a major driving force in pharmacogenetics research has been the promise of individualized drug therapy to maximize drug efficacy and minimize drug toxicity. In recent years, the convergence of advances in pharmacogenetics with rapid developments in human genomics has resulted in the evolution of pharmacogenetics into pharmacogenomics, and led to increasing enthusiasm for the "translation" of this evolving discipline into clinical practice. Here, we briefly summarize the development of pharmacogenetics and pharmacogenomics, and then discuss the key factors that have had an influence on—and will continue to affect—the translation of pharmacogenomics from the research bench to the bedside, highlighting the challenges that need to be addressed to achieve this goal.

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The end of the twentieth century, and the beginning of the twenty-first, witnessed the convergence of two separate but intertwined developments in medicine and biomedical science. The "genomic revolution" has resulted both in a striking increase in our knowledge of genomics and in the development of techniques for rapidly obtaining large quantities of genomic data (1, 2). At the same time, a "therapeutic revolution" has resulted in the development of drugs that can be used to successfully treat or control diseases that range from hypertension and depression to childhood leukaemia (3, 4).

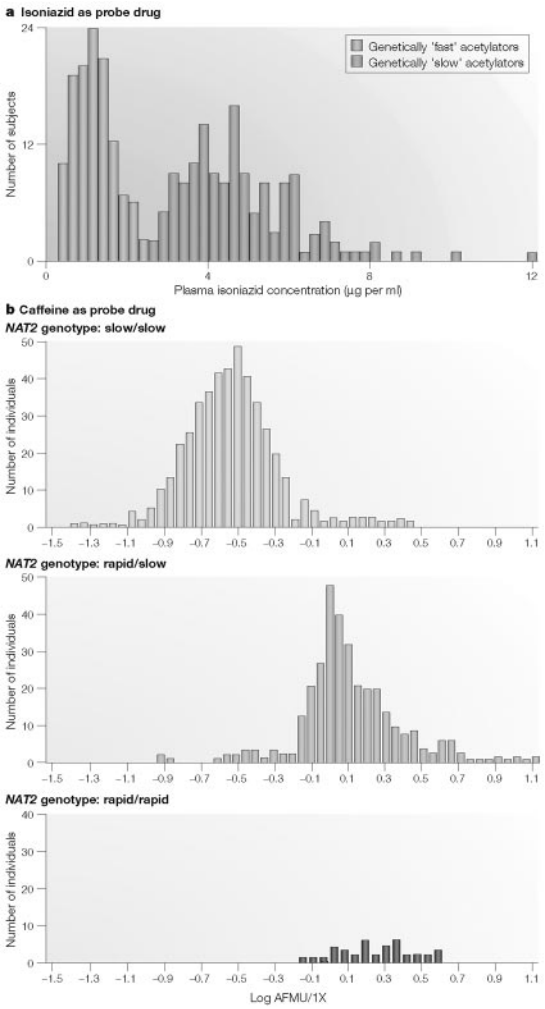
However, the development of these potent and effective therapeutic agents also increased the importance of inter-individual variation in drug response—differences that varied from potentially life-threatening adverse drug reactions at one end of the spectrum, to a lack of desired therapeutic effect at the other end. At the same time, the application of classical genetic techniques led to the realization that inheritance was an important factor responsible for individual variation in drug response (5). That realization half a century ago—well before the Human Genome Project—led to the birth of the discipline of pharmacogenetics (5–7). Obviously, many factors other than inheritance, such as age, sex, other drugs administered to the patient and underlying disease states, also contribute to variation in drug response. However, the convergence of rapid developments in genomics and molecular pharmacology has provided an unusual opportunity to move towards the goal of individualized drug therapy.

The ultimate promise of pharmacogenetics is the possibility that knowledge of a patient's DNA sequence might be used to enhance drug therapy to maximize efficacy, to target drugs only to those patients that are likely to respond and to avoid adverse drug reactions. The subsequent discussion will briefly review the process by which the disciplines of pharmacogenetics and pharmacogenomics have developed, and then turn to challenges associated with the "translation" of these disciplines from the research laboratory to the bedside, with the eventual goal of developing truly individualized drug therapy.

Pharmacogenetics to pharmacogenomics

The concept that inheritance can have an important role in individual variation in drug response originally grew out of clinical observations of large differences among patients in their response to "large" doses of a drug. Attempts to understand that variation led to twin studies that demonstrated that plasma concentrations or other pharmacokinetic parameters are highly heritable for some drugs (8, 9), as well as the simultaneous discovery of large variations in drug levels or metabolism that were inherited as Mendelian traits. Many of those early examples, and many of the most striking examples even today, involved pharmacokinetic factors—that is, factors that influence drug concentration. When a patient takes a drug, that drug must be absorbed, distributed to its site of action, interact with its target and, finally, undergo metabolism and excretion (10).

Figure 1. Classic Pharmacogenetic Traits: Inherited Variation in *N*-acetylation



a) Plasma concentrations of the antituberculosis agent isoniazid in 267 subjects 6 hours after an oral dose. The bimodal distribution results from polymorphisms in the gene encoding *N*-acetyltransferase-2 (*NAT2*), which catalyses the metabolism of isoniazid. b) NAT2 acetylation, measured as a ratio of the caffeine metabolites 5-acetylamino-6-formylamino-3-methyluracil (AFMU) and 1-methylxanthine (1X), in 795 unrelated German subjects. The antimode log AFMU/1X was -0.3 ($10^{-0.3} = 0.5$). 45.3% of the subjects were phenotypically rapid acetylators and 54.7% were phenotypically slow acetylators. *NAT2* genotypes showed that 444 (55.8%) were slow/slow, 312 (39.2%) were rapid/slow and 39 (4.9%) were rapid/rapid. Therefore, 5.7% of subjects were genotype-phenotype discordant (71). Part a modified with permission from Ref. 15. © BMJ Publishing Group (1960). Part b modified with permission from Ref. 71. @ Marcel Dekker (1999).

The majority of "classic" pharmacogenetic traits have involved drug metabolism. For example, one such trait, which was recognized half a century ago, is inherited variation in *N*-acetylation, now known to be due to polymorphisms in the *N*-acetyltransferase-2 (*NAT2*) gene (11). Genetic variation in *NAT2* is responsible for phenotypic variation in the pharmacokinetics—and, therefore, the effects—of drugs as disparate as the antihypertensive hydralazine, the antiarrhythmic drug procainamide and the antituberculosis agent isoniazid (12–14). The effect of *NAT2* pharmacogenetics on plasma levels of isoniazid is shown in Fig. 1A. The bimodal frequency distribution shown in Fig. 1A illustrates the effects of genetically "rapid" acetylation (low plasma drug levels) and genetically "slow" acetylation (high plasma drug levels) (15). Many early examples of pharmacogenetic variation in drug metabolism involved the measurement of this type of phenotype: plasma drug concentrations, urinary drug excretion, peak plasma levels, drug half-life and so on.

In effect, isoniazid was used as a "probe drug" for *NAT2* polymorphisms to generate the data depicted in Fig. 1A; the plasma concentration of isoniazid provided an indirect reflection of the effects of sequence variation in the gene encoding NAT2, which catalyses isoniazid metabolism (11). However, as shown in Fig. 1B, in which the NAT2 phenotype has been determined with caffeine as the probe drug, genotype and phenotype do not correlate perfectly—a lesson to be remembered whenever DNA-based testing is used in a clinical setting. As described subsequently, "probe drug assays" such as those shown in Fig. 1A,B have been a commonly used pharmacogenetic research tool, beginning at a time before any of the cDNAs or genes encoding proteins responsible for the phenotype being measured had been cloned or characterized. A slightly different approach, involving the assay of a different phenotype, is represented by the original studies of another "classic" example of pharmacogenetics, the thiopurine *S*-methyltransferase (*TPMT*) genetic polymorphism (Fig. 2A) (16, 17). In the case of TPMT, the phenotype studied was the level of this drug-metabolizing enzyme activity as measured in an easily accessible cell type, the red blood cell (RBC) (16, 17). Because the *TPMT* genetic polymorphism is of such striking clinical significance, it is described in detail in Box 1 as an example of this type of pharmacogenetic trait.

The use of a "probe drug" assay as illustrated for *NAT2* in Fig. 1A,B, or by the administration of drugs such as DEBRISOQUINE to determine cytochrome P450 2D6 (CYP2D6) phenotype (Fig. 3A) (18–22), was a mainstay in pharmacogenetic research in the late twentieth century. The frequency distribution depicted in Fig. 3A shows that this Northern European population sample included a group of "poor metabolizers" (PMs) for debrisoquine, a large group of "extensive metabolizers" (EMs) and a small number of "ultra-rapid metabolizers" (UMs), some of whom have been shown to have multiple copies of the *CYP2D6* gene (23). These UM subjects can display an inadequate therapeutic response to treatment with "standard" doses of drugs metabolized by CYP2D6. Although the occurrence of this phenomenon is relatively in-

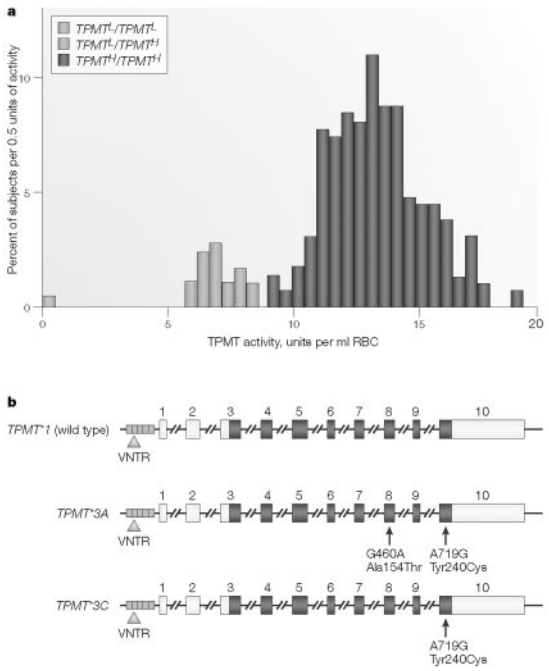
frequent among Northern Europeans, such as the subjects used to obtain the data shown in Fig. 3A, in East African populations the frequency of ALLELES with *CYP2D6* gene duplications can be as high as 29% (24). The frequency distribution histograms of *CYP2D6* and *NAT2* phenotypes that are shown in Figs. 1, 3 have become "icons' of pharmacogenetics, reproduced in countless textbooks and articles, including the present review (15, 20)! However, the same probe drug assays used to generate these frequency distributions have also been a barrier to the rapid translation of pharmacogenetics into the clinic. Physicians resisted the requirement that a probe drug be given to patients, and a sample of urine or plasma be obtained, before administration of the desired therapeutic agent. It was at this point that advances in genomic science offered a potential solution to this practical problem and, as a result, an opportunity to help move pharmacogenetics to the bedside.

The application of DNA-based assays in pharmacogenetics promises to make DNA sequence information available to the physician on a timescale such that it can be used practically to help select the best drug and/or dose for each patient. That possibility is indicated symbolically in Fig. 3, in which Fig. 3A shows CYP2D6 phenotype data after the administration of the probe drug debrisoquine and Fig. 3B shows a photograph of a cytochrome P450 microarray that can be used to genotype selected CYP genes, including *CYP2D6*. The data shown in Fig. 3A, and those generated by the device shown in Fig. 3B, both provide insight into variation in drug response, but the DNA-based technology is potentially faster and requires only a single blood sample without the need for prior administration of a probe drug.

However, it must be acknowledged that our present lack of comprehensive knowledge of genotype-phenotype correlations represents a limitation of the application of genotyping for pharmacogenomic decision making. The phenotype is what the physician wants to know and, unfortunately, present DNA-based tests can fail to reflect the full range of phenotypic variation. As a result, a major challenge for companies designing DNA-based tests is to develop dependable, economical, high-throughput genotyping platforms, and a major challenge for pharmacogenomic science is to determine comprehensive, clinically useful genotype-phenotype correlations.

The *NAT2*, *TPMT* and *CYP2D6* genetic polymorphisms behave as monogenic Mendelian traits, as do many other "classic" examples from pharmacogenetics. These relatively simple, but striking, examples helped to provide the foundation for our present understanding that inheritance can play an important role in individual variation in drug response by influencing efficacy, toxicity or both. Many additional examples have continued to accumulate in recent years. However, in its 2003 draft "Guidance for Industry Pharmacogenomic Data Submissions" (25), the US FDA singled out as examples of "valid biomarkers" for pharmacogenomics only the *CYP2D6* and *TPMT* polymorphisms—both of which were originally described approximately a quarter of a century ago (16, 18, 26). The FDA definition of a valid biomarker is one for which an established and validated assay exists and—most important—for which an established body of evidence exists that supports its pharmacological and/or clinical significance (25). Among the challenges facing pharmacogenomics is how to move beyond *CYP2D6*, *TPMT* and other classical genetic polymorphisms to broaden the discipline and to move this knowledge from the research laboratory to the patient care environment.

Figure 2. Classic Pharmacogenetic Traits: The Thiopurine *S*-methyltransferase Polymorphism



a) Activity of the drug-metabolizing enzyme thiopurine *S*-methyltransferase (TPMT) in red blood cells (RBCs) from 298 randomly selected Caucasian blood donors. Presumed genotypes for the *TPMT* genetic polymorphism are also indicated. $TPMT^{L}$ and $TPMT^{H}$ are designations for alleles resulting in "low" and "high" activity, respectively. These allele designations were used before the molecular basis for the polymorphism was understood. b) *TPMT* alleles. *TPMT*1* is the most common allele (wild type) and *TPMT*3A*, with two nonsynonymous coding single-nucleotide polymorphisms (SNPs), is the most common variant allele in Caucasian subjects. *TPMT*3C* is the most common variant allele in East Asian subjects (62). Rectangles represent exons, with blue areas representing the open reading frame. The arrows indicate two SNPs, as well as a polymorphic variable number of tandem repeats (VNTR) in the promoter. Part a modified with permission from Ref. 16. © University of Chicago Press (1980).

Box 1. Pharmacogenetics of Thiopurine *S*-methyltransferase

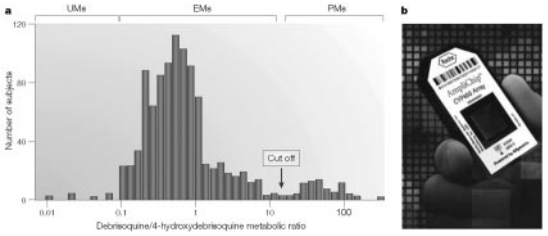
Clinical pharmacogenetics
Thiopurine *S*-methyltransferase (TPMT) catalyses the S-methylation of thiopurine drugs (57, 58). These drugs are used to treat *acute lymphoblastic leukaemia of childhood, inflammatory bowel disease* and organ transplant recipients (59). Thiopurines are very useful agents, but they have a "narrow therapeutic index"; that is, the difference between the dose required to achieve the desired therapeutic effect and that causing toxicity is small (59). The major toxicity of thiopurines is myelosuppression (bone-marrow suppression), which can be life-threatening (27, 59).

Molecular pharmacogenetics
The most common variant allele for *TPMT* in Caucasians is *TPMT*3A*, an allele primarily responsible for the trimodal frequency distribution shown in Fig. 2A, that has a frequency of approximately 5% in Caucasian populations (28, 60, 61). This variant allele has two nonsynonymous coding single-nucleotide polymorphisms (cSNPs)—SNPs that result in alterations in the encoded amino acids (Fig. 2B) (60). *TPMT*3A* is rarely, if ever, observed in East Asian populations, in which *TPMT*3C* is the most common variant (Fig. 2B) (62). Individuals homozygous for *TPMT*3A* are at greatly increased risk for life-threatening myelosuppression when treated with standard doses of thiopurine drugs (27, 29). However, they can be treated with these drugs at approximately one-tenth the standard dose, but even then only with careful monitoring (17).

Molecular mechanisms
The allozyme encoded by *TPMT*3A* is degraded rapidly by a ubiquitin-proteasome-mediated process (63, 64); so, subjects homozygous for this allele have little or no detectable TPMT protein in their tissues (60, 65) and very little protein is observed after the transfection of cultured mammalian cells with expression constructs for this allozyme (60, 63). There is also evidence that chaperone proteins such as heat-shock protein-70 (HSP70) and HSP90 might be involved in targeting the *TPMT*3A* variant allozyme for degradation (63). Decreased protein level—often resulting from accelerated degradation—is a common pharmacogenomic functional mechanism (66).

The *NAT2*, *TPMT* and *CYP2D6* polymorphisms—as well as a series of similar monogenic pharmacogenetic traits—represent easily understood examples that helped to establish that inheritance is an important factor accounting for individual differences in drug response. They served to stimulate the development of the discipline, but even the *TPMT* and *CYP2D6* polymorphisms fail to explain all variation in response to drugs metabolized by these enzymes—nor would anyone who has ever written a prescription expect that a single factor would be able to explain all variation in such a complex phenotype. Therefore, to state the obvious, no pharmacogenetic trait, and no test for that trait, should be expected to explain all the observed variation in drug response. For example, there are many reasons why patients with leukaemia who are treated with thiopurine drugs as well as other cytotoxic agents might develop myelosuppression, and a genetically low level of TPMT is only one of those reasons (Box 1). However, if a patient is homozygous for *TPMT*3A*, the evidence is now overwhelming that their physician should anticipate significant and perhaps life-threatening myelosuppression in response to treatment with standard doses of thiopurine drugs (17, 27–29).

Figure 3. Classic Pharmacogenetic Traits: Polymorphisms in Cytochrome P450 2D6



a) Cytochrome P450 2D6 (CYP2D6) pharmacogenetics determined using the ratio of debrisoquine to its metabolite, 4-hydroxydebrisoquine, in 1,011 Swedish subjects. This population sample included a group of "poor metabolizers" (PMs), a large group of "extensive metabolizers" (EMs) and a small number of "ultra-rapid metabolizers" (UMs). The box labelled "cut off" indicates the cut off between data for subjects with "poor" metabolism as a result of decreased or absent CYP2D6 activity and subjects with "extensive" metabolism. b) Roche AmpliChip P450 Array. The photograph shows a device that can be used to determine genotypes for alleles of selected CYP genes including *CYP2D6*. The authors have used the Roche device only for purposes of illustration; it does not imply endorsement of this particular technology. Part a modified with permission from Ref. 20 © American Society for Clinical Pharmacology and Therapeutics (1992). Part b used with the permission of Roche Diagnostics.

The contrast between pharmacokinetic and pharmacodynamic pharmacogenomic effects is outlined schematically in Box 2, which illustrates two examples of polymorphic enzymes that result in pharmacokinetic variation, CYP2D6 and NAT2. Those two examples are contrasted with two "pharmacodynamic" examples, the *ALOX5* gene that encodes 5-lipoxygenase and the epidermal growth factor receptor (*EGFR*) gene. As described in more detail in Box 2, subjects with a variant VARIABLE NUMBER OF TANDEM REPEATS (VNTRs) in the *ALOX5* promoter have decreased transcription of the gene (30) and, as a result, respond less well to treatment with the 5-lipoxygenase inhibitors that are used to treat asthma (31). On the other hand, mutations in the *EGFR* gene in tumour DNA in non-small-cell lung carcinomas, all occurring within the ATP-binding pocket of the tyrosine kinase domain of this receptor, are associated with enhanced tumour response to the EGFR tyrosine kinase inhibitor gefitinib (Iressa; AstraZeneca) (32, 33). In these studies, the frequency of these EGFR mutations varied from as low as 2% in patients in the United States to 26% in patients in Japan (32, 33).

These examples of genetic variation in drug targets might be representative of a large part of the "future" of pharmacogenomics—a future in which,

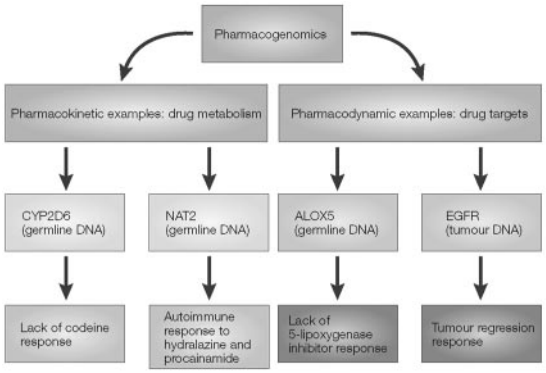
before therapy, patients will be stratified on the basis of their ability to respond or not respond to a therapeutic agent. However, this future scenario will have significant economic implications for the pharmaceutical industry, as discussed subsequently.

The development of pharmacogenetics occurred in parallel with rapid changes in genomic science, most significantly the conception, implementation and completion of the Human Genome Project (1, 2). At the end of the twentieth century, the convergence of these two areas of biomedical research resulted in the evolution of pharmacogenetics into pharmacogenomics (34, 35). Although it might seem that there are nearly as many definitions of "pharmacogenomics" as there are investigators engaged in the discipline, the terms "pharmacogenetics" and "pharmacogenomics" are often used interchangeably. From the perspective of the authors of this review, pharmacogenomics emerged from the convergence of the step-wise advances that occurred in pharmacogenetics during the twentieth century with the striking changes that occurred in genomic science at the end of that century, such as the completion of the Human Genome Project, and the development of expression profiling, as well as high-throughput DNA sequencing and genotyping (see Refs. 34, 35 for recent reviews).

Whatever definition of pharmacogenomics one might choose to use, the latter portion of the twentieth century witnessed the emergence of the concept that inheritance is a major factor responsible for variation in drug response. Once that principle had been established, the question immediately arose of the best way by which to translate this information to the bedside. Furthermore, as the twentieth century ended, that question was being asked within the context of rising enthusiasm for all things "genomic"—an enthusiasm that might have led to unrealistic expectations with regard to our ability to "individualize" drug therapy on the basis of genomics. Those unrealistic expectations might have occurred in part because of the understandable enthusiasm of investigators in this area of research; in part because of naivete with regard to the difficulty of the clinical validation and acceptance by practicing physicians of laboratory-based observations; and, in part, because of a need to raise venture capital by start-up biotechnology firms that were attempting to commercialize pharmacogenomics.

Regardless of the reasons, the fact is that although pharmacogenomic testing had been predicted to be one of the first broad applications of genomics to clinical medicine (36)—and this might ultimately prove to be correct—such applications so far have been limited to a few tests that are used mainly within academic referral centres. The relatively slow pace of the incorporation of pharmacogenomics into clinical practice has, in turn, resulted in impatience and even disillusionment with regard to the clinical potential of this area of biomedical science (37). Therefore, the questions of why the pace has been so "measured," and what might be done to accelerate the translation of this body of knowledge to the bedside, need to be addressed. The subsequent discussion will attempt to briefly outline some of the challenges that exist as we attempt to move pharmacogenetics and pharmacogenomics into the clinic, as well as issues that will have to be addressed if that process is to be accelerated.

Box 2. Pharmacokinetic and Pharmacodynamic Effects

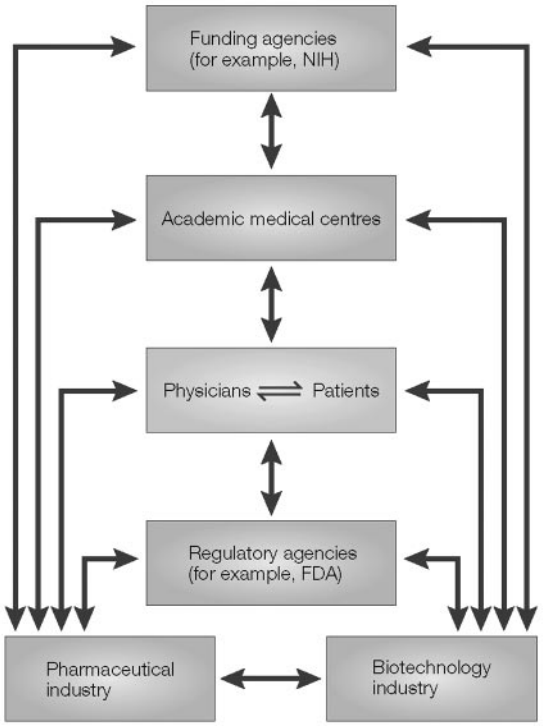


Variations in drug effects can be classified as those due to either "pharmacokinetic" or "pharmacodynamic" factors. The figure presents a diagrammatic representation of "pharmacokinetic" and "pharmacodynamic" pharmacogenomic effects.
The two pharmacokinetic examples involve the drug-metabolizing enzymes *N*-acetyltransferase-2 (NAT2) (Fig. 1A) and cytochrome P450 2D6 (CYP2D6) (Fig. 3A). Poor metabolizers for CYP2D6 fail to experience an analgesic effect from codeine, which is a "PRO-DRUG" that must be converted to morphine by CYP2D6 *in vivo* (67, 68), whereas "slow metabolizers" for NAT2 are at increased risk for autoimmune responses to the antihypertensive drug hydralazine and the antiarrhythmic agent procainamide (69, 70).
The two examples of pharmacodynamic pharmacogenomics involve the *ALOX5* gene and the gene encoding the epidermal growth factor receptor (*EGFR*). Inhibitors of 5-lipoxygenase, the protein encoded by *ALOX5*, are used to treat patients with asthma. There is a variable number of tandem repeats (VNTRs) in the promoter for *ALOX5*, and subjects homozygous for repeat numbers other than the "wild-type" version with five repeat elements express less of this enzyme (30). These patients also respond less well to treatment with 5-lipoxygenase inhibitors than do those with the wild-type VNTR (31). An even more dramatic example of genetic variation in a drug target involves the gene encoding EGFR. In one recent study, approximately 10% of patients with non-small-cell lung carcinoma responded to treatment with the EGFR inhibitor gefitinib (32). Most of those patients had mutations involving multiple-nucleotide deletions or nonsynonymous coding single-nucleotide polymorphisms in the tyrosine kinase domain of EGFR. These mutations were present in tumour DNA, but not in germline DNA (32, 33).

PHARMACOGENOMIC CLINICAL TRANSLATION

Introduction. First and foremost among the challenges we face as we attempt to transfer pharmacogenomics to the bedside is the science itself. Unless there is strong scientific evidence in support of the value of pharmacogenomic testing for patient

Figure 4. Schematic Representation of Pharmacogenomic "Players" and Their Relationships



FDA, Food and Drug Administration; NIH, National Institutes of Health.

care, there is no reason to make that testing part of the therapeutic encounter. We also need to be sensitive to the fact that the development of pharmacogenomics is happening at a time when the biomedical research enterprise as a whole is undergoing significant change. Another significant issue is the fact that several major "players" (Fig. 4) will determine how rapidly this branch of biomedical science advances and how quickly scientific advances will move to the bedside. Included among those players are research funding agencies, academic medical centres, the pharmaceutical/biotechnology industry, drug regulatory agencies, the healthcare professionals who will use this information for patient care—and, finally, the patients themselves.

Pharmacogenomic science. During its first half century, pharmacogenomics produced a series of "success stories," such as TPMT and CYP2D6 (Ref. 28). However, even though monogenic traits such as the TPMT and CYP2D6 polymorphisms helped to demonstrate that inheritance can influence drug response, this "monogenic model" might not apply to the majority of drugs. Multiple proteins participate in the metabolism and transport of most drugs and there is also the potential for inherited variation in their targets (31, 32). Therefore, it will become increasingly necessary to simultaneously study genes encoding a variety of proteins that participate in both pharmacokinetic and pharmacodynamic "pathways" to evaluate the full contribution of inheritance to variation in drug response. To do that will require large, well-controlled studies that have been designed especially to test pharmacogenomic hypotheses. That type of study will require the application of cost-effective, high-throughput assays to genotype a large number of polymorphisms—or, more likely, HAPLOTYPES (38)—for genes encoding all of the proteins in these pathways, and/or the application of genome-wide scans to identify genes of possible pharmacogenomic importance.

Because multiple genes, intragene haplotypes and gene-gene interactions will be studied, the POWER CALCULATIONS will demand very large studies (39). This type of study will also require the assembly of research teams that include individuals with a wide range of expertise—as well as an infrastructure that includes sophisticated facilities for genotyping and phenotyping. In the future, that infrastructure will also have to expand to include the ability to perform "pharmacoproteomic" and "pharmacometabolomic" studies. The size and breadth of this type of study exceeds the resources of many academic medical centres and would be difficult to fund through most traditional peer-review mechanisms. It should be emphasized that these developments in pharmacogenomic research, especially the research required to identify clinically relevant haplotypes and/or gene pathways, merely reflect in a microcosm forces that are reshaping the entire biomedical research enterprise.

In recognition of the changes that are occurring in biomedical research, the *National Institutes of Health* (NIH) recently conducted a strategic planning exercise entitled "The NIH Roadmap" (40). That exercise led to recommendations that an emphasis be placed on the need to understand complex biological systems and the need to assemble teams of scientists with differing, but complementary, expertise to address the growing complexity of those systems. The NIH Roadmap also stressed the need to "redesign" the clinical research enterprise, in part to help facilitate the translation of emerging disciplines such as pharmacogenomics (40). The bottom line is that if this science is to be rapidly translated to medical practice, a paradigm that includes large studies—not clinical trials designed to determine drug efficacy, but rather trials designed to test pharmacogenomic hypotheses—will be required.

One "experiment" is already under way that is testing some of the concepts outlined in the NIH

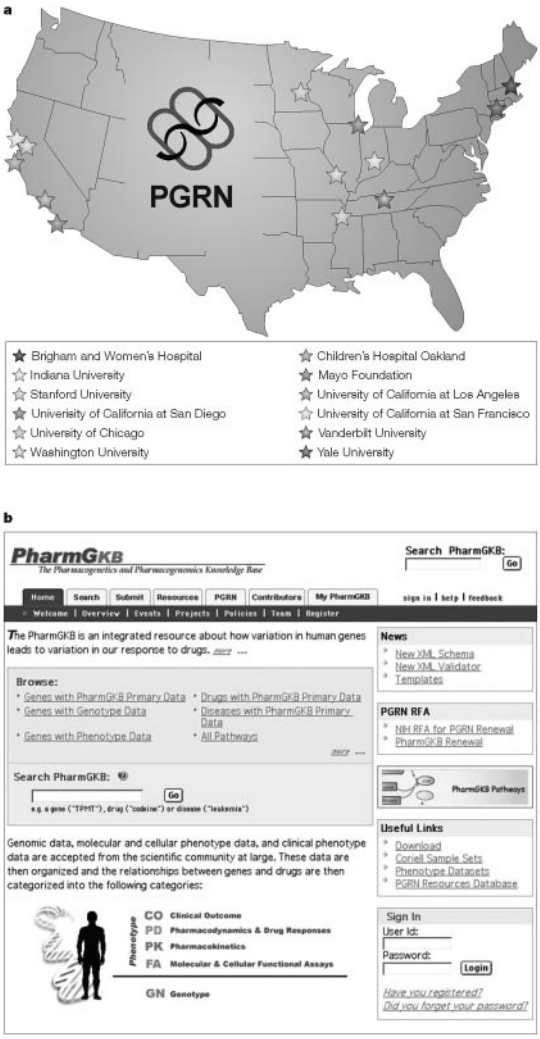
Roadmap. That experiment involves an NIH-supported multidisciplinary, multi-institutional Pharmacogenetics Research Network (*PGRN*). Each PGRN centre includes a series of integrated groups with expertise in pharmacology, genomic science, bioinformatics and clinical science. Twelve PGRN centres were funded initially, one of which is a database group located at Stanford University that is responsible for the development of a *Pharmacogenetics and Pharmacogenomics KnowledgeBase*, a public database that focuses on genotype and phenotype data relevant to pharmacogenomics (41). There are also research centres scattered across the United States that function as a "network" in support of pharmacogenomic research (see Fig. 5A for a map showing the locations of NIH PGRN centres and Fig. 5B for the PharmGKB homepage). This model obviously represents only one attempt to make it possible for academic centres to continue to contribute to the development of pharmacogenomics at a time when, although the traditional investigator-initiated NIH R01 grant will remain the backbone of biomedical research in the United States, R01 support is inadequate to allow any one laboratory to mount this type of large translational study. Obviously, there is no single "model" for pharmacogenomic research, but it is clear in this era of the NIH Roadmap that the organizational structure of this area of biomedical research is evolving.

Finally, research funding agencies such as the NIH have, in the past, not necessarily seen their role as including stimulation of the translation of pharmacogenomics into the clinic, because that was viewed as more appropriately the responsibility of the pharmaceutical industry and drug regulatory agencies. On the face of it, this conclusion seems logical because drugs are developed by the pharmaceutical industry and their availability and use are controlled by the regulatory agencies. However, the major "players" in this area of biomedicine (Fig. 4) all have their own agendas and incentives, and those incentives have not always facilitated the transfer of pharmacogenomics into the clinic.

Translational interaction. The major players with a potential stake in pharmacogenomics have differing agendas. For example, the pharmaceutical industry, as outlined in a recent review in *Science*, is highly focused on the development of "blockbuster drugs" (42). The essence of the blockbuster drug is the concept that "one size fits all—or nearly all". That type of focus might have resulted in incentives for the pharmaceutical industry to downplay the importance of individual variation in drug response. As a result, pharmacogenomics was initially viewed with caution by industry because its application would result in market segmentation and revenue reduction as a result of the exclusion of patients who—on a genetic basis—might not respond to a drug or class of drugs. This concern with regard to market segmentation and its potential impact on the economics of the pharmaceutical industry initially served, at the very least, to inhibit enthusiasm for testing pharmacogenomic hypotheses.

However, in recent years the pharmaceutical industry has begun to incorporate pharmacogenomics into the drug development process. As viewed from the outside, each company has taken a slightly

Figure 5. An Example Initiative to Facilitate the Translation of Pharmacogenetics: The Pharmacogenetics Research Network



a) Supported by the National Institutes of Health, the Pharmacogenetics Research Network (PGRN) at present consists of twelve centres (locations indicated with stars) across the United States, each of which includes a series of integrated groups with expertise in pharmacology, genomic science, bioinformatics and clinical science. b) One of these centres, based at Stanford, is responsible for the development of the Pharmacogenetics and Pharmacogenomics KnowledgeBase, a public database that focuses on genotype and phenotype data relevant to pharmacogenomics; the homepage is shown here.

different approach, with some enthusiastically embracing the emerging concept of pharmacogenomics and others moving a good deal more cautiously. In theory, pharmacogenomics might help to "rescue" drugs that have failed during the development process. For example, individuals who might, on a genetic basis, be predicted to have adverse responses or fail to respond when administered a given agent could be excluded from exposure to the drug. However, that would require pharmacogenomic testing before administration of the drug, and most pharmaceutical companies have, understandably, resisted marketing drugs that require an initial "test." In fact, merely incorporating a modification in the labelling of approved drugs to include pharmacogenomic information with regard to well-validated, clinically relevant genetic variation, such as that involving the *TPMT* genetic polymorphism (Box 1), has generated controversy. However, there are already examples of situations in which a "test" provides such useful information with regard to response that it is indicated before therapy.

One of the best known of these examples is the enhanced response to trastuzumab (Herceptin; Roche) by breast-cancer patients who display overexpression of the *ERBB2* (also known as *HER2/neu*) gene (43, 44). The effect of mutations of the *EGFR* gene in tumour DNA on gefitinib response could represent another example in which science and marketing considerations converge to create a situation in which data from clinical trials creates a set of incentives that will encourage both the pharmaceutical industry and regulatory agencies to cooperate in bringing a therapeutic agent to market "bundled" with a test. Ultimately, each individual company will have to perceive a competitive advantage for embracing this new science or that will not occur.

Obviously, regulatory pressure for the inclusion of pharmacogenomic data during drug development would provide a strong stimulus for the incorporation of this science into the drug development process, as well as its acceptance by the pharmaceutical industry. Unfortunately, regulatory agencies such as the FDA have also been relatively slow to incorporate pharmacogenomics into the drug approval process. However, to the credit of the FDA, a draft "Guidance" (25) with regard to pharmacogenomics was issued in 2003. (Readers are referred to a recent series of articles on this topic (45–48), as well as the companion article in this series by Lesko and Woodcock, for a summary of the approach presently taken by the FDA to pharmacogenomics.)

Healthcare professional and patient education. Most of today's healthcare professionals were educated before the advent of the genomic revolution. If pharmacogenomics is to be translated into individualized drug therapy, a concerted effort will have to be directed to the "genomic" education of all healthcare professionals—including physicians, dentists, nurses and physician's assistants. That educational effort will have to begin with the genomic "vocabulary," the "ABCs" of genomic science as applied to medicine. For example, most physicians were educated at a time when it was not clinically important to understand what a "TATA BOX" is. However, a VNTR involving the TATA box of the *UGT1A1* gene is important in the pathophysiology of *Gilbert's syndrome* (benign unconjugated hyperbilirubinaemia) as a result of decreased glucuronide conjugation in subjects having seven rather than six repeat elements (49–51). Furthermore, this same polymorphism contributes to inherited variation in the toxicity of drugs such as the antineoplastic agent irinotecan (Camptosar; Pfizer) (52).

Although it is not important for clinicians to know what a "VNTR" is, it is important that they be familiar with the broad concepts of genomics and pharmacogenomics. Therefore, the example provided by the *UGT1A1* VNTR illustrates the need for continuing education programmes in genomic medicine that are directed to all members of the healthcare team. Medical journals have already recognized this need, and, for example, both the *New England Journal of Medicine* (53) and the *Mayo Clinic Proceedings* (54) have published series of articles intended to inform the practicing physician with regard to the application of genomics to clinical medicine.

Finally, patients will also have to be educated and will have to understand and accept pharmacogenomic testing. Furthermore, significant social and ethical issues must be addressed if the science underlying pharmacogenomics is to have its full potential impact on the clinical practice of medicine and if patients and physicians are to embrace this new science enthusiastically. In some ways, the ethical issues in pharmacogenomics are simplified because, in this area of genomic medicine, the data are generally non-stigmatizing and the physician can "do something" in response to a test result, such as raise or lower the dose of a drug, or select a different drug. For example, in the case of the *TPMT* genetic polymorphism, a genomic test result might even dictate that the physician lowers the drug dose. Administration of a standard dose of 6-mercaptopurine to a patient homozygous for the *TPMT*3A* variant allele would clearly endanger the patient (Box 1) (27–29).

However, in many ways, the ethical and social issues involved in pharmacogenomics do not differ from those that exist elsewhere in genomic medi-

cine. First and foremost among these is the need to protect patient confidentiality and enhance public confidence that genomic information will be used only for the benefit of the individual patient and not for purposes of discrimination (55, 56). Ultimately, society has to find politically acceptable ways to ensure that patients can be certain that they will receive the benefits of genomic medicine without the risk of discrimination. Obviously, those solutions will differ from country to country because of differences in their systems of healthcare delivery and variation in political climates. Box 3 summarizes major issues that will have to be addressed if pharmacogenomics is to be successfully translated into the clinic.

Box 3. Pharmacogenomic Clinical Translation

Pharmacogenomic science
Pharmacogenomics is moving beyond single-gene effects to study the effects of inheritance on pharmacokinetic and pharmacodynamic pathways involving multiple gene products. This type of study will require a large number of subjects and multidisciplinary teams of investigators with complementary expertise, as well as the ability to genotype a very large number of polymorphisms or haplotypes.

Translational incentives
Successful translation of pharmacogenomics into the clinic will require the creation of positive incentives that will stimulate research funding agencies, academic centres, the pharmaceutical industry and drug regulatory agencies to work together to achieve translation (Fig. 4).

Healthcare professional education
The translation of pharmacogenomics to the bedside will require the education of physicians and other healthcare professionals in clinical genomic science generally, and in its application to therapeutics in particular.

Patience acceptance
Patients will also have to become informed with regard to the application of genomics to drug selection and dosage. In addition, an effort will have to be made to keep patient expectations of pharmacogenomics realistic. Finally, patients must be assured that the confidentiality of their genomic information will be protected.

Conclusions

Pharmacogenetics and pharmacogenomics hold out the promise of helping to achieve the goal of individualized drug therapy. Many factors other than inheritance contribute to individual variation in drug response, but recent developments in genomic and pharmacological science have raised the possibility of providing the physician with objective information that might make it possible to tailor drug selection and/or dose to the likely response of the patient to that class of drug, that specific agent or that dose on the basis of their genetic make-up. However, in spite of the excitement surrounding pharmacogenetics and pharmacogenomics, their translation into the clinic has been relatively slow. It is now clear that although examples such as the *CYP2D6* and *TPMT* genetic polymorphisms make it possible to predict clinically relevant genetic variation that can be used to individualize drug therapy, the principal value of these examples has been to emphasize the fact that inheritance is an important factor responsible for individual differences in drug response.

Unfortunately, a series of countervailing pressures might have slowed the translation of pharmacogenomics into the clinic. Included among these is the increasing need for large and complex studies designed to test pharmacogenomic hypotheses in clinical settings; economic disincentives for the pharmaceutical industry to enthusiastically accept the implications of individual, inherited variation in drug response; and the parallel and relatively measured pace of the inclusion of this new science in the drug evaluation process by regulatory agencies. However, it is clear that we have already discovered clinically relevant examples of pharmacogenomics, such as the *TPMT* and *CYP2D6* polymorphisms, and that their broad application would result in benefits to patients. The further development of pharmacogenetics and pharmacogenomics, and the impending incorporation of pharmacoproteomics and pharmacometabolomics into this area of science—which is increasingly requiring integrated teams of investigators with complementary areas of expertise—will undoubtedly result in many additional examples in the future. Ultimately, the application of pharmacogenomics to patient care could help make it possible during the therapeutic encounter to treat each patient as the complex, unique and fascinating individual whom they are.

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ONLINE LINKS

DATABASES

The following terms in this article are linked online to: Entrez Gene: http://www.ncbi.nlm.nih.gov/LocusLink/

ALOX5 | CYP2D6 | EGFR | ERBB2 | NAT2 | TPMT | UGT1A1

Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

Gilbert's syndrome | inflammatory bowel disease

National Cancer Institute Cancer List: http://cancer.gov/cancertopics/alphalist/a-d

Acute lymphoblastic leukaemia of childhood

FURTHER INFORMATION

Pharmacogenetics Research Network: http://www.nigms.nih.gov/pharmacogenetics/

Pharmacogenetics and Pharmacogenomics KnowledgeBase: http://www.pharmgkb.org/

Access to this interactive links box is free online.

DEBRISOQUINE
An antihypertensive drug that is metabolized by cytochrome P450 2D6.

ALLELES
Different versions of the same gene.

PRO-DRUG
A pharmacologically inactive compound that is converted to the active form of the drug by endogenous enzymes or metabolism.

HAPLOTYPE
A combination of alleles or sequence variations on the same chromosome.

POWER CALCULATIONS
A statistical calculation of the ability of an experiment to avoid false positive and/or negative results.

TATA BOX
DNA sequence motif of importance for transcription initiation.

NOTES