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Pharmacogenomic Promises: Reflections on Semantics, Genohype, and Global Justice

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Pharmacogenomics is an emerging medical specialty that investigates the role of genetic factors in drug response and adverse effects. It differs from its predecessor discipline pharmacogenetics by having a larger scope of inquiry: pharmacogenomics aims to characterize genetic differences among patients across the entire human genome. By contrast, pharmacogenetic studies typically involve investigations of single or a limited set of genes (Ozdemir and Lerer 2005). It is anticipated that a better understanding of genetic factors underlying individual differences in drug effects will help the customization of drug prescriptions.

The field of pharmacogenomics had its origins in 1950s with the creation of human biochemical genetics and the discovery of single gene variations associated with enzyme deficiencies. These enzyme defects were responsible for certain unexpected adverse drug reactions, such as peripheral neuropathy in slow-acetylators of the anti-tuberculosis drug isoniazid. Twin studies in the 1970s subsequently confirmed the important role of genetics in drug disposition. These developments did not, however, permeate through mainstream medical research until the late 1990s, when DNA technologies spun off from the Human Genome Project became more widely available in clinical and research laboratories.

A key element of pharmacogenomic research is that it deals with questions of variability in drug effects. This approach runs counter to certain established and deterministic norms in medical practice and pharmaceutical industry drug development (Olivier et al. 2008). That is, drug researchers, policy makers, and industry representatives have traditionally approached drug efficacy and safety at a population level; rather little attention has been given to subpopulations or persons with a differential risk for treatment resistance or drug toxicity.

Much of the technical debate on pharmacogenomics and the promise of personalized medicine has centred on upstream applications that can facilitate research to discover new drug targets or the identification of

patients with different molecular subtypes of disease. Although personalization of the choice of medicines or their doses is often highlighted in forward-looking statements on pharmacogenomics, little is mentioned about exactly how this may be achieved. Pharmacogenomics has also been advocated as a means of improving the efficiency (and thus reducing the cost) of drug discovery, clinical trials, and the drug approval process. But the very nature of the pharmacogenomics approach—its emphasis on individual variability in treatment outcomes—threatens the traditional business model associated with one-size-fits-all drug development and commercialization. To this end, reflections on the ethical and policy concerns associated with pharmacogenomic research have tended to focus on, for example, informed consent and banking of genetic material in clinical trials, privacy considerations, or potential for stigmatization (Tutton and Corrigan 2004; Weijer and Miller 2004).

As pharmacogenomic applications emerging from industry and academic laboratories start to enter the doctor's office (e.g., as genetic tests and individualized drug therapies), numerous other ethical concerns arise. In this chapter, we analyze three of these: (1) the semantic representations and significance of genetics language in public and policy discourse on drug efficacy and safety, (2) the implications of excessive genohype for the realistic application of pharmacogenomic technologies, and (3) the promise and challenges of applying pharmacogenomics for essential medicines used to treat diseases predominantly affecting people in developing countries.

Historical Context and Genealogy of Personalized Therapeutics

During the last century, and in particular the last thirty years, contemporary Western medicine has shifted its focus from the development of pharmaceutical drugs (whether prescription or over-the-counter) for rare medical conditions and infectious diseases to the development of treatments for common illnesses. Drugs are being used to alleviate both acute and chronic conditions, and as prophylactic measures to reduce risk of long-term morbidity and mortality—in the West, drugs now constitute the primary treatment modality. Although drugs can be life-saving in some patients, there is growing concern over the marked uncertainty in drug toxicity or efficacy; these concerns relate both to new compounds in clinical trials and those already in clinical use.

A review of the published data on the efficacy of major drug classes being prescribed for common human diseases concluded that response rates vary substantially across various therapeutic areas. For example, while 80 percent of patients responded positively to pain medications such as COX-2 inhibitors, response rates dropped to 30 percent for treatments directed at Alzheimer's disease and 25 percent for cancer chemotherapies (Table 11.1). Although many drugs in the major therapeutic classes can be life-saving,

Table 11.1

Response rates of patients to major drug classes in selected therapeutic areas

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (COX-2)	80
Asthma	60
Cardiac arrhythmias	60
Depression (SSRI)	62
Diabetes	57
HIV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Source: Reproduced with permission from Spear, Heath-Chiozzi, and Huff (2001).

only about 50 percent of patients actually respond positively to their medications (Spear, Heath-Chiozzi, and Huff 2001). Of serious concern, then, are the remaining 50 percent of patients for whom their medication is either ineffective or even toxic.

A meta-analysis of prospective studies investigating drug safety in the United States indicated that 6.7 percent of hospitalized patients experience serious adverse drug reactions (ADRs), while 0.3 percent die from toxic drug effects. This translates into more than two million serious ADRs and an annual death rate of 106,000 patients. These estimates rank ADRs as the fourth leading cause of death in the United States (Lazarou, Pomeranz, and Corey 1998a). Subsequent extended analyses of thirty-two non-US studies from industrialized countries support the conclusion that fatal ADRs are a significant global public health concern (Lazarou, Pomeranz, and Corey 1998b). Interestingly, serious ADRs were observed during treatments with usual drug dosages, despite the exclusion of cases that were due to intentional or accidental overdose, human errors in drug administration, non-compliance, or drug abuse.

The patient and public health implications of non-response or toxic reaction to common medications, and the development of means to reduce these negative effects, have for decades been core research questions in the medical sciences (Reidenberg 2003). By better understanding the degree of

and mechanisms governing the predictability of drug effects, biomedical scientists—and especially clinical pharmacologists—aim to rationalize the choice of drugs and customize dosages for individual patients and sub-populations, that is, the goal is personalized medicines (Sheiner 1997).

Some experts suggest that the origins of personalized medicines can be dated to about 510 BCE when Pythagoras, in Croton, in southern Italy, warned of “dangers of some, but not other, individuals who eat the fava bean” (discussed in Nebert 1999). The molecular basis of this historical observation was later found to be haemolytic anaemia attributable to glucose-6-phosphate dehydrogenase deficiency (Nebert 1999). Interest in the rational choice of therapies can be traced to the eighteenth century, when English naval surgeon James Lind demonstrated in 1747, in the first formal comparative trial of its kind, that scurvy could be cured by citrus juice but not by the other leading remedies of the day—cider, vinegar, sea water, or purgative mixtures (Sutton 2004).

Numerous recent policy initiatives have added support to the drive to develop personalized therapies (Kohn, Corrigan, and Donaldson 2000). Pharmaco-epidemiology studies have, however, highlighted important barriers to the rationalization of therapeutics, due in large part to the lack of reliable predictors for the marked inter-individual and population-to-population variability in drug treatment outcomes (Spear, Heath-Chiozzi, and Huff 2001).

One of the prominent research strategies for discovering and applying the requisite genetic predictors (i.e., biomarkers) needed to develop personalised medicines is pharmacogenomics. Employing a broad survey of the human genome made possible by recent advances in DNA sequencing and the identification of thousands of single nucleotide polymorphisms, pharmacogenomics studies the role of genetics on inter-individual and population-to-population variability in drug effects (Evans and McLeod 2003). As single nucleotide polymorphisms, genes or other biological markers are identified and associated with particular drug effects (therapeutic response, toxicity, or treatment-resistance), it becomes possible to offer genetic testing to patients or population groups in order to individualize the selection of the type and/or dosage of a medication, thereby improving efficacy and reducing the risk of ADRs.

An important difference, then, between the present interest in pharmacogenomic-guided personalized medicine and previous attempts using more descriptive or demographic predictors (e.g., age, ethnicity, geographic origins) is that sufficient causal information now exists to allow for the development of DNA-based diagnostics and customized therapeutic interventions. This has led to the development of drugs such as Abacavir (for HIV/AIDS), Herceptin (for metastatic breast cancer) and Gleevec (for chronic myeloid leukemia). The hope is that such first generation pharma-

cogenomic applications will revolutionize medical practice by inaugurating the age of personalized medicines.

However, despite growing knowledge of the importance of genetics in drug effects, there is also an awareness that environmental and social factors play a significant role. Factors such as poor nutrition, low socioeconomic status, lack of education, or inadequate health insurance contribute substantially to lack of efficacy or toxicity, a situation that applies to both mainstream and pharmacogenomic drugs (Corrigan 2002). Such a complex interaction of genetic, social, and environmental factors therefore requires more detailed and nuanced social and epidemiological research to better understand the etiology of drug effects. Consequently, although research into personalized medicine has become firmly placed on the social policy and science agendas and is a topic of public and media interest, this interest has been matched by increased scrutiny of the promises, timelines, and likely impact of pharmacogenomics on therapeutics and patient care (Corrigan 2005; Ozdemir and Lerer 2005).

Semantics Revisited: “Genetics” in “Biological Dogma” and “Risk Assessment”

The elucidation of the structure and functioning of DNA, and the growing understanding and application of genetic information in the biological sciences, has led to the deployment of powerful metaphorical language in scientific, public, and policy discussions. The human genome, for example, has variously been described as a “blueprint,” an “instruction book,” or, in the words of former US president Bill Clinton, “the language in which God created life.” In drawing the map of the human genome, scientists are said to be building an “encyclopaedia,” an orderly reference book that can be deciphered to predict health and well-being, individual behaviour, and personal destiny. Personalized medicines, gene therapies, genetically modified organisms, and genetic tests are “revolutionary” applications of knowledge from “the book of life,” or instances of unacceptable hubris that “play God” and run the “risk” of unleashing “Frankenstein” creations (Hellsten 2005).

The use of metaphors and scientifically imprecise language is arguably an important means of translating, explaining, and simplifying complex ideas and is thus widespread in popular science and media discourses. But such language is not unproblematic (López 2004; Petersen, Anderson, and Allan 2005). Public representations of genomics research and applications often invoke simplistic, reductionist, or deterministic explanations for things that are significantly more complex. The mention of “genetics” or “genetically tailored drugs” creates expectations that highly effective and safe designer medicines will soon be available to the general public (Smart 2003). Similarly, when the diagnostics industry or academic groups seek-

ing research funding or venture-capital discuss the implications of their findings (e.g., in relation to variability in treatment outcomes), these are often attributed to “genetics” and thus tend to dismiss the role of non-genetic factors (Bowen, Battuello, and Raats 2005; Williams-Jones 2006).

Despite its frequent use, the term “genetics” is rarely contextualized in sufficient detail. Specifically, it is important to understand the different meanings of “genetics” in “biological dogma” and in “risk assessment” for medical outcomes such as drug response and disease susceptibility.

Biological dogma is a term that describes a fundamental process in cell biology: the unidirectional flow of biological information from the nucleotide sequences coded in individuals’ genetic material (DNA), to messenger RNA (mRNA), through the process of gene transcription, and finally to proteins via translation of mRNA by cellular ribosomal machinery. Seen through the lens of biological dogma, then, DNA and genes are undoubtedly the indispensable currencies of all eukaryotic life forms (including humans), and thus a key focus for genomics research. Pharmacogenomics research, however, is about “risk assessment” and so poses a conceptually different question: Does human genetic *variation*, either in gene sequence or in the regulation of gene expression (transcription), explain person-to-person differences in drug efficacy or toxicity? Hence, while genes are an indispensable requirement in the context of the biological dogma, they are only one of many factors that contribute to the final composite risk for drug-related problems. The interchangeable use of the term *genetics* in either context—biological dogma or pharmacogenomics-based risk assessment—incorrectly implies a greater role for hereditary factors in pharmacogenomics.

Unfortunately, representations of “genetics” in the media or industry promotional press releases often erroneously refer to the biological dogma itself as the key focus of pharmacogenomics or human genetics research (Terwilliger and Weiss 2003). Rhetoric about the role of genes in sustaining “life” (i.e., more accurately, the biological dogma) is presented to support the importance of genetic factors for drug response. Such genetics talk is inherently misleading to non-specialist consumers of genomic technologies and may ultimately breach the public’s trust in science and genetics research (Nelkin 2001). Thus, it is important to ensure that the public, as potential consumers of pharmacogenomic tests, and their physicians, as prescribers of personalized medicines, are able to adequately distinguish different meanings of “genetics” in risk assessment or discussions of the biological dogma.

Promissory Science and Genohype in the Evolution of Pharmacogenomics

The use of simplistic and reductionist language in public and policy discourse also links in important ways to concerns about the extent to

which the promises of genomics and biotechnology will be actualized in clinical practice. Can pharmacogenomics deliver personalized medicines in a timely manner, or will it go the way of other genomics promises where “genohype” did not lead to “genoreality” (Ozdemir et al. 2005; Webster et al. 2004)?

The substantial historical—and continued—investment in genomics research by governments and corporations of developed and developing nations has been publicly justified on the grounds that this so-called new science would produce the necessary knowledge and derivative biotechnologies to solve many of the world’s most challenging social, environmental, and economic problems. The Human Genome Project, for example, was billed as the means for identifying both rare and common disease susceptibility genes (e.g., for obesity, cancer, diabetes), information that could be quickly translated into cheap and accurate diagnostics to be followed soon after by gene therapies and personalized medicines. Genetics was (is) to be the future of medicine (Collins and McKusick 2001; United Kingdom Department of Health 2003).

Yet, while the completion of the Human Genome Project may have allowed the “language” of DNA to become “readable”, knowing the sequence of coding “letters” (base pairs) and deciphering some of the “words” (genes) has proven insufficient for a complete comprehension of the structure and function of the genome. The publication of the completed human genome map has thus been followed by other maps (e.g., the International HapMap Consortium)—genomics is only the beginning of what is likely to be a decades-long research endeavour to understand the complex interactions among genes, proteins, environment, socio-economic, and cultural factors (Heymann et al. 2005; Terwilliger and Weiss 2003).

As numerous science, policy, and social science commentators have noted, the promissory fields of genomics and biotechnology have yet to deliver on most of the predicted “revolutionary” technologies (Ozdemir and Godard 2007). There have been important discoveries and developments, but these have tended to be incremental, following pre-existing and well-established lines of research (Nightingale and Martin 2004). For example, while a growing number of medical genetic tests have become available in the clinic and the marketplace, many of these tests were developed after decades of research involving detailed and extended family histories of hereditary disease. And for the most part, these tests are useful only for identifying or providing risk information about rare hereditary diseases; seldom are they sufficiently accurate for wider population screening (Baird 2000; British Medical Association 2005). Similarly, while many of the technical advances (e.g., DNA microarrays) can be represented as “engineering triumphs,” they still require interpretation in the context of

biology, clinical biomedicine, and commercial biotechnologies. The translation of genomics knowledge into scientifically and economically important biotechnologies has proven far more complicated than expected.

In the case of pharmacogenomics, proponents argue that the genetic customization of drugs will both radically improve medical outcomes by eliminating ADRs and develop new avenues for commercialization of pharmaceuticals and genetic technologies (Roses 2000). As with genetic testing, pharmacogenomics is being applied and is proving useful for some people (Dervieux, Meshkin, and Neri 2005). But despite high expectations, only a small number of pharmacogenomic products have actually entered clinical practice, and even these remain contentious (Woelderink et al. 2006).

For Herceptin, one of the first generation of personalized medicines, there has been some debate about whether or not this drug is in fact an instance of pharmacogenomics (Hedgecoe 2005; Lindpaintner et al. 2001). Herceptin is a monoclonal antibody directed at the human epidermal growth factor receptor 2 (HER2). It was approved by the US Food and Drug Administration in 1998 as an anti-cancer therapy for breast cancer patients who are HER2 positive. The Herceptin pharmacogenomic test involves the characterization of HER2 expression levels in tumour biopsy materials. A clearly discernible drug target, HER2 was a foreseeable candidate for diagnostic testing, the clinical adoption of which was facilitated by the relatively easy access to biopsy samples. In other medical specialties, such as psychiatry, obtaining target organ tissue samples for measurement of gene expression is not possible for obvious practical and ethical reasons. Instead, genetic tests using DNA from peripheral tissues (e.g., blood) remains the sole means of pharmacogenomic testing. Another notable aspect of the HER2 test is that it was not identified by a genome-wide search but rather by virtue of HER2 being a drug target whose expression levels may understandably influence treatment outcomes. In this light, HER2 is perhaps more appropriately framed as a product of classical pharmacogenetics rather than as an instance of a revolutionary pharmacogenomic technology.

Abacavir, a drug used to treat HIV-1, is associated with systemic hypersensitivity reactions in about 5 percent of patients. Genetic screening of these persons for the human major histocompatibility complex identified several susceptibility loci (Symonds et al. 2002). One particular allele, HLA-B*5701, was overrepresented among the Abacavir-hypersensitive patients in studies reported from Western Australia and North America and thus could be used as a pharmacogenomic test to identify at-risk persons who should not receive the drug (for an overview, see Quirk, McLeod, and Powderly 2004). Some would argue, however, that the Abacavir story is hyped and that the utility of pharmacogenomic testing is at best limited

(Lindpaintner 2002). The HLA-B*5701 allele does not account for all adverse reactions to Abacavir because people who do not carry this allele can also have a hypersensitivity reaction. Moreover, because exposure to Abacavir can lead to serious medical complications in hypersensitive patients, it is critical that the full complement of genetic and environmental risk factors be identified before pharmacogenomic testing can effectively guide prescription decisions.

Gleevec, a drug to treat persons with chronic myeloid leukemia who test positive for the Philadelphia chromosome (an abnormally short chromosome 22 identified in 1960), is likely a more clear-cut case of a functioning pharmacogenomic test and drug application. But this drug-test combination is based on a relatively simple cytogenetic test and would probably have been feasible without genomic technologies. An important point to note, then, is that the discovery of these drugs *did not* emerge from “genome-wide” searches per se, one of the long advocated key deliverables of pharmacogenomics research. The attendant diagnostic tests were developed through more focused candidate gene studies (i.e., pharmacogenetics) or simply by using classical cytogenetic approaches. Further, the development of diagnostic tests for drug response appears to be an ad hoc effort rather than a prospective systematic approach in response to a serious adverse drug event or lack of efficacy.

An important goal of pharmacogenomics has been the identification of genes or biomarkers that are difficult to forecast from existing knowledge of a drug’s chemistry or the disease pathophysiology. As with research into gene therapy, the enormous complexity of pharmacogenomics research and technology development means that much work remains before scientific discoveries will be readily translated into clinical applications (Freund and Wilfond 2002).

Investors, governments, and some in the pharmaceutical industry have also placed much hope on pharmacogenomics as the vehicle for re-energizing and reshaping the struggling pharmaceutical sector. Pharmaceutical companies have in the last ten years been finding it increasingly difficult to develop and market new blockbuster drugs—most new medications are “me too” drugs (Center for Drug Evaluation and Research 2005; Horrobin 2000). Further, a large number of blockbuster composition of matter patents are due to expire over the next several years, further threatening big pharma’s economic model (Service 2004). In this context, upstream pharmacogenomic applications promise to help academic and industry researchers identify new disease-associated genes, some of which may serve as novel drug targets. Developments in pharmacogenomics may also enable companies to risk-proof their drug development pipelines by preventing catastrophic and extremely costly late-stage drug withdrawals (or class action lawsuits) because of unacceptable toxicity or lack of efficacy.

Pharmacogenomics may even revive, in specific subpopulations, patented and developed but uncommercialized drugs that failed during the clinical trial stage because of safety concerns or lack of efficacy in the broader patient population (Ozdemir and Lerer 2005).

The economic potential of pharmacogenomics, and the corresponding benefit for the pharmaceutical industry, may not however be so straightforward. The process of identifying genetic markers in individuals and communities creates pharmacological and disease subtypes that inevitably fragment both the disease and its treatment. That is, by personalizing medicines, pharmacogenomics undermines the traditional blockbuster model of drug development and marketing. No longer is it sufficient to develop a one-size-fits-all medication that will hopefully generate billions of dollars in revenues (i.e., be a blockbuster) (Danzon and Towse 2002); instead, a variety of personalized medications will be necessary for each molecular genetic subtype of disease or individual drug response. The upshot is a fragmented market and increased competition (or more complex collaborations) between drug manufacturers and biotechnology companies. Not surprisingly, then, individual pharmaceutical companies may have divergent views within their own constituents (e.g., among directors of marketing, genetics, or chemistry departments) about the appropriateness of pursuing pharmacogenomics, at least in the short term (Williams-Jones and Corrigan 2003). It is very likely, however, that pharmacogenomics will make future predictions on drug efficacy and safety more reliable and reduce the risk for catastrophic and costly late-stage drug withdrawals from the market; but when and to whom these benefits will accrue is much harder to discern (Eisenberg 2002).

Such profound disconnects between the promises and realities of genomic knowledge and technologies have led many commentators to question the motivations of genomics advocates (whether they be academics, pharmaceutical or biotechnology industry representatives, or venture capital firms), and the veracity of their claims, and even to label these promises as “genohype” (Fleising 2001).

Hype may well be an important, even essential, part of the developmental phase of a new science or technology. Positive spin can facilitate collaboration and uptake of new ideas; help in the acquisition of human, financial, and technical resources; and create a future-oriented consciousness about how the “new” will be an improvement over the “old” (Brown 2003; Hedgecoe and Martin 2003). However, while hype can be an effective means of achieving near-term objectives, it can also be counterproductive in the long run when not matched by tangible products.

Unfilled promises can severely undermine the credibility of stakeholders, be they scientists, technologists, companies, or governments. For example, when surrounded by academic, commercial, or other supporters

of the promissory science, and in the face of hype and unrealistic public expectations, scientists genuinely committed to the attendant field of enquiry may become discouraged, feel pressured to pursue short-term goals centred on immediacy, or even decide to shift their research entirely to less hyped areas of scientific enquiry. By focusing on the short- to medium-term potentials of particular fields of enquiry or early-stage technologies, hype may also obscure the long-term potential of a new field of innovation (Caulfield 2000).

A more subtle and yet significant consequence of genohype is that it diverts attention from how the benefits of pharmacogenomics are to be distributed among the world's populations and the ways in which pharmacogenomic testing may shape healthcare delivery and treatment of diseases predominantly affecting developing countries.

Pharmacogenomics in the Developing World and the “90/10 Gap”

As discussed above, pharmacogenomics has traditionally been framed in the context of individualization of patented first-line drugs for illnesses such as type 2 diabetes or cancer, diseases that primarily affect the populations of developed and affluent countries. It is not surprising, then, that some would question the relevance of pharmacogenomics to the discovery and cost-effective delivery of drugs that will actually benefit patients in the developing world (Pang 2003).

Private and public investment in health research is estimated to be more than US\$70 billion per year (Vijayanathan, Thomas, and Thomas 2002). However, less than 10 percent of global funding for research is directed toward diseases that affect more than 90 percent of the world's population—the so-called “90/10 gap” (Institute for OneWorld Health 2004). This situation is made worse by often inadequate research infrastructure and lack of trained personnel in developing countries who can conduct or advocate for research to tackle prevalent diseases such as malaria or tuberculosis. Because of wide disparities in wealth distribution and lack of a middle socio-economic class in resource-poor nations, efforts to develop local research capacity by training personnel abroad may also prove challenging. In particular, there may be uncertainty about who should have the opportunity to pursue academic training abroad (e.g., based on scientific and individual merit or socio-economic privilege?), not to mention difficulties in ensuring professional commitment and encouraging highly skilled scientists to return to their native countries (Hyder, Akhter, and Qayyum 2003).

In 1977, the World Health Organization (WHO) launched the Model List of Essential Medicines to identify and facilitate the provision of safe and effective treatments for communicable and chronic diseases affecting the vast majority of the world's population. This list is updated every

two years by an expert committee to include drugs that will satisfy the priority healthcare needs of the population. The selection criterion takes into account public health relevance, evidence on efficacy and safety, and cost-effectiveness (Day et al. 2005). The concept of essential drugs is also a valuable measure to reduce irrational drug combinations or counterfeit products; the WHO donor programs use only the drugs listed in the model list.

Yet, of the 1,393 new drugs developed between 1975 and 1999, only 1.1 percent (16 drugs) were for the treatment or prevention of tropical and other diseases prevalent in developing countries (Trouiller et al. 2002). The commercial logic of contemporary drug development and marketing is such that developing countries are simply not a good market for first-line pharmaceuticals, nor are their diseases worth the research investment. Unlike drugs for chronic diseases that require multiple prescription refills (e.g., statins to lower cholesterol levels and reduce cardiovascular risk), and thus for which there is a substantial market in the West, antiviral drugs are not a profitable investment unless they also affect affluent countries (e.g., drug cocktails for “chronic” HIV infection or vaccines for avian influenza) because they are prescribed for a limited period.

A second critical element is ability to pay. Developing countries lack the large-scale public and private health-insurance programs common in North America and Europe that would cover the costs of prescription medications, nor do the peoples of developing countries have the personal wealth to afford costly drugs—one-third of the world’s population lives on less than US\$2 a day. Thus, while sub-Saharan Africa, for example, could provide a very large “volume” of clients for antiviral drugs or vaccines, they are too poor to pay even a reduced bulk price that might be offered by the big pharmas. Multinational regulation of trade and intellectual property rights, in particular the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), may further hinder access to patented drugs in developing countries. Although the TRIPS Agreement, in the event of a public health emergency, allows for compulsory licensing by local governments, it is unclear whether this provides any help for countries with limited manufacturing infrastructure.

The high relative cost of pharmaceuticals in developing countries has a profound economic and social impact (Hale, Woo, and Lipton 2005). According to the WHO, “while spending on pharmaceuticals represents less than one-fifth of total public and private health spending in most developed countries, it represents 15 to 30 percent of health spending in transitional economies and 25 percent to 66 percent in developing countries. In most low-income countries pharmaceuticals are the largest public expenditure on health after personnel costs and the largest household health expenditure. And the expense of serious family illness, including

drugs, is a major cause of household impoverishment" (WHO Medicines Policy and Standards 2007).

The result is global injustice and a widening gap in access to essential medicines between developed and resource-poor nations. Through no fault of their own—one's birthplace is obviously outside one's control—those people least able to afford basic (but costly) drugs live in poverty and in countries unable to provide affordable healthcare services. These people spend the largest percentage of their incomes acquiring essential medicines, whereas the majority of their wealthy neighbours in the North have access to a surplus of me-too drugs, a diversity of relatively affordable generic medicines, and a health insurance system to cover much of the costs. Given these profound social inequities, of what relevance is a developing but still not fully actualized and thus very expensive technology such as pharmacogenomics?

Given the upfront costs of genomics research and the development of pharmacogenomics technologies, in all likelihood drugs developed by pharmacogenomic guidance will be prohibitively costly for equitable access in developing countries. It is reasonable, then, to argue that other tested public health measures, such as the provision of clean water and equitable access to housing, would be a better use of the limited financial resources available for international development (Heymann et al. 2005). Thus, although genomics research or applied biotechnologies may benefit wealthier populations or individuals, it is not at all clear to many commentators how these technologies will address the serious issues of global public health and distributive justice (Dwyer 2005).

Despite these important critiques of pharmacogenomics (and other biotechnologies), there are two areas in which pharmacogenomics research might help with the equitable and timely provision of appropriate medicines in developing countries. The application of pharmacogenomics might (1) enable the provision of inexpensive generic drugs in subpopulations defined by pharmacogenomic tests wherein drugs display an optimal benefit-to-risk ratio, and (2) facilitate investment in the discovery of medicines for diseases such as malaria or parasitic infections.

It is conceivable, particularly given growing concerns about equitable access to safe and effective medications, that an internationally accepted and peer-reviewed essential biomarkers directory similar to the essential medicines library maintained by the WHO could be established. Such a biomarker directory would enable a broader utility for pharmacogenomic biomarkers by permitting the reintroduction of less costly second-line generic drugs with suboptimal safety as first-line treatments in subpopulations that demonstrate an improved benefit-risk ratio (Ozdemir et al. 2006). This possibility (i.e., a means of marketing patented but uncommercialized drugs) is also one of the hopes of pharmacogenomic advocates in the phar-

maceutical industry, but for it to be applicable in the context of developing countries, it would have to be applied in concert with a different market model of drug provision. Specifically, drug developers would need to accept that the opportunity to market patented but shelved drugs brings with it a corollary obligation to market those drugs at a price affordable to developing countries. The payoff for drug companies would be profits from the sale (of relatively) large volumes of a medication that would otherwise be generating no revenues, as well as a means of enhancing their rather tarnished public images by seriously addressing the critical public health concerns of people in developing countries.

As part of their corporate social-responsibility programs, many big pharmas already donate drugs to developing countries; for example, Merck donates the drug ivermectin (Stromectol) for the treatment of river blindness in western and central Africa. However, these donations have had a limited effect on the provision of treatments for the broad range of diseases affecting developing countries. Another and more innovative approach is the development of public-private partnerships, wherein drug companies partner with not-for-profit foundations to engage in drug development for marginalized or orphan disease areas. A notable example is the Institute for OneWorld Health, a non-profit drug-development company that is partnering with big pharmas, small biotechs, and large public trusts such as the Bill and Melinda Gates Foundation to conduct clinical trials and develop a range of drugs for diseases affecting peoples in developing countries. For example, with a broad licence donation of a molecule owned by Celera Genomics, OneWorld Health is developing a treatment for Chagas' disease (Hale, Woo, and Lipton 2005).

Such a merging of innovative business strategies with developments in biotechnology and pharmacogenomics research may allow for more cost-effective identification of novel drug targets and pharmacological mechanisms for neglected diseases, and, it is hoped, lead to increased local access to affordable and effective drugs (Daar and Singer 2005). But although pharmacogenomic technologies may be valuable tools for improving global public health (in the long run), there are serious concerns over their representation as tools that will necessarily benefit science and the public interest in the near term. In comparison with other well-known social, cultural, or economic responses to the profound healthcare challenges facing developing nations or transitional economies, the potential and cost-effectiveness of pharmacogenomic technologies remains a contentious issue. Whether these technologies are applied as part of the standard big pharma business model or integrated in public-private partnerships around non-profit drug development, ultimately the question remains, who is going to fund the long-term research to actualize the potential of pharmacogenomics and translate knowledge into action (Pang, Gray, and Evans 2006)?

Conclusion: An Equitable Integration of Pharmacogenomics in Healthcare?

For pharmacogenomics “genohype” to become “genoreality,” basic scientific and clinical discoveries associated with the genetics of drug effect and response must be converted into technologies that actually make a difference in the real world. Short of such translation of knowledge into product, the public as citizens and taxpayers may come to feel they have again been sold a bill of goods, so to speak. A related point is that pharmacogenomics, so far, has been largely an engineering triumph—the vast amount of information generated by genomics research is being transformed into pharmacogenomic tests that are helping researchers build more sophisticated understandings of individual and population variability in drug response. But translational biomarker research that transforms knowledge into functional pharmacogenomic tests and linked drugs will be crucial if this field is to also achieve a biological triumph. Only when the engineering triumph is matched with a biological triumph will the genohype become a genoreality. It is tempting to say, then, that part of the cause of genohype is the mismatch between these two very different types of triumph.

Developed and more affluent countries have a vested self-interest in advocating for global justice in access to essential medicines and provision of healthcare services in resource-poor countries. Recent world events such as the SARS outbreak in 2003, the AIDS pandemic, and the threat of avian influenza have shown the close relationships among national interests, global public health emergencies (regardless of geographical localization), and access to equitable healthcare services, including pharmacotherapy.

While reflecting on the promises of pharmacogenomics, it thus seems appropriate to pay attention to the ways in which new genomic technologies can benefit developing countries, for example, by the discovery of new drug targets for infectious diseases or treatment of resistance forms of tuberculosis. However, inadequate recognition of the strengths and limitations of pharmacogenomic technologies can widen the already existing gap in pharmaceutical research and access to equitable pharmacotherapies. In particular, the “90/10 gap” may become more pronounced unless the emerging pharmacogenomic technologies are appropriately evaluated regarding their implementation in populations with divergent socio-economic predicaments.

Finally, given the continued lack of access to essential medicines in developing countries, profound questions remain about how best to deploy limited financial resources, whether it be for the individualization of drug therapy or for other measures known to markedly improve health and prevent disease, such as access to clean water, education on sexually transmitted diseases (e.g., AIDS), adequate housing, and employment. Ultimately, however, it will still be important to evaluate both the social

(environmental, economic, and cultural) and biological (genetic) factors, as well as their complex interactions, in order that biotechnologies and pharmacotherapies can collectively aid in the improvement of global public health (Heymann et al. 2005).

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