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*Commentary*

# Drug Therapy and Personalized Health Care: Pharmacogenomics in Perspective

**Wolfgang Sadee**[1,2]

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## THE ERA OF DRUG DISCOVERY: WHERE DO WE GO FROM HERE?

Drug discovery was shaped by the era of the 'magic bullet', coined by Paul Ehrlich early in the twentieth century. Expectations of a cure achieved through drug therapy seemed to have come true with antibiotic treatments of infectious diseases—but the emergence of drug-resistance cautions one to declare victory. Where then do we stand in this unprecedented age of pharmacotherapy? Do we anticipate ever more powerful drugs, emerging from new insights provided by the human genome project—ushering in a new era of accelerated drug discovery? While genomics has yielded numerous potential new drug targets, it also reveals the complexity of a single cell, not to mention an entire organism. Curing complex diseases with single chemical entities may have been an unrealistic expectation. As a result, current therapies move towards drug combinations to hit diverse biological targets, as seen in the treatment of HIV/AIDS and cancer. The purpose of this essay is to address the question how pharmacogenomics can yield clinically useful biomarkers that guide therapy of individual subjects.

While novel molecularly targeted therapies hold much promise, particularly in cancer, complex systems such as the human body require more than simple—or single minded—solutions. Where will the most dramatic and significant advances in therapy come from, and how will they look like? Certainly, novel drug discovery will continue to play a key role, including protein drugs and gene therapy strategies targeting single proteins, or regulatory factors such as non-coding RNAs. Yet despite the 'genomics revolution', the pipeline of new chemical entities is insufficient to maintain the pharmaceutical industry with current strategies (blockbuster drugs). A more targeted approach may be needed to enhance the benefit/cost ratio (niche markets tackling well defined pathophysiologies). On the other hand, we can reasonably expect that optimizing drug therapy for each patient could significantly improve treatment outcomes, even with existing drugs, in the re-emerging era of personalized medicine. As a third option, we are beginning to see other treatment modalities, including the use of complex biological systems as therapies, such as stem cells, homing lymphocytes, neuronal tissues, and autologous engineered organs. Cells are capable of receiving instructions from surrounding tissues, adjusting and evolving desirable functions, for example as neural implants. Lastly, we are beginning to consider the immune system as an important contributor to health and disease, and therefore a target for interventions. Add to this the extraordinary diversity of the human microbiome, commensal partners shaped by adaptive co-evolution (1). Metagenomics of the bacterial flora in the gut is revealing millions of genes present in the ~10 trillion microbial cells coexisting in the human gut, with yet largely uncharted effects on human diseases, such as obesity and inflammation. Clearly, advances in human health and disease therapy will have to come from all of these areas, reflecting human complexity, both biologically, ethnically, and culturally.

## PERSONALIZED HEALTH CARE—AN ANCIENT PRINCIPLE WITH A NEW FACE?

Greater insight into the biology of the human body, and the etiology of disease, enables increasingly accurate prediction of risk and treatment outcomes. Yet, a vast majority of our current resources in the health care sector targets complex, advanced chronic diseases that become increasingly prevalent with old age but also resist effective therapy. Probably a more fruitful approach, focus on early therapy and disease prevention has the potential to transform our health care system. Anticipating this trend, many academic centers have implemented large-scale programs in predictive or preventive medicine. At the Ohio State University Medical Center, we prefer the term personalized health care, to emphasize maintenance of health and wellness as a principal goal (2).

Whereas medicine has traditionally dealt with the individual patient, drug therapy has often followed the principle of one-drug-fits-all, maybe in part an offshoot of the industrialization over the past two centuries. But this

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[1] Department of Pharmacology, Program in Pharmacogenomics, College of Medicine, The Ohio State University, Columbus, Ohio 43210-1239, USA.
[2] To whom correspondence should be addressed. (e-mail: wolfgang.sadee@osumc.edu)

approach is changing rapidly. Increasing use of biomarkers to guide therapy is the means by which therapies can be individualized, or response measured. Traditional biomarkers include blood laboratory tests (glucose, lipids, electrolytes, amino acids, enzymes, etc). Specific to drug therapy, pharmacokinetics–pharmacodynamics (PK-PD) has introduced a quantitative approach to therapeutics across a population of individual subjects. Drug levels in the blood were introduced as 'biomarkers' to study interindividual differences and adjust drug dosages where feasible. More recently, genomics based biology has opened a Pandora's box of potential biomarkers. Typical pharmacogenetic biomarkers include genetic variants in CYP enzymes (oxidative metabolism), UTG1A1 (glucuronidation), VKORC1 (warfarin target), EGFR (example of growth factor receptors driving cancers), NAT2 (acetylation), MDR1 and BRCA (efflux transporters), and more. While the clinical utility of these biomarkers remains under debate, an entire industry has emerged within a short time period dedicated to the generation of novel biomarkers—a subject that I will address in more detail further below. The principal goal of these new biomarkers is to enable predictions about disease risk and progression, and treatment outcomes, tailored for each individual patient. In addition, biomarkers can serve as surrogates for measuring treatment response. As a result, personalized health care as it is understood today is intimately linked to biomarkers, genetic/genomic and otherwise.

In some instances, combination of the drug with a biomarker—predicting response rate or risk of toxicity—could become obligatory, potentially a mainstream future trend, even though currently still in infancy. This approach to drug therapy has been termed theranostics, defined in Wikipedia in a way that highlights the main points discussed here: "*Theranostics* is the term used to describe the proposed process of diagnostic therapy for individual patients—to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results. It encompasses the possible utilisation of a wide range of subjects that includes: predictive medicine, personalized medicine, integrated medicine, pharmacodiagnostics and Dx/Rx partnering. This method is looked upon as the possible end result of new advances made in Pharmacogenomics, Drug Discovery using Genetics, Molecular Biology and Microarray chips technology."

## PHARMACOGENOMICS: WHAT IS THE PROMISE AND WHERE ARE THE LIMITS?

Pharmacogenetics, and in a broader sense pharmacogenomics, exploit genetic/genomic information in drug discovery, development, and therapy (3). Pharmacogenetics is traditionally defined as the study of genetic causes of variability in drug response, while pharmacogenomics incorporates a broader approach, involving all the -omics disciplines, and serving alternately for drug discovery, development, and therapy. Colloquial use of these terms is still in flux and quite diverse. Beyond genetics in the strict sense, pharmacogenomics may include complex phenotypes, such as the transcriptome, proteome, metabolome, and glycome (although these are all phenotypes, not genotypes). Because a number of genes encoding important drug metabolizing enzymes and transporters are highly polymorphic (4), this has attracted pharmaceutical scientists who already had studied the interindividual variation in PK-PD for some time. Mainly geared towards avoiding drug toxicity in the early studies, pharmacogenetic principles begin to enter clinical practice, for example to facilitate dosage titrations with the anticoagulant warfarin, using polymorphisms in two genes (*CYP2C9* and *VKORC1*) (5). Recently, the FDA has revised prescribing information for warfarin to include pharmacogenetic information, thereby, officially introducing genotype as a factor into mainstream therapy—although guidance on how to adjust warfarin dose is not provided in the revised labeling. While adverse drug reactions (ADRs) were deemed 'unavoidable', we have shown that the worst ADR-causing drugs are often metabolized by polymorphic enzymes such as CYP2D6 (6). Therefore, prospective genotyping may result in reduced incidence of ADRs – potentially a significant improvement as ADRs are considered a leading cause of morbidity and mortality (7). It is noted that genetic biomarkers are most useful for predicting risk and outcomes, not to gauge treatment response, the latter requiring phenotypic biomarkers such as cholesterol levels, and mRNA or protein profiles, except in cancer where one might follow cells with somatic mutations.

On the other hand, low efficacy is a second serious issue with current medication, even those blockbuster drugs hailed as critical advances in therapy: antipsychotics, antidepressants, anticancer drugs, to name just a few. Representing the top-selling drug class, statins reliably lower lipid levels in a vast majority of subjects, but they reduce myocardial infarction (MI) by only 30–40%. Cholesterol levels can serve as excellent biomarkers guiding statin therapy, but critical elements in the etiology of MI remain hidden—encompassing other aspects of lipid metabolism, and processes involved with coagulation and inflammation. Pharmacogenomic biomarkers targeting key processes in the etiology of MI would be immeasurably valuable for predicting treatment failure. While countless studies have already been performed to resolve the factors that might determine risk of MI, none of these provide sufficiently robust predictive value to alter clinical practice at present. For example, early studies on *CETP* (encoding cholesterol ester transfer protein) suggested that an intronic SNP of still unknown functionality, *TaqIB*, is associated with HDL-C levels—a critical factor in MI risk—and moreover, that the same SNP was also related to treatment outcome with pravastatin. A meta-analysis of multiple follow-up studies revealed that *TaqIB* was indeed associated with HDL-C and clinical outcomes, but not with response to pravastatin (8). Our own results (unpublished) indicate that several polymorphisms may be active in *CETP*, with different associations in male and female subjects—potentially leading to more predictive *CETP* haplotypes (two to three SNPs) that could become useful clinically.

Insights gained from these studies can also guide development of drugs targeting any one of the relevant causes of MI suspected to play a role in individual patients. In this regard, pharmacogenomics interfaces with medical genetics/genomics of disease, an area of intense current study. While progress in understanding complex diseases has been slow because of their multigenic character, drug therapy typically impinges on specific pathways that are understood in some detail. Moreover, response to specific drugs is likely to reveal subgroups of patients with distinct etiology of a

broadly defined disease such as hypertension. As a result, we can expect odds ratios and predictive power of a pharmacogenetic biomarker to be higher than those predictive of disease risk and progression *per se*. Hence, pharmacogenomics biomarkers have considerable promise in revealing drug targets (e.g., imatinib mesylate (Gleevec) and dasatinib in CML) and predicting outcomes.

The FDA maintains a Website with validated pharmacogenomics biomarker tests, (http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm), classifying these into 'required' (four tests), recommended' (nine tests), and for 'information only' (12 tests, as of June 08). In view of the massive efforts underway in pharmacogenomics, the number of required tests is still very small but rapidly growing: *CCR5* in HIV/AIDS therapy with maraviroc, EGFR (ERBB1) expression in therapy of colorectal cancer with EGFR inhibitors, Philadelphia chromosome (*BCR-ABL1*) positive CML (and a subset of ALL) in therapy with dasatinib (and imitinib mesylate (not mentioned)), and HER2/NEU (ERBB2) expression in cancers treated with trastuzumab and lapatinib.

'Recommended' indicates that significant associations of the genotype (or protein expression) have been found with drug response or toxicity, but the decision whether to perform the test prospectively is left to the therapist. Tests labeled for 'information only' include the highly polymorphic *CYP2D6*, even though clear relationships between variants and drug metabolism are evident. Yet, drug metabolism is modulated by other factors as well, such as enzyme induction, and moreover, our results suggest that not all frequent mutations have been mapped as yet, even in the best studied genes. In addition, the relationship of genotype with *in vivo* pharmacokinetics and response is confounded by parallel metabolic pathways—ambiguities that all diminish the potential clinical value of a biomarker test. It is therefore critical to assess the relative contributions of genetic and other factors for each gene, drug, and disease.

There is however at least one looming caveat that sheds doubt over the value of genetic biomarkers: what if the genetic causes of disease risk and therapy outcomes are minimal compared to environmental factors, or they are so complex—involving numerous genes each with low penetrance—that predictions for individual patients become moot? The most likely answer is that the penetrance of genetic factors varies from insignificant to predominant, depending upon the disease, the drug therapy, and the individual's characteristics, molded by both environment, age, and genetic factors (race, sex, and epistatic genetic variants). What do we need to know to assess the potential of pharmacogenomics in therapy? First, without a firm understanding of the main disease factors—environmental and genetic—approaches to therapy remain empirical, including the use of biomarkers. Second, I submit that our knowledge of genetic variants is still rather limited because earlier studies have largely focused on polymorphisms altering the protein coding sequences while regulatory polymorphisms appear to be considerably more prevalent. Moreover, we have paid scant attention thus far to the significance of the RNA world: much of the genome is transcribed into RNAs whereas protein coding sequences account for only ~1% of the genome. New insights into the significance of non-coding RNAs such as microRNAs are slow to filter into the realm of drug therapy, for example affecting response to anticancer drugs (9). Third, we expect gene–gene interactions to be prevalent in drug response, leading to a pathway approach involving many genes; however, integrating polymorphisms in multiple genes into a predictive test for drug therapy has proven extremely challenging. The following discussion focuses on genetic biomarkers, leaving out any of the other possible biomarker types even though we expect successful biomarker panels to consist of multiple types of tests.

## HOW TO IDENTIFY, EVALUATE, AND APPLY GENETIC BIOMARKERS IN DRUG THERAPY?

While viable biomarkers may include mRNA, protein, and metabolite profiles, useful for assessing the current status of disease progression or treatment response, genetic variants have the advantage of being stable and accessible throughout life (except for diseases such as cancer with chromosomal and microsatellite instabilities). To understand the impact of polymorphisms it is helpful to consider the nature of genetic variations and their functional relevance (Fig. 1). By far the most intense efforts have been directed towards genomic loci linked to the expression of proteins – involving the transcribed regions with introns and exons, and more specifically the protein coding portions of the exons. On the other hand, regulatory polymorphisms modulating transcription can be located anywhere in the gene locus, even at considerable distances of up to 1 million base-pairs. Polymorphisms come in different flavors, but single nucleotide polymorphisms are most abundant (SNPs). Recently, copy number variants (CNVs) of genomic DNA regions have emerged as potentially important factors, but I will focus vicariously on SNPs. Shown in Fig. 1, we distinguish between coding SNPs that change the amino acid sequence (nonsynonymous cSNPs),

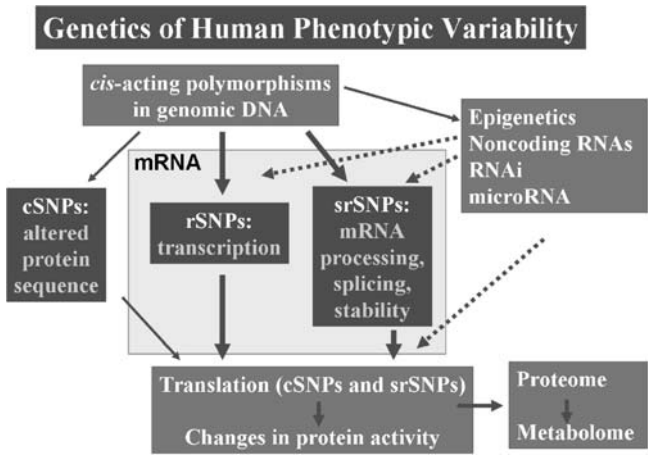


**Fig. 1.** *Cis*-acting polymorphisms affecting protein-coding genes. Nonsynonymous cSNPs alter protein sequence, while rSNPs affect transcription in *cis* at the gene locus where they occur, and srSNPs change mRNA processing or translation, or both. rSNPs and srSNPs that alter mRNA expression are detectable with use of allelic mRNA expression assays (10,11). Changed protein function can have multiple downstream effects on biochemical pathways, cellular metabolism, and transcription acting in *trans*, which can be discovered with mRNA expression profiles and genome-wide association analysis. Non-coding RNAs and epigenetics further modulate many of these processes. Adapted from (11).

regulatory rSNPs that affect transcription, and polymorphisms that alter the processing/splicing and functions of mRNA and non-coding RNAs (we use the term structural RNA SNPs, or srRNA) (10). There is a consensus building in the genomics field that regulatory polymorphisms are more prevalent than nonsynonymous SNPs. While often neglected, srSNPs could be even more prevalent as single stranded mRNAs are highly susceptible in their folding structures to SNP substitutions (10,11), and countless proteins physically interact with hnRNA/mRNA at multiple sites. Mutations affecting gene expression and mRNA processing might be favored as evolutionary tools as their impact is defined by the cellular context and can be organ-specific, whereas nonsynonymous SNPs affect protein structure in all tissues and are often selected against. rSNPs have been reported to exist in numerous genes, including *CYP2D6* and *CYP3A4* (12–15). Yet, because reporter gene assays performed in heterologous tissues to validate rSNPs do not always represent *in vivo* activity (10), one needs to be cautious in interpreting these results. On the other hand, srSNPs—although less commonly considered—have been discovered in a rapidly growing number of genes, often with clinical relevance. For example, splice variants in CYP2D6 result from SNPs residing in splice enhancer of suppressor sites (19). Similarly, a very frequent intronic SNP in *CYP3A5* determines wheter the functional isoform is expressed (13–15). We have identified srSNP in *MDR1* (affecting mRNA turnover) (16), TPH2 (enhanced splicing to the active form of tryptophan hydroxylase 2) (17), and *DRD2* (promoter SNP and two SNPs causing enhanced formation of the L splice isoforms) (18). I suspect that the vast majority of rSNPs and srSNPs remain to be discovered.

Gene transcription, mRNA processing and splicing, translation, and protein functions are further affected by an array of non-coding RNAs, such as the recently discovered set of 500–1,000 microRNAs that are thought to regulate 30% of all mRNAs (Fig. 1) [see references in (9)]. Add to this the pervasive influence of epigenetic factors—i.e., relatively stable modifications of chromatin structure and of DNA by methylation without altering the primary sequence, that can be transmitted during somatic cell division and even through the germ line—a topic deserving of discussion in much greater detail than possible here. Taken together, we must acknowledge that successful application of genetic/genomic information to predictive medicine is but in its infancy.

I expect that the best biomarkers will consist of diverse panels involving genes, proteins, and any other types of measure related to risk, disease status, and outcomes. If it is difficult to validate a single biomarker, the problem is amplified when multiple biomarkers are used in combination. To make progress, there is a compelling need for resolving causative relationships, rather than using heuristic models that are predictive only in the population where they have been tested. With respect to genetic biomarkers, we must demonstrate that the selected polymorphisms are indeed functionally relevant *in vivo* in the target tissues. Moreover, we need to address the questions whether the known polymorphisms account for the genetic variability in that gene across different populations. Given the sometimes tenuous relationship between a genetic variant and a downstream event such as treatment outcome, at the least we should strive to discover all relevant mutations above a given threshold frequency (0.1–1%). But such quantitative analysis is rarely done so that the true genetic contribution to a phenotype remains obscure. In genetic terms, it is critical to understand whether a mutation is recessive or dominant, and whether heterozygosity (haploinsufficiency) can be clinically relevant even if the trait is considered recessive. Current genetic biomarker tests in drug therapy typically focus on frequent variants; however, it is important to consider adding rare mutations if their effect is known, to be considered together with a more frequent variant, allowing for the chance of compound heterozygosity (two different mutations in the two alleles—and hence strong penetrance with respect to function even for rare SNPs.

Clinical genetic association studies have moved to center stage because of the ease of genotyping thousands if not millions of SNPs, needed for genome-wide association studies (GWAS). This approach has revealed a number of novel candidate genes, but it requires subsequent validation and search for the functional polymorphisms—the latter lagging far behind. Because countless hypotheses (SNPs) are tested, the subjects cohorts must be large (>>1,000) to attain statistical significance (after adjustment or correction for the number of hypotheses (SNPs) tested. Replication studies are then norm as false positives are always possible while many functional polymorphisms could be missed. Currently there is a growing trend towards studying each validated gene for the underlying molecular mechanisms, and whether one or more polymorphisms per gene are active. However, progress is still slow because rSNPs and srSNP are difficult to identify. The clear advantage of using a known functional polymorphism in a validated candidate gene for clinical association studies is avoidance of multiple hypothesis testing. As a result, much smaller cohorts can yield significant associations that nevertheless must be replicated—and expanded upon by looking at multiple phenotypes: disease characteristics, clinical laboratory data, drug response, etc. Predictive biomarkers for complex diseases typically have relatively low effect ratios (odds ratio (OR) <2, indicating the relative risk or chance of a particular outcome), whereas pharmacogenetic biomarkers often attain ORs >3, sufficient for consideration as a biomarker. For example, we have detemined that an exon9 SNP in *TPH2*, the key enzyme making serotonin in the brain, enhances expression twofold (17). Subsequently, and independently, Tzvetkov *et al.* (19) have found that response to SSRI antidepressants is highly correlated with this same SNP, showing an odds ratios of ~3. This example highlights the potential that pharmacogenetic biomarkers can yield higher effect ratios because drugs impinge upon a disease *via* well defined biological pathways, characteristic for a subpopulation in a larger cohort of patients with similar symptoms, such as depression. In a sense, the drug is a chemical probe to discover subsets of the overall disease, rendering pharmacogenetic biomarkers of great interest to biotech companies.

## A GENERAL APPROACH TO DETECTING GENETIC BIOMARKERS BASED ON RSNPS AND SRSNPS

In my laboratory we have implemented a general approach for finding regulatory polymorphisms (rSNPs and srSNPs), generally applicable to drug metabolizing enzymes,

transporters, and drug targets (10,11). We first measure allelic mRNA expression, *i.e.*, the expression of mRNA specifically from the maternal and the paternal chromosome in the same tissue, to search for differences in allelic mRNA ratios in comparison to that of genomic DNA. If an allelic expression imbalance (AEI) is detectable, this must be caused by a *cis*-acting factor, genetic or epigenetic, within the same gene locus. These experiments are performed in physiological target tissues as transcription and mRNA processing are tissue-specific. To accomplish this, we have collected human blood lymphocytes and autopsy tissues from brain, liver, heart, intestine, kidney, and lung obtained from multiple subjects. The results have revealed an unexpected abundance of AEI in candidate genes that had already been intensely studied previously (10). For a number of genes, we have then used AEI ratios as the phenotype to scan the gene locus for the responsible regulatory variants, followed by molecular genetic analysis to determine the underlying mechanisms. In line with the countless possible ways by which mRNA expression can be disturbed, we have encountered distinct genetic mechanisms in every gene studied, including promoter and enhancer SNPs (*DRD2, VKORC1, ACE*) (18,20), intronic and exonic SNPs that affect splicing or mRNA maturation (*DRD2, TPH2, OPRM1*) (17,18,21), and SNPs that affect mRNA turnover (*MDR1*) (16).

In a few cases, we have subsequently translated these molecular genetic results into clinical association studies. For example, two intronic SNPs in *DRD2* (dopamine D2 receptor) shown to affect mRNA splicing, were found to modulate memory performance and activity of dopaminergic pathways during memory processing in normal adults, measured with fMRI (18). Similarly, we have identified a set of promoter SNPs in *ACE* (angiotensin converting enzyme) showing high frequency only in Africa Americans, linked to reduced expression of ACE in heart tissues. Our initial clinical results indicate that these SNPs are strongly associated with risk of myocardial infarction in hypertensive patients (Johnson *et al.*, in revision). *ACE* polymorphisms have been assessed for linkage to clinical phenotypes in several thousand (!) association studies, without evidence that the selected SNPs are indeed functional *in vivo* [see (10) for references]. In another study, we have demonstrated that the likely functional polymorphism in *VKORC1* (the target of warfarin) is in the promoter region and can account for dosing differences between Caucasians and African Americans (20). Use of other highly linked SNPs in *VKORC1* may lead to false results as the linkage disequilibrium between the true functional SNP and other tagging SNPs used as an alternative biomarker is incomplete in some ethnic groups. These examples demonstrate the importance of using the genetic biomarker with proven functional effects, rather than a surrogate marker identified by clinical associations that may not be valid in all populations, introducing unnecessary ambiguity. We are currently studying genes encoding the main CYP enzymes important in drug metabolism (2D6, 2C9, 3A4), finding evidence for yet unknown regulatory polymorphisms. In particular, a new intronic SNP in *CYP3A4*—involved in metabolism of ~40% of drugs—is highly associated with altered mRNA expression (D. Wang, unpublished data), and because of its intermediate allele frequency, may have significant impact on interindividual differences in drug response.

I conclude that we need to understand the molecular genetic mechanisms and quantitate the impact of genetic variability in biomarker genes. Further, we need to evolve a process for validating diverse biomarkers in a panel where knowledge of biological mechanisms becomes increasingly important to avoid heuristic solutions applicable only under limited circumstances.

## HOW DO WE APPROACH ECONOMIC, LEGAL, ETHICAL AND CULTURAL ISSUES RELATED TO PERSONALIZED HEALTH CARE AND THE USE OF BIOMARKERS AS INDIVIDUAL IDENTIFIERS?

I cannot address these issues in detail here. Suffice to say that we must be concerned about privacy issues, in particular with respect to genetic information. The economic implications are staggering as our current health care system is approaching the limit of sustainability, while new solutions such as theranostics may simply introduce more cost with limited return—unless policies and regulations change. Getting a new biomarker test approved by the FDA, getting it to market, and enticing insurers to pay for it could well equal the cost of bringing a new drug to market—hence the reluctance of the pharmaceutical industry to embrace this concept. The new biomarker tests are costly as they are produced by a newly emerging industry relying on patent protection for each single test. We are nowhere near the routine clinical chemistry tests that are highly multiplexed, providing a wealth of information at reasonable cost. If we plan to implement biomarker panels, stringing together multiple single tests is prohibitively costly at present, even though genotyping itself can be done at very low cost. To provide incentives for applying biomarkers—to optimize therapy for the individual—reimbursement policies need to be implemented that reflect the clinical benefit, rather than the number of prescriptions or biomarker tests sold. In one possible implementation, if reimbursement for expensive treatments occurs only if the patient responds well, a strong incentive is provided to predicting why an individual patient will or will not respond.

Genetic biomarkers can further distinguish between ethnic groups, introducing systematic differences in therapies. While this could be seen as an advance, avoiding ineffective therapies or selecting the most effective treatments, it also raises ethical and cultural issues that need to be understood and considered in health care policies.

A particularly intriguing new development is the public access to genetic biomarker panel tests (22), offered by a rapidly growing number of genetic testing companies, including: 23andMe, Navigenics, DeCODEme, Athena Diagnostics, DNADirect, GeneDx, Genetic Technologies, Genzyme Genetics. Knome in Cambridge MA has begun to offer complete genome sequencing for individuals. One can order tests for *CYP* enzymes, *SERT-LPR* [questionable validity for guiding treatment of depression (23)] or the *APOE4* allele associated with increased risk of Alzheimer's. How good are these current genetic biomarkers? How do we interpret a relatively small increase in disease risk? Who will do the counseling? Whether or not one endorses this new development of public access, it is here to stay. We better make the best of it by performing the research needed to optimize the

value of biomarkers, and providing the needed education to health care professionals and the public, to take advantage of this wealth of new information.

## WHAT WILL BE THE MAIN FUTURE CONTRIBUTIONS OF PHARMACEUTICAL SCIENTISTS?

Drug discovery, development, and therapy—all main emphasis areas for pharmaceutical scientists—will remain primary drivers of the pharmaceutical industry for some time. However, single 'magic bullets' are not likely to emerge in therapy of complex diseases. On the other hand, pharmaceutical scientists are well positioned to optimize existing and new therapies at many levels—drug formulations and delivery, targeting, dosing schedules, individualizing drug therapy. Extensive expertise in quantitative analysis and model building, for example in PK-PD, enables optimization of therapies—a task that is far from complete if one considers the complexities of designing the most effective combination of one or more drugs and treatment modalities, in conjunction with novel biomarkers.

Personalized health care spawns numerous new research directions and professional goals. The discovery, evaluation, and development of biomarkers could rival drug development in complexity, representing a potentially large new field. It remains to be seen whether pharmaceutical scientists will adopt this area as one of their core research directions. This may be well advised since an obligatory link between medications with a biomarker test—theranostics—could become a mainstream future trend. Similarly, pharmacogenetics/genomics falls into the realm of the emerging -omics disciplines, but in this case, colleges of pharmacy have already implemented pertinent courses and research programs. Such proactive steps are less evident in other areas of biology that impinge on biomarkers in therapy. Moreover, novel treatment modalities, such as application of stem cells, do not fit the traditional picture of the pharmaceutical sciences. It is evident that for the pharmaceutical sciences to remain a vibrant research area, a much broader view is required as to what the most important future advances will be, and how each of the biomedical science disciplines need to adjust and interconnect. But personalized health care requires more than the study of biology: increasingly, we are challenged to assess economic, legal, cultural, and ethnic issues, again an area where colleges of pharmacy have a long-standing tradition of research and professional activity.

## OUTLOOK

We can expect an increasing diversity of treatment modalities; increased emphasis on early therapy/prevention; marked emphasis on optimization of existing therapies in personalized health care; fewer new single mega-drugs but emergence of combination therapies; molecularly targeted therapies for niche markets (together with cost reduction in drug development to achieve economic sustainability). Thus, personalized health care requires diverse disciplines that go far beyond the traditional pharmaceutical sciences. And yet, a principal tenet of the pharmaceutical scientist is a quantitative approach to pharmaceutical and biological systems, and response to therapies. As a result, we see a growing expansion of the scope of pharmaceutical sciences in biomedical engineering, material sciences and computational sciences, chemistry, systems biology, genetics, ethics, economics, and more. Indeed, well-defined disciplines in the traditional sense may be too rigid to contribute to future developments in the biomedical arena. It might be wise to abstain from defining 'pharmaceutical sciences', but rather, to let the emerging directions in the health care system guide its evolution. While the future path for the pharmaceutical sciences cannot be accurately predicted, we already have seen tremendous changes in the scope of research ongoing at colleges of pharmacy around the world. Surely, this will be a good time for aspiring young scientists to enter the fray.

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