ORIGINAL CONTRIBUTION

Asymmetry in Scientific Method and Limits to Cross-Disciplinary Dialogue: Toward a Shared Language and Science Policy in Pharmacogenomics and Human Disease Genetics

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Pharmacogenomics is a hybrid field of experimental science at the intersection of human disease genetics and clinical pharmacology sharing applications of the new genomic technologies. But this hybrid field is not yet stable or fully integrated, nor is science policy in pharmacogenomics fully equipped to resolve the challenges of this emerging hybrid field. The disciplines of human disease genetics and clinical pharmacology contain significant differences in their scientific practices. Whereas clinical pharmacology originates as an experimental science, human disease genetics is primarily observational in nature. The result is a significant asymmetry in scientific method that can differentially impact the degree to which gene-environment interactions are discerned and, by extension, the study sample size required in each discipline. Because the number of subjects enrolled in observational genetic studies of diseases is characteristically viewed as an important criterion of scientific validity and reliability, failure to recognize discipline-specific requirements for sample size may lead to inappropriate dismissal or silencing of meritorious, although smaller-scale, craft-based pharmacogenomic investigations using an experimental study design. Importantly, the recognition that pharmacogenomics is an experimental science creates an avenue for systematic policy response to the ethical imperative to prospectively pursue genetically customized therapies before regulatory approval of pharmaceuticals. To this end, we discuss the critical role of interdisciplinary engagement between medical sciences, policy, and social science. We emphasize the need for development of shared standards across scientific, methodologic, and socioethical epistemologic divides in the hybrid field of pharmacogenomics to best serve the interests of public health.

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Coalescence of Clinical Pharmacology and Human Disease Genetics by Shared Application of New Genomic Technologies

The scope of scientific inquiry in clinical pharmacology and human disease genetics has expanded over the past several years with the development of population-based databases (eg, UK Biobank, the Estonian Genome Project, GenomEUtwin, CARTaGENE) and the introduction of new genomic technologies, such as high-throughput analysis of gene expression.[1–5] These genomic technology platforms aim to characterize multiple genes, often on the order of tens of thousands, to enable an integrated view of genetics and its role for drug efficacy and safety. The origin of the genomic technologies is not, however, rooted in pharmacology but can be traced back to advances made on the heels of the Human Genome Project.[6–8]

Intensive deoxyribonucleic acid (DNA) sequencing efforts in the late 1990s, facilitated by the coalescence of traditional methodologies used in human genetics and cell biology, resulted in technology platforms capable of generating large volumes of data in very short time frames. Genomic technologies are now increasingly adopted in pharmacologic sciences, with an attendant expansion of the scientific process. These advances start with the view that a broader investigation of the multiple components of a complex biologic pathway targeted by a pharmaceutical compound may provide better insights into the mechanisms of drug action and ultimately allow individualization of drug therapy.[9] Hence, clinical pharmacology and human genetics research are rapidly coalescing, in part owing to such broad and shared applications of genomic technologies.

When scientific disciplines meet toward a common goal, both technical expertise and expectations of practitioners for what constitutes scientific merit inevitably struggle for position. The extent of similarities and discrepancies among the views of scientists from the respective disciplines and the ensuing critical debate on new hypotheses or technologies in a given field often serve as catalysts for the rejection or wide adoption of new hypotheses and technologies.[10] Important innovations emerge from creative interdisciplinary sharing of methods and concepts, yet it is essential that precautionary principles are adhered to in standards for scientific validity and reliability.[11–14]

Whereas clinical pharmacology is an experimental science, most genetics research on human diseases uses a scientific approach that is primarily observational. This results in an asymmetry in scientific method that can differentially impact the degree to which environmental components of phenotypic variability are controlled, including the sample size requirements of each discipline. The number of subjects participating in observational genetic studies of diseases is often used as a key criterion of attendant scientific value; it is also a significant driver of which 'disease gene' discovery is worthy of further policy-oriented translational research or application at the point of patient care. Because environmental factors (and the attendant confounding) are difficult to discern or control in observational study designs, there is an expectation, particularly on the part of the policy makers familiar with population health and large-scale epidemiologic studies, of a large sample size (eg, from several hundreds to thousands) in genetic studies on disease predisposition. Yet these requirements do not necessarily apply to experimental study designs.

Environmental confounding can (and we suggest should) be monitored more readily by scientists in experimental sciences (eg, in pharmacology or pharmacogenomics) prior to or during the execution of the study. Failure to discern such discipline-specific nuances for differential environmental confounding in genetic studies rooted in either pharmacology or disease predisposition will bias expectations for sample size requirements, along with perceptions of the merit of new genomic discoveries. Such interdisciplinary differences in norms and expectations regarding scientific merit may lead to inadvertent dismissal of methodologically sound small-scale exploratory pharmacogenomic studies as new policies are being developed for genomics research in population-based databases. Some of these pharmacogenomic studies may well have appropriate statistical power to detect genetic components of pharmacologic variability.

Pharmacogenomics is usually defined as the study of variability in drug response using information from the entire genome of a given individual patient.[1,2,4] Pharmacogenetics, by contrast, is hypothesis driven

and focuses on a limited set of candidate genes selected based on a priori observations of disease susceptibility, drug absorption, metabolism, transport, and excretion, as well as drug targets, as opposed to a genome-wide hypothesis-free approach in pharmacogenomics. It is noteworthy that pharmacogenetics and pharmacogenomics are also interdependent: once a novel gene(s) of relevance for mechanism of drug action is identified through the genome-wide pharmacogenomics search, such individual genetic biomarkers require further validation and follow-up by pharmacogenetics before they can be routinely applied in clinical medicine. For the purpose of the present discussion, we use the term *pharmacogenomics*, but many of the concepts discussed herein will also be applicable to pharmacogenetic investigations.

The objective of the present comparative analysis is to identify and elaborate on these significant asymmetries between clinical pharmacology and human disease genetics in the hybrid field of clinical pharmacogenomics. We emphasize the importance of recognizing pharmacogenomics as an experimental form of science. This broader view of pharmacogenomics addresses an ethical and science policy imperative to favor prospective clinical pharmacogenomic investigations over the ad hoc retrospective biomarker investigations that have, thus far, typified biomarker applications at the point of patient care or late-stage drug development.

Expectations and Challenges for Policy Making in Interdisciplinary Science

Expectations about the merit or promise of a biotechnology or a new scientific field evolve through a complex and subtle interaction of (1) media interest and consumer demand in the society (eg, patients, caregivers, and physicians) for better therapeutic products and services; (2) dialogue among scientists, governments, and policy makers to ensure that the latest scientific standards are met and empirically grounded interdisciplinary science policies are developed; and (3) corporate or private sector marketing of resulting technologies.

Within the process of policy making, there may be increased complexity (and unpredictable outcomes) when disciplinary boundaries are crossed by individual regulators or scientists investigating the broad application of a novel discovery or technology in multiple fields of scientific inquiry. This situation is particularly evident with the application of genomic, proteomic, or other high-throughput '-omics' technologies in fundamental and applied bioscience research. Such cross-disciplinary journeys are not without their challenges. Scientists regularly encounter stigma and resistance to novel hypotheses or methods, and collaborations can reach an impasse when the norms governing scientific merit in a discipline are not mutually reconciled or renegotiated in light of the particular attributes of each field of inquiry. Thus, while evaluating new technologies and concepts borrowed from diverse but complementary disciplines, regulators engaged in policy making need to employ multiple lenses to discern disciplinary nuances.[15–17] This is a timely consideration for, as noted earlier, many countries and the private sector in applied genomics are in the process of developing large-scale genomic databases and biobanks.[3,18,19] When drawing conclusions on the public health significance of new genetic discoveries and their potential for application in patient care, identification of the particular characteristics of human disease genetics and pharmacogenomics that strengthen or weaken the credibility of the resulting methods or products should be taken into account.

Contrast between Observational and Experimental Study Designs: Why Is This Relevant to Interdisciplinary Policy Development for Pharmacogenomics?

Since the late 1990s, the idea of exploring pharmacologic phenotypes (eg, drug effectiveness and side effects) as another promising dimension of genetic research has attracted a number of human geneticists to the field of clinical pharmacology and vice versa. This bidirectional exchange of scientific expertise benefited and complemented the classic pharmacologic approaches to questions of variability in pharmacokinetics and pharmacodynamics. At the same time, there has been a tendency to view pharmacologic responses akin to disease phenotypes. There are, however, several fundamental differences between human disease genetics research and clinical pharmacogenomics that require particular attention for a balanced interpretation of scientific merit in genetic studies of pharmacologic phenotypes (Table 1).

A fundamental goal of human genetics research is to establish the causal links between genes and disease phenotypes or characteristics. Yet most common complex human diseases initiate and progress over a considerable period of time before clinical signs and symptoms manifest. This means that environmental contributions to disease phenotypes are difficult to determine without longitudinal studies. It can be prohibitively expensive to discern disease-environment interactions when long-term observation and follow-

Table 1 Distinctions in Scientific Method (Experimental vs Observational) between the Disciplines of Clinical Pharmacogenomics and Human Genetics, Respectively, that May Differentially Influence the Sample Size Requirements and the Attendant Perceptions on Scientific Merit

Discipline-Specific Attribute	*Clinical Pharmacogenomics*	*Genetics of Common Complex Human Diseases*
Study design considerations		
Most common design	Experimental; the investigator can actively manipulate the drug dose or exposure	Observational; the investigator does not induce the disease and instead quantifies phenotypes, usually after disease is clinically manifested
Within-subject study design	Feasible	Not feasible or can be unethical
Reduction of bias in study design with use of randomization	Feasible	Not feasible; disease susceptibility is not subject to assignment and, rather, is observed
Phenotype considerations*		
Temporal attributes of phenotype	Both prospective and retrospective samplings are feasible	Often retrospective sampling of disease phenotypes is required or the only feasible option
Repeated measures data collection to enrich phenotypic characterization	Feasible	In most cases, it can be prohibitively expensive owing to long time frames required for clinical manifestation of disease signs and symptoms
Environmental contribution to phenotypes	Calculable	Often incalculable; difficult to control or eliminate when calculable
Baseline phenotypes	Discernible prior to drug administration; this allows unequivocal calculation of the net drug-related phenotypes by subtracting the predrug phenotypes from the composite phenotypes obtained post–drug administration	Often not discernible owing to slow initiation and progression of most common complex human diseases over many years
Rechallenge/challenge with independent variable (ie, drug treatment or disease induction or susceptibility)	Phenotype ascertainment and its 'drug-relatedness' can be further strengthened by discontinuation of drug treatment followed by subsequent rechallenge with drug treatment	Disease processes often cannot be experimentally switched 'on' or 'off' to ascertain the attendant clinical phenotypes
Other distinctions		
Feasibility of in vitro studies to estimate the scope of allelic or locus genetic heterogeneity	Drug itself can be used as a 'probe' by virtue of its physicochemical interactions with drug-metabolizing enzymes, transporters, or molecular targets for efficacy to discern the high-priority candidate pharmacokinetic and pharmacodynamic pathways and the attendant locus and allelic genetic heterogeneity In vitro studies are feasible to estimate the upper-bound limit on the number of plausible candidate genes, particularly in the case of pharmacokinetic pathways or molecular drug targets	Often no biologic or physicochemical probe is available to empirically discern the type or the number of disease-related biologic pathways (with the exception of certain environmentally induced cancers or diseases)

*Our comparative analyses should not suggest that clinical pharmacogenomics, as a discipline, is uniformly at a greater advantage in achieving optimal phenotype ascertainment and study design than human disease genetics research. Instead, the distinctions highlighted are context specific and emanate primarily from the differences in the scientific method between the two disciplines (experimental vs observational, respectively). Moreover, phenotypic ascertainment of certain pharmacologic phenotypes, particularly in the case of categorical treatment outcomes (eg, responders and nonresponders), can meet with discordance among physicians, whereas the availability of disease diagnostic criteria (eg, *International Classification of Diseases*) may facilitate uniformity in phenotype ascertainment in human disease genetics research.

up are required in ostensibly healthy individuals who are predicted to develop a disease phenotype in the far too distant future. By contrast, as an experimental science, clinical pharmacology is able to elicit phenotypes (in a controlled laboratory or hospital setting) within a matter of a few minutes (eg, antihypertensive drugs), days, or weeks (eg, anticancer medications), during which it is feasible to measure and account (to a certain extent) for environmental components of pharmacologic variability. Seen in this light, it is possible to understand drug effects as an acquired form of biologic variance.[20]

The measurability of drug effects and the recognition that drugs are well-characterized modifiers of normal life processes or (patho)physiologic events led, nearly 50 years ago, to establishment of the origins of pharmacogenomics as a new medical subspecialty.[1,2,9] The technical advances over the past decade have, in effect, blurred the interdisciplinary boundaries in pharmacogenomics research. For example, even though the observational and experimental nature of human disease genetics and pharmacogenomics, respectively, may allow different degrees of control over environmental influences, such disciplinary nuances are not always recognized. This recognition is important since sample size requirements to achieve an optimal signal to noise ratio for discovery of genetic markers of pharmacologic phenotypes and disease-related traits can markedly differ.

It should be stressed that reproducibility of new genetic findings in independent samples is required in both human disease genetics research and pharmacogenomics, in part owing to population-to-population differences in the type and frequency of genetic susceptibility loci for a given phenotype in the human genome. In addition, large sample sizes are often required to detect the small individual effects of numerous genes and their complex gene-gene/gene-environment interactions on drug response or disease phenotypes. We suggest, however, that a smaller sample size is sufficient for such replication studies in clinical pharmacogenomics owing to greater control of environmental confounding in pharmacologic phenotypes.

In the late nineteenth century, Paul Ehrlich proposed the presence of ''chemoreceptors'' on microorganisms and cancer cells that differ from the host organism—a precursor to the current concept of molecular drug targets and selective toxicity of modern medicines.[21] The presence of discernible targets suggests that drugs can serve as invaluable probes to guide the identification of plausible pharmacokinetic or pharmacodynamic biologic pathways. One concrete example is in vitro drug metabolism studies that reliably identify the CYP450 enzymes that may contribute to clinical pharmacokinetics of a new therapeutic candidate. Because only a handful of CYP450 enzymes are responsible for drug metabolism, these in vitro approaches can provide a practical upper-bound limit on the number of candidate genetic loci and, by extension, the scope of genetic heterogeneity causally related to variability in a clinical pharmacology phenotype.[17,22]

These theoretical and applied nuances collectively underscore the fact that environmental factors and genetic heterogeneity can be discerned or controlled more readily (although never totally controlled) in clinical pharmacogenomics than human genetics by virtue of pharmacology's nature as an experimental science (see Table 1).[23] Hence, for a given sample size, our ability to detect genetic markers may be significantly enhanced by careful consideration and accounting for environmental effects through experimental study designs in pharmacogenomics. Additionally, the application of randomized and prospective pharmacogenomic studies is an entirely feasible strategy through which confounding by environmental factors can be further reduced.

A rational strategy is needed to assign priority to drugs that are subject to a higher degree of genetic regulation.[22] This would enhance the signal to noise ratio for genetic factors and could permit pharmacogenomic association studies in smaller number of subjects. Typically, heritability estimates are obtained using the twin method. Twin studies are very useful to establish the genetic components for common complex disease phenotypes (eg, breast cancer) but have limited applicability in pharmacologic responses to drugs. Some of these limitations include difficulties in recruitment of twins and obtaining clinical outcome data in both twins (since the twin pairs may not suffer from the same disease at the same time), as well as the financial cost of twin investigations. To remedy the difficulties associated with the twin approach, a repeated drug administration (RDA) method was proposed by Kalow et al wherein between- and within-subject variances in drug efficacy or safety are compared.[22,24,25] The RDA method requires the following considerations. In a given individual, within-subject variance (SD_w^2) is determined by environmental factors and measurement errors ($SD_w^2 = SD_{environment}^2 + SD_{measurement\ error}^2$). Notably, the second term ($SD_{measurement\ error}^2$) includes not only measurement error but also biologic variation, random and nonrandom (eg, circadian). On the other hand, between-subject variance (SD_b^2) can be formulated as

($SD_b^2 = SD_{environment}^2 + SD_{genetic}^2 + SD_{measurement\ error}^2$). As originally proposed by Kalow and colleagues,[24] the genetic component (r_{GC}) of variability in a time-dependent pharmacokinetic or pharmacodynamic occurrence can be estimated with the following equation:

$$r_{GC} = \text{Genetic component} = \left(SD_b^2 - SD_w^2\right)/SD_b^2$$

The r_{GC} values approach 1.0 point to overwhelming genetic control, whereas those close to zero suggest that environmental factors dominate. In essence, any dynamic biologic process exhibiting time-dependent decay and negligible carryover effects between repeat observations can be amenable to RDA studies to dissect the genetic contribution to interindividual variability in the corresponding biologic phenotype.[22] Recent applications of the RDA method demonstrate that genetics plays a paramount role in pharmacologic traits hitherto not subjected to pharmacogenomic analysis, such as renal drug disposition and pharmacokinetic variability of the antiretroviral drug didanosine.[26,27]

In our focused comparison of clinical pharmacogenomics and human disease genetics research, it should be clear that despite the application of prospective design, clinical pharmacogenomics cannot completely account for the diverse socioeconomic and environmental factors (eg, other medications, alcohol, diet, workplace, etc.) that will actually affect the patient and potentially result in adverse drug reactions in their day-to-day use of the medication.[28] Moreover, phenotypic measurement of drug effects remains particularly problematic in fields such as psychopharmacology, even in the presence of strict monitoring of environmental effects. The temporal and geographic plasticity of human behaviors (independent from drug treatment) and limitations of clinical rating scales to capture nuanced changes in behavioral responses to drugs introduce uncertainty in ascertainment of pharmacologic phenotypes in psychiatric pharmacogenomics.

Increased Ability to Generate High-Throughput Genomic Data Creates New Sociotechnical Actors and Control Points in the Scientific Process

High-throughput genomic technologies can generate large volumes of genetic data, but they also create a particular statistical conundrum. To attain adequate statistical power and to allow association analysis between multiple genetic factors and clinical phenotypes, researchers require an increasingly larger number of human subjects or biologic specimens (eg, biopsy material from cancerous tissue) to match the high-throughput data generated by new genomic technologies. At first glance, this may come across solely as a logistical issue concerning subject recruitment for clinical pharmacogenomic investigations. Indeed, subject recruitment is, and has always been, an important barrier to successful execution of clinical investigations, whether they are in the area of human disease genetics or pharmaceutical research. However, present throughput of the data generated by genomic methods is vastly greater, by at least several orders of magnitude, compared with only a decade ago.

Reflecting on the three key components of scientific process, from (1) conception of new ideas or study design and (2) execution of a study protocol (eg, including subject recruitment) to (3) analysis and interpretation of new findings, it becomes evident that subject recruitment or collection of clinical phenotypic data is increasingly the de facto critical rate-limiting step or bottleneck in pharmacogenomics.[29,30] The cost of genotyping or other genomic methods has declined markedly, and sophisticated but affordable bioinformatics software and trained personnel are available for association analysis to establish the link between genomic data and clinical phenotypes. This, then, invariably affects the nature of stakeholders and the attendant sociotechnical networks.[29] The role of scientists as gatekeepers in genomic science is being fundamentally altered.[29] In particular, those scientists with small-scale innovative laboratories with limited subject recruitment infrastructure are particularly vulnerable to this new type of large-scale recruitment-driven genomic science. New sociotechnical actors and research coordinators who are not necessarily grounded in human genetics, pharmacology, or social sciences may thus become influential in subject recruitment and, by extension, in research governance.[29,30]

Returning to genomics and science policy, it is noteworthy that the present emphasis on large study sample sizes in clinical pharmacogenomics in part reflects the expectations carried over from observational genetic studies on disease susceptibility as the two disciplines coalesce around shared genomic technologies. If the experimental nature of clinical pharmacogenomic inquiries and the attendant ability to better control or eliminate environmental contributions are not fully appreciated, there will be a risk of premature dismissal of small sample–sized pharmacogenomic studies, even though, as noted earlier, they may have adequate statistical power. Thus, the differences in scientific method in clinical pharmacogenomics and human disease genetics present challenges to practitioners in both research fields. There are

also, however, untapped opportunities to increase adoption and acceptance of genomic technologies at the point of patient care. In particular, the recognition that pharmacogenomics is an experimental science creates an avenue for a systematic policy response to the ethical imperative to prospectively pursue genetically customized therapies before regulatory approval of pharmaceuticals.

Visions of Pharmacology as an Experimental Science: An Ethical Obligation to Conduct Prospective Pharmacogenomic Studies?

In general, the drug development process spans between 10 and 15 years from the discovery of a new drug molecule to regulatory approval for the drug to be marketed to the public. Understandably, a lag period is anticipated before new therapeutics developed with the use of -omics technologies, such as pharmacogenomics or proteomics, will be available in the clinic. For drugs that are presently in clinical use, one might expect that pharmacogenomics would have been already adopted prospectively in phase 4 clinical trials (ie, postmarketing studies of large patient populations) as there has been a dramatic increase in the availability of -omics technologies in biomedical research laboratories over the past decade.[6,11] It is interesting to note, then, that there is an acute shortage of prospective clinical studies designed to individualize drug labels, that is, formally limit a drug's target population to those people with a certain genotype.[8,15,31]

To date, most pharmacogenomic studies have been conducted in clinical trials designed for another purpose: to demonstrate efficacy or safety for drug registration by regulatory bodies such as the US Food and Drug Administration (FDA). The highly structured time frames in these trials may not always permit adequate scientific rigor or flexibility for exploratory research oriented toward genetic test development for individualization of drug therapy. In certain cases, this may lead to an ad hoc retrospective sampling of clinical trial data (eg, only when or if a compound displays toxicity after introduction into the market), even though, as noted earlier, prospective study designs are entirely feasible in pharmacology. By contrast, an abundance of discovery-oriented research (ie, remote from direct clinical applications to customize drug therapy) with genomic technologies is taking place for identification of new drug targets or proof of concept in early-phase clinical trials.[15] But this early-phase upstream basic research does not necessarily guarantee the eventual downstream access to genetic testing or delivery of personalized medicines at the point of patient care.[15,31–33] A number of concerns, such as small market sizes in narrowly defined therapeutic fields, have been presented in the past as an explanation for the obvious trepidation associated with the prospective development of pharmacogenomic tests at the point of care.[31,32,34]

We suggest that the motivations for prospective clinical pharmacogenomic applications to proactively influence drug labels and prescriptions may also be shaped by the type of pharmaceutical associated with specific pharmacogenomic tests. In 2004, of the 113 new drug applications (ie, marketing approval) approved by the FDA, only 17 (15%) were considered significant improvements compared with already marketed products.[35] Although there is much to be celebrated in terms of singular success stories on selected innovative medicines developed by the pharmaceutical industry, many of the pharmacotherapies introduced into the market every year are 'me-too' drugs, displaying comparable efficacy and safety profiles with already existing medicines (Figure 1).[35–37] These me-too drugs may be economically very profitable and in some cases will even constitute 'blockbusters' that generate billions of dollars in revenue. But for our purposes, it is important to note that in the context of customized therapeutics, me-too drugs (whether blockbuster or not) may adversely influence motivations for pharmacogenomic testing in the clinic in ways that were previously unanticipated.

Consider a hypothetical therapeutic area (eg, statins to reduce blood cholesterol or selective serotonin reuptake inhibitor antidepressants) that is characterized by an abundance of me-too drugs, with 60 to 80% of the available drugs exhibiting a similar pharmacologic mode of action or efficacy or safety profile. A pharmacogenomic test for a me-too drug may be equally predictive of treatment outcomes for most, if not all, drugs within the same me-too category, potentially redistributing the financial gains made on the diagnostic test and drug combination product from an individual pharmaceutical company to multiple firms that manufacture similar me-too drugs.[15] Hence, the past and present focus on me-too drug development may serve as a barrier to both innovation in pharmacotherapy and the development of targeted therapies in conjunction with pharmacogenomic tests.

Another hitherto overlooked consideration is the significant reduction over the past decade in the duration of tenure and increased turnover of chief executive officers (CEOs) in various multinational corporations. For example, in a survey of CEO

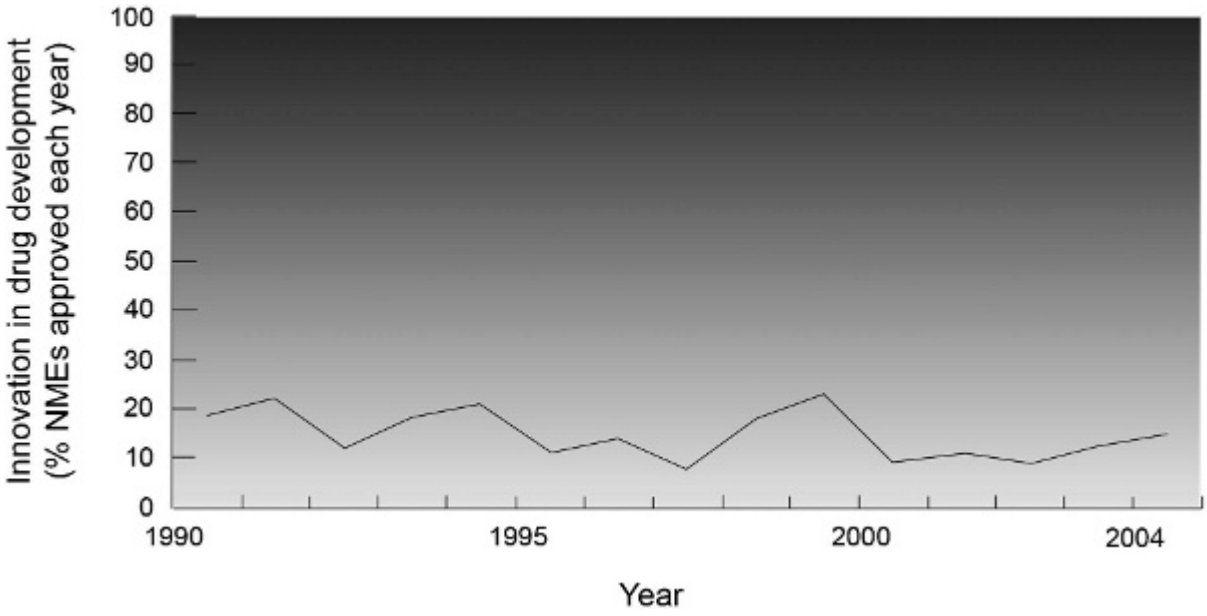

Figure 1 New drug applications (NDAs) approved in calendar years 1990–2004 by the US Food and Drug Administration (FDA) and the new molecular entities (NMEs) subjected to priority regulatory review while offering a significant improvement compared with marketed products in the treatment, diagnosis, or prevention of a disease. Innovation in drug development, as defined by the percentage of these breakthrough NMEs in relation to all NDAs approved in each calendar year, remained low for more than a decade. This further underscores the importance of recognizing (1) pharmacology and pharmacogenomics as experimental lines of scientific inquiry and (2) the attendant ethical obligation to prospectively pursue pharmacogenomics-guided drug development models (instead of the traditional 'wait-and-see' approach) that can improve innovation rates in drug development. Reproduced with permission from Ozdemir V.[16]

succession at the world's largest 2,500 publicly traded companies, Lucier and colleagues found that 14.2% of CEOs left office in 2004, a 300% increase in CEO departures since 1995.[38] Within the health care sector in 2004, CEO dismissals rose to 16.2%.[38] Nearly a third of all CEO resignations in 2004 were related to failure to meet demands for financial returns by increasingly impatient shareholders. Notably, the CEOs removed for inadequate performance had a median tenure of 5.2 years in the United States; in Europe, the situation was more difficult, with poorly performing CEOs remaining only for a median of 2.5 years. According to Lucier and colleagues, corporations "have reached a tipping point, in which power in the corporation is permanently shifting away from chief executives." In this climate of risk-averse and demanding shareholders and CEOs increasingly anxious about maximizing returns on a quarter-by-quarter basis, new pharmacogenomic technologies are being implemented.[39,40] Thus, it is difficult to reconcile the short-lived (2.5–5.2 years) tenure of the CEOs with new health technologies (eg, -omics biomarker platforms) that require long-term investment before tangible financial returns can be observed.

What incentives, then, can be put in place for corporate directors (as well as shareholders) to voluntarily exhibit socially responsible commitments to genomic technologies to achieve targeted therapeutics that, while potentially reducing short-term revenues,[34] may increase long-term retention of products (ie, safe and effective drugs) in the market? In the case of new genomic technologies, important social structural aspects,[15,32,33,38–40] such as those discussed above (eg, increased executive turnover and shareholder demands in favor of expediency), that can impact commercial or academic pharmacogenomic research and professional conduct may be dismissed or mistakenly ignored in the framing and future projections of these technologies.[41,42] To this end, a multidisciplinary learned society, such as the American Federation for Medical Research (AFMR), would be uniquely positioned to play a pivotal leadership role in facilitating dialogue across different professional languages and norms at the intersections of

social sciences, research governance in public and private sectors, and professional practice of clinical pharmacology and human genetics research to best realize the dream of pharmacogenomics-guided personalized medicines.

Regardless of the various sociologic, technology-based, or commercial factors and motivations that impede or facilitate the development of pharmacogenomic tests at the point of care, the fact is that the traditional model of drug development, with its focus on finding 'the next blockbuster drug,' is increasingly viewed as no longer realistic or viable.[37] Often overlooked is the fact that most recent blockbuster drugs were likely the 'lower-hanging fruits' resulting from rational and scientific drug development in the second half of the twentieth century. Further, many blockbuster drugs initially developed for broad use in the population have, on prescription in larger patient samples, been withdrawn from the market because of serious toxicity, a lack of effectiveness, or adverse drug-drug interactions. In effect, drug development without accompanying clinical biomarkers to customize prescriptions amounts to a statistical time bomb: when drug exposure exceeds the 1,000 to 3,000 patients collectively enrolled in typical premarketing clinical trials, members of the broader patient population who do not reflect the 'average' biologic or demographic attributes of trial participants are invariably exposed, leading to adverse drug-related events.

Exposing patients in clinical trials or during the postmarketing phase to partially preventable risks becomes a more acute and palpable social and ethical concern, especially when we consider that pharmacology is an experimental science amenable to proactive and prospective biomarker applications long before drug-related problems emerge. We submit that it is essential for both drug developers and regulators to adopt a longer-term vision that projects beyond the immediate goal of obtaining regulatory approval toward an enhancement of the entire life cycle and quality of a medicinal product. That is, prompt and timely introduction of new drugs to patients should be balanced against their sustainable use in the clinic, without postregistration withdrawal.[43]

Introducing noncustomized drugs in the clinic does not, in the long run, benefit many of the key actors in knowledge-based economies, whether they are patients or industry shareholders. Any costs incurred for postmarketing safety monitoring of drugs, such as frequent liver or kidney function tests, are ultimately transferred from the drug manufacturer to the patients and the payors.[44] Looking through the lens of global public health,[45] unfavorable perceptions about the societal commitment of a drug manufacturer on a given product withdrawn from the clinic will also have multiple detrimental effects on other compounds in their drug development pipeline: employee morale may suffer, thereby seriously undermining corporate initiatives to develop an equitable and attractive workplace environment that will retain highly trained and costly staff, whereas the broader mission of creating public benefit and ultimately safeguarding corporate and fiduciary responsibilities toward shareholders will be jeopardized.[46–48]

Future Outlook

As noted by David and Foray, commenting on the evolution of knowledge-based economies and civil societies, ''[d]iscoveries in many domains are...made in the course of unplanned journeys through information space.''[49] The genealogy of scientific progress can be even more complex in the case of interdisciplinary dialogues and experiments. Simply 'chunking' pharmacogenomics and human genetics together in conceptual proximity as two identical disciplines would be inadequate for a balanced reconciliation of their nuanced differences in science policy. Nor would such an approach acknowledge how these two fields might, in turn, impact both real and perceived expectations, for example, on sample size requirements in studies on the development of genetic tests for customization of drug therapy. More in-depth and realistic projections of their codevelopment as a new hybrid and intellectually richer discipline necessitate self-reflection that extends beyond the classic disciplinary boundaries. Hence, although the fields of clinical pharmacogenomics and human genetics research are increasingly coalescing through technology and knowledge transfer, it is critical to discern the ways in which discipline-specific traditions, tacit knowledge, and expectations of practitioners may influence the course of scientific dialogue and collaboration at their disciplinary boundaries and interdisciplinary junctions.

As academic institutions move increasingly toward serving a dual role as engines for economic growth and a knowledge commons (research and teaching),[50–52] future public policy debates on pharmacogenomics, genetic testing, and personalized medicine will need to be reframed to incorporate these subtle but significant characteristics (see Table 1). Ultimately, the recognition that pharmacology is an experimental science should also elevate the ethical standards and accentuate the moral obligation to develop pharmacogenomic or other biomarkers prospectively before obtaining mar-

keting approval. For drugs that have already been in clinical use, an equal effort should be made to facilitate their targeted use for individuals and patient populations. Blockbuster drugs may increase the profits in selected cases, but they also unethically concentrate the risks of drug development in specific groups and communities.[53]

The expansion in scope of scientific research enabled by new genomic technologies may soon result in fragmented but more diversified and narrowly defined therapeutic fields or markets for drugs that will ultimately benefit patients while also shaping the varied expectations for long-term and sustainable growth in the pharmaceutical industry. This expansion also creates new control points and sociotechnical actors in academic research governance. By contextualizing genomic technologies as important technical and social sources of momentum that unites human geneticists and pharmacologists, one sees the future of personalized medicine or clinical pharmacogenomics contingent on often indeterminate or multifactorial events.[54,55] Yet while the future remains undecided and uncertain, there is arguably an actual ethical responsibility on the part of regulatory scientists, human genetics, molecular medicine, pharmacogenomics, and social science researchers to engage in a sustained interdisciplinary, open, accountable, and transparent dialogue aimed at the development of shared standards and science policies that demonstrate optimal methodologic rigor to favorably advance discoveries and serve the best interests of patients' and public health.

In increasingly overspecialized, hypercompetitive, and fragmented biomedical research with semantic and disciplinary discontinuities,[56,57] the only assurance for continuity and objectivity in interdisciplinary fields of inquiry (eg, pharmacogenomics) will thus depend on certain human qualities in scientific professional practice and, more broadly, in public health research. These qualities include an open recognition of our own discipline-specific biases and shortcomings, giving credence to (at least noticing) hitherto disenfranchised professional viewpoints and the boundaries surrounding each discipline or individual scientific methodologies.[58] Reductionist conceptual juxtapositions of one discipline next to another (ie, pharmacology and human disease genetics presented as pharmacogenomics) or borrowing technologies from one discipline and applying in another without adequate reflection, in the best of circumstances, may only lead to multidisciplinary summation of scientific inquiries. But this is not necessarily equivalent to interdisciplinary synthesis and reasoned reconciliation of norms at disciplinary intersections. It is only when we comfortably place ourselves in that interdisciplinary space and acknowledge the attendant semantic and methodologic uncertainties that we can begin to dispassionately learn from other disciplines while building a more certain and ethical future for pharmacogenomics, personalized medicine, and equitable public health policies.

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