

Human Genomic Variation Studies and Pharmacogenomics Are Critical for Global Health

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Introduction

Many people in the world still lack access to essential medicines. The World Health Organization (WHO) has attempted to address this inequity by creating the essential medicines list (See <http://www.who.int/medicines/publications/essentialmedicines/en/>). This list is intended to help countries with limited resources focus health expenditures on medicines likely to produce the most health benefits. However, as pointed out in a recent report by Marsh et al.¹ if we consider that most of these drugs have been developed and tested in predominantly male Caucasians in industrialized countries, then how can we be sure we are indeed maximizing health benefits globally? We know that there is individual variability in drug response and that human genetic variation is partly responsible for how humans respond to therapeutics. There is also a growing body of evidence demonstrating ethnic variability in drug response. Recent trends in genetic research and the quest for improving drug therapy indicate that, at least in industrialized countries, the adoption of pharmacogenomics is inevitable due to regulatory incentives, increases in biomarker validation, pharmacoeconomic evidence and patient demand.²

When it comes to the developing world however, some believe that pharmacogenomics applications will be too expensive to adopt, and argue that the traditional focus on improving environmental conditions is the most practical approach to improve population health.³⁻⁵ While such approaches are important for solving global health inequities, scientific developments can complement this effort and should not be suppressed when they have much potential; it has recently been argued that pharmacogenomics can also be practically applied to improve the health of people in the developing world.^{1,2,6} As advances in pharmacogenomics progress, it is likely that new drugs will be developed by—and for—industrialized countries. Therefore, to ensure that developing countries share in the potential social and economic benefits of the genomics revolution and to prevent the emergence of a “pharmacogenomics divide,” it seems reasonable to assume that understanding and harnessing genomic variation (SNPs, gene duplications and deletions, mutations in regulatory genes and large-scale copy number variations) in developing world populations will help them improve efficiency of medication use in resource-limited settings, and potentially develop therapeutics that meet their local health needs. To understand how this can become a reality, we need to explore the

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connection between pharmacogenetics, genotyping projects in developing countries, and the evolution of the pharmaceutical industry in both the developed and developing worlds. Indeed, the stimulus for the large-scale adoption of pharmacogenomics is already apparent in some developing countries, such as Mexico (Table 2), that are initiating their own large-scale genotyping studies.

Although pharmacogenomics may provide benefits to industrialized and developing nations alike, special considerations apply in the case of developing countries, which face increasing challenges in their healthcare systems. Considering ethical, legal and social issues is necessary to facilitate the successful implementation of pharmacogenomics. Table 1 provides a brief overview of these issues, some of which have been extensively reviewed in the literature⁷ and will not be revisited in this chapter. Instead, we classify these issues into drivers for—and barriers to—the implementation of pharmacogenomics in the developing world. Using this framework, we will focus the remainder of this chapter on exploring, in more depth, what we perceive to be key benefits to—and challenges for the adoption of pharmacogenomics in developing countries. Some of these key benefits and challenges relate to three core themes: (1) controversy over growing scientific evidence that there is genetic variation between ethnic groups; (2) cost of implementation of human genomic variation studies may be perceived as a short term barrier (3) proper scientific, human resource and intellectual property infrastructure needs to be developed in order to make adoption of a genomic medicine platform possible. We thus begin this chapter by discussing the use of “race” in pharmacogenomics studies because, at least in the short term, many genetic studies in both developed and developing countries (including admixture studies) will be making use of “race” or “ethnicity” as a proxy marker and the controversy this has generated merits attention. Secondly, we address the issues of cost and feasibility pertaining to the adoption and implementation of pharmacogenomics in the developing world and finally, we briefly mention some of the regulatory issues that may affect the adoption of pharmacogenomics in the developing world.

The Use of ‘Race’ in Genetic Studies Is Controversial

Due to the ambiguity inherent in ‘race’, we will avoid using the term. We use *geographical ancestry* to refer to population clusters based on genetic differences that some experts attribute to evolutionary pressures. These differences refer to varying frequencies and patterns of certain polymorphisms. Differences based on geographical ancestry would encompass phenotypes such as skin colour, but also include other variation that may not be visible. Outward characteristics do not necessarily correlate with geographical ancestry. These phenotypic differences are often conflated with social constructions so that individuals may identify with a certain group based on culture, geographical location, parentage etc. We use *ethnicity* to refer to these social constructions inherent in self-identification and distinguish them from objective genetic designations. These genetic differences, although they are dwarfed by common genetic heritage, are significant in the field of pharmacogenomics. We will review the relevance of geographical ancestry to genomic medicine, before exploring the difficulties attendant to clustering, based on current knowledge.

Genetic differences among population groups do exist, and it is possible with some degree of accuracy to determine an individual’s ancestry by studying genetic variation at a small number of loci.^{17,18} Many scientists believe that exploring differences among ancestral groups will provide valuable insights into complex diseases and, ultimately, improve global health.¹⁹ Although categories of social organization do correlate with health outcomes, we need to separate those components that may be attributable to beliefs, practices and healthcare disparities from those that are determined by genetic variation. We should “look through race to ascertain genetic factors” that affect drug response and disease susceptibility.²⁰ It seems likely that geographical ancestry will continue to be useful as long as such categorization ‘explains’ variation unexplained by other factors and it is likely that more specific knowledge of genetic variation will actually resolve the social issues that arise from the use of ethnicity.

Table 1. Drivers for and barriers to the adoption of pharmacogenomics in developing countries

	Driver	Barrier
Ethical	<ul style="list-style-type: none">-Need for innovative approaches to reduce healthcare disparities-Responsibility of each country to meet domestic health needs-Need to build local scientific capacity so local health needs can be addressed-Ensuring that developing countries benefit from the ‘genomics revolution’ so as to prevent further increases in health inequities-Importation of products in market where they have not been tested is unethical	<ul style="list-style-type: none">-Public conflates ELSI issues specific to pharmacogenomics with general genetics ELSI issues: Informed Consent, Privacy, Stigmatization, Discrimination, Determinism, and Benefit Sharing⁸⁻¹¹-New approaches may divert scarce resources from traditional strategies such as environmental or social interventions-Use of socially constructed definitions of race in pharmacogenomics studies
Legal	<ul style="list-style-type: none">-TRIPS* implementation will force developing countries to respect patent laws—encouraging them to develop innovative products rather than relying on generics (for example India has become TRIPS compliant as of 2005)-Laws, regulations, and policies which encourage research and clinical developments-Litigation might play a role in driving the adoption of pharmacogenetics not only in industrialized countries but also in emerging markets (see Box 1).	<ul style="list-style-type: none">-Weak infrastructure for developing proper IP protection in developing countries
Social	<ul style="list-style-type: none">-National pride and identity building-Increasing patient demand for pharmacogenetic testing as positive scientific and economic benefits begin to surface	<ul style="list-style-type: none">-Lack of optimal infrastructure to develop genomic medicine-Potential for exploitation of vulnerable groups in research-Social identity and self-identity may be questioned if results of large-scale human genotyping reveal the existence of ancestral lineages that were previously unknown in certain groups
Economic	<ul style="list-style-type: none">-Contracts for research (outsourcing) and collaborative projects with other countries boost local economies and lower implementation costs for developing country partners-Noncommunicable diseases are of common interest with industrialized countries-Market segmentation may result in niche market opportunities for small domestic biopharmaceutical companies¹²-Need to generate a knowledge-based economy in the developing world so as to be competitive in the world economy	<ul style="list-style-type: none">-Cost of implementation-Market segmentation may lead to expensive therapies

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Table 1. Continued

	Driver	Barrier
Scientific	<ul style="list-style-type: none">-Genotyping projects are already established and generating data that shows association between certain genotypes and disease predisposition or drug response-Opportunities for research to improve healthcare, design better drugs, and decrease risk in drug development-Improving biomarker validation-Drugs designed by developing countries for their own populations may also be beneficial for minority groups in developed countries, fostering north-to-south collaboration	<ul style="list-style-type: none">-Shortage of trained professionals who can work in R&D in pharmacogenomics and who can interpret the results in clinical settings

* The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is an international treaty that sets minimum standards for intellectual property rights and their enforcement which apply to all member countries of the World Trade Organization (see http://www.wto.org/english/docs_e/legal_e/legal_e.htm#TRIPs)

The challenge in using geographical ancestry as a useful variable in genomic variation research lies in determining how to define group categories. Grouping subjects according to their outward physical differences, such as skin colour, is problematic.^{21,22} As rates of migration and admixture increase, ethnic categories are becoming less accurate as a proxies for genetic variants.²³ Although many still doubt the validity, if not the accuracy, of self-reported ethnicity in biomedical research, a recent study demonstrated that self-reported ethnicity can provide a

BOX 1. Cassidy versus SmithKline Beecham: Filed in December 1999 in Pennsylvania, this class action suit was the first of many in which claimants alleged SmithKline Beecham (now GlaxoSmithKline) failed to warn both doctors and the public of the risks associated with their LYMERix vaccine.^{13,14} The vaccine was based upon the Osp A surface protein of *Borrelia burgdorferi*, the causative agent of lyme disease.¹⁵ As of the early 1990s, there was speculation that, in individuals positive for the Histocompatibility Antigen DR4 biomarker (roughly one third of the general population), the vaccine may trigger autoimmune arthritis.^{13,15} Thus, claimants argued that the manufacturer had a duty to warn genetically susceptible patients and as such, should have provided the genetic screening tests required to determine genetic susceptibility.¹³⁻¹⁵

In response to these adverse event reports, the Food & Drug Administration and the Centre for Disease Control conducted a follow-up study analyzing both adverse reactions reported during the clinical trial and those reported post approval. However, they found no statistical evidence of a causal link between LYMERix and autoimmune disease.¹⁶ Nevertheless, in February 2002, amidst increasing pressure, SmithKline Beecham withdrew LYMERix from the market in response to poor sales.^{14,15}

Currently, Baxter Vaccines, in Vienna, is developing a new vaccine for lyme disease based on the same Osp A surface protein. However, the protein region believed to be responsible for inducing autoimmunity has been omitted.¹⁵

Box 2. BiDil® (hydralazine and isosorbide dinitrate; NitroMed Inc.), a drug to treat heart-failure in African-Americans, is the first drug approved by the FDA for a specific sub-population. A previous attempt to patent this fixed combination of drugs was rejected by the FDA, as the initial study in a mixed population showed no demonstrable benefit. A retrospective analysis of the data from this study showed increased efficacy in African-American cohorts resulting in a second clinical trial testing its use in a population of self-identified African-Americans. This subsequent study was halted early for ethical reasons when there was a significant reduction in mortality rate (43%) in those treated with the combination therapy as opposed to the placebo group.³⁵ Currently, NitroMed is struggling to increase sales in the face of controversy over BiDil. However, BiDil illustrates the potential of pharmacogenomics for different ethnic groups. Although the genetic basis for this difference is still unknown, studies addressing this question are underway. While controversial, BiDil® could be of interest to Africans who share their geographical ancestry with African-Americans.*

Box 3. Losartan® is an anti-hypertensive drug that is metabolized by the enzyme CYP2C9. A defective variant of this enzyme (CYP2C9*5) has been associated with poor response to the drug and is restricted to sub-Saharan Africans and their descendants. The health implications for sub-Saharan Africans who are treated with Losartan® and have this variant would have remained unknown if studies had only been carried out on populations with European geographic ancestry.²³*

reasonable measure of genetic classification.²⁴ In addition, there is striking evidence of an association between ethnicity and variable drug response. At least 29 different drugs have been reported in the literature as eliciting different drug responses between ethnic groups.²⁵ Notable examples of these drugs include warfarin, BiDil® (Box 2) and Losartan® (Box 3). One future challenge will be validating and standardizing frequencies of causal genetic variants in these different populations, since values vary.²⁶⁻²⁸

Risks of Using Ethnicity as a Proxy Need to Be Mitigated

The practical benefits of using ethnic categories in research must be weighed against the potential risks to society. The purpose of pharmacogenomics is to stratify a population into smaller genetically homogeneous subpopulations characterized by their different responses to particular drugs. The consequences of this segmentation are unclear for ethnic groups.²⁹ Some groups might receive unequal access to treatment, since drugs would not be targeted towards them because companies may not view them as large and/or profitable markets.²⁵ Moreover, as Foster states, “pharmacogenomics might increase the social significance of differential drug response between ethnic groups, potentially leading to reification of health disparities”.³⁰ On the other hand, without pharmacogenomics, drug companies may abandon drugs that actually benefit the majority of the population but have serious adverse effects in a small group. If frequencies of alleles vary across ethnic groups, then the groups included in clinical research will be most likely to benefit from pharmacogenomics.³¹ As mentioned in the introduction, inattention to ethnicity in clinical research means most clinical trials were conducted on white males, and the weight-adjusted results have been applied to minorities, women, and children. However, this extrapolation is inaccurate and groups excluded from trials are disadvantaged

*From Daar, Dabu and Seguin’s contribution to the technical section of the WHO report, “The Ethical, Legal, and Social Considerations for Pharmacogenomics in the Developing World” (upcoming).

because they receive less effective treatment.³² Furthermore, there is an ethical imperative to broaden the scope of clinical research to include a variety of ethnic groups. Developing countries are repositories of human genetic diversity that can help to define patient subgroups for pharmacogenomics, and this diversity needs to be explored. Specifically, developing countries could benefit from such exploration in the following ways:²

- Pharmaceutical companies in the developing world could license drugs previously withdrawn from the market and develop them both for local populations and for others in the developing world who are either not genetically predisposed to the adverse effects or for whom efficacy can be demonstrated to a greater extent. For example, IressaTM, a drug meant for lung cancer treatment, was found to have low efficacy in the US but appears to significantly improve overall survival in Japanese patients³³ and is now available in several countries around the world, including the US, Canada, Japan and Australia
- Pharmaceutical companies in developing countries could capitalize on emerging trends in genotyping and their application to understanding variable drug responses and disease susceptibility. Theoretically they could do this by developing drugs specifically for sub-populations that are more likely to benefit without side effects.
- Compounds discovered in the laboratories of developing countries could be of interest to pharmaceutical companies in the developed world if they are relevant to selected minority subpopulations living in developed countries, leading to potentially beneficial partnerships.

In the short term, the use of pharmacogenomics will be most valuable in guiding the use of existing medicines. Pharmacogenomics may help bring back to market previously withdrawn drugs by identifying populations that can benefit from these drugs and are not susceptible to the adverse effects responsible for their original withdrawal (referred to as “drug resuscitation”). While the social implications of the use of ethnicity in pharmacogenomics are debatable, further research in the field should inform the way subpopulations are characterized. This will ultimately contribute to a mature understanding of human diversity and render race, as a useful concept, obsolete.³⁴

Implementing Pharmacogenomics Is Feasible for the Developing World

Infrastructure for a Pharmacogenomic Platform Needs to Be Developed

In order to realize the benefits of pharmacogenomics, developing countries will need to surmount certain obstacles.^{4,5} Although developing countries vary with regard to their resources and scientific capacity, in general, there is hesitance on the part of developing countries to adopt pharmacogenomics at the expense of more popular public health initiatives that address social and environmental causes of disease. If we deconstruct this hesitance we find that the challenges facing implementation of pharmacogenomics in the developing world relate to a shortage of human resources and to cost. The former may be due to an absence of training facilities, brain drain,^{36,37} or high morbidity and mortality as a result of disease epidemics, as is the case in Africa, where a significant number professionals such as nurses, doctors and pharmacists have died from HIV/AIDS. The additional costs associated with the uptake of pharmacogenomics, from training personnel to buying equipment, represent another barrier. Nevertheless, some developing countries are embarking on SNP projects, drug development initiatives, and other research closely related to pharmacogenomics (Table 2). The impact of the Human Genome Project will vary, since countries differ with regard to burden of disease, financial resources, education, scientific and technological capacity, and health systems.³⁸ Least developed countries, such as those in sub-Saharan Africa, need to be distinguished from developing countries that have a high capacity for science and technology (S&T), such as India, China, Mexico and Brazil.³⁹ As Table 2 illustrates, countries in the latter group are already conducting genomics research on their own. Although the least developed countries face many more challenges, they may be the ones that need pharmacogenomics the most.

Box 4. The government of India supports human genomic variation research.

India is one country which has already started conducting genotyping studies. The Indian Genome Variation consortium consists of six laboratories of the Council of Scientific and Industrial Research (CSIR) that will conduct research to provide data on validated SNPs or repeats and gene duplications in over one thousand genes. Genes relevant to pharmacogenomics and disease etiology are the focus. The project, which started in 2003, has received tenure for five years from the Government of India, which supports pharmacogenomics and encourages research that can improve the health of the Indian population.⁴³ The Department of Biotechnology has issued guidelines on pharmacogenomics research on its web-site in response to increasing numbers of research proposals from scientists. These guidelines stress that studies in India should have national relevance. The Central Drugs Standard Control Organization (CDSCO), in its *Guidelines for Bioavailability and Bioequivalence Studies*, suggests that genotyping should be considered for exploratory bioavailability studies, crossover studies, and all studies using parallel group design. It also encourages studies performed on subjects known to have a major genetic polymorphism relevant to drug response. Again, the guidelines state that pharmacogenomic issues should be considered in the context of the Indian population.

Box 5. Mexico is characterizing its genomic variation and developing a platform for genomic medicine.

The National Institute of Genomic Medicine (INMEGEN) of Mexico, created by the Mexican Congress, is currently sampling regions in Mexico in order to understand the genetic structure of the population. The Mexican government has made genomic medicine a priority, because new strategies are needed to meet long-term healthcare costs in Mexico. INMEGEN aims to uncover disease-related genetic variation and generate products that will benefit the Mexican population, so that Mexico does not have to import applications developed for other populations. The project is expected to contribute to economic growth and ease the financial burden of healthcare.⁴¹

While governments of some developing nations (Boxes 4 and 5) are creating their own institutions for genomics research, collaborating with industrialized countries is a strategy developing countries can take to reduce start-up costs. Countries from the developing and developed world are forming partnerships based on common interests. While infectious disease epidemics continue to ravage developing nations, the rates of noncommunicable disease are also spiraling upwards. Currently, one third of all deaths in the world are caused by cardiovascular diseases. Of these deaths, nearly 80% occur in developing nations. By 2020, the number of new cancer cases will increase a staggering 73% in developing countries as opposed to only 29% in developed countries.⁴⁴ One example of collaboration between industrialized and developing nations, in order to address this global problem, is a partnership between the Organization for Nucleotide Sequencing and Analysis (ONSA) in Brazil and the Ludwig Institute in Switzerland, which is contributing half of the cost of sequencing human cancer-related genes.⁴⁰

Industrialized countries are also interested in communicable diseases that are devastating populations in the developing world. Public-private partnerships, such as the Medicines for Malaria Venture, have formed to discover other treatments for diseases prevalent in the developing world.² In addition to public-private partnerships, there is an increasing trend for

Table 2. Initiatives in the developing world aimed at characterizing population-based genetic differences*

Initiative	Description
National Institute of Genomic Medicine (INMEGEN), Mexico	INMEGEN is one of twelve National Institutes of Health in Mexico. Created in 2004, it aims to develop a national platform in genomic medicine focused on national health problems and based on the genomic structure of Mexican populations. Most of Mexico’s modern population is considered Mestizo resulting from a dynamic admixture of over 65 ethnic groups, Spaniards and, to a lesser extent, Africans, within the last 500 years. INMEGEN is genotyping 600 Mestizos from different regions of Mexico, analyzing 500,000 to 600,000 Single Nucleotide Polymorphisms (SNPs). This information is triggering a series of disease-related genomic studies in Mexico that will be used to improve healthcare for the Mexican population, and is likely to be useful to other countries in Latin America where the Mestizo admixture is the origin of most of their populations. Investigators expect to complete the study in 2007. ^{40,41} http://www.inmegen.gob.mx
HUGO Pan-Asian SNP Initiative	The HUGO Pacific Pan-Asian SNP Initiative is composed of a coalition of scientists from China, India, Indonesia, Japan, Korea, Malaysia, Nepal, Philippines, Singapore, Thailand and Taiwan. The researchers will look at 50,000 SNPs in each study participant. The goal of this initiative is to uncover both the breadth of genetic diversity and the extent of genetic similarity in Asia. ⁴²
The Indian Genome Variation Consortium	This network program was initiated by the Council of Scientific and Industrial Research (CSIR) and is funded by the Government of India. The Indian Genome Variation Consortium aims to create a database of genetic variants inherent to the people of India and make it available to researchers for understanding disease predisposition, adverse drug reaction, population migration etc. Fifteen thousand unrelated individuals of different subpopulations will be sampled. ⁴³
Thailand SNP Discovery Project	This project is the result of a collaborative effort between the National Center for Genetic Engineering and Biotechnology (BIOTEC, Thailand) and Centre National de Genotypage (CNG, France). The aim of the project is to identify intragenic SNPs frequent in Thai populations. A SNP database will be completed of all the genes identified in the entire human genome and their regulatory regions with allele frequency and linkage disequilibrium (LD) block patterns in Thai and other (French, Japanese and African) populations. http://thaisnp.biotec.or.th:8080/thaisnp
University of Cape Town’s Division of Human Genetics/ The Africa Genome Education Institute (South Africa)	The Africa Genome Education Institute is devoted to educating the public about the structure and function of genomes as well as studying the genetic basis of diseases relevant to the South African population. http://web.uct.ac.za/depts/genetics

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Table 2. Continued

Initiative	Description
REFARGEN	Rede Nacional de Farmacogenetica/farmacogenomica (REFARGEN) or the Brazilian National Pharmacogenetics/Pharmacogenomics network is a network of Brazilian researchers from various institutions situated in five regions of the country. It aims to create a repository of biological samples for pharmacogenomic studies and archive pharmacogenomic data for the Brazilian population. A significant focus is on its large, admixed population. ²² http://www.refargen.org.br
The Pharmacogenetics for Every Nation Initiative (PGENI)	Based out of the University of North Carolina, PGENI is an interdisciplinary group of collaborators who aim to promote the integration of genetic information into drug formulary decision-making. PGENI will work with developing country partners to sample the population, publicize global genotype profiles, and provide the Ministry of Health department with recommendations. Initially, PGENI is partnering with 108 countries that have moderate to good health system infrastructure, representing 78% of the global population. ¹ http://pgeni.unc.edu

*From Daar, Dabu and Seguin’s contribution to the technical section of the WHO report, “The Ethical, Legal, and Social Considerations for Pharmacogenomics in the Developing World” (upcoming).

pharmaceutical companies to contract research and clinical trials to developing countries, which may also help build scientific capacity and reduce implementation costs.² Collaborations such as these indicate that pharmacogenomics is also relevant for lesser developed nations that may not be able to conduct genomics research independently on a national scale. As developing countries undertake their own projects and build up infrastructure, they will build up their own capacity in genomic medicine.

Market Segmentation May Lead to Niche Markets

One concern is that pharmacogenomics will lead to market segmentation and result in unaffordable therapeutics with limited accessibility in the developing world. However, this may not necessarily be true; pharmacogenomics research may also create new niche markets and boost the private sector in developing countries. Pharmacogenomics research is expected to uncover between 5000 to 10 000 new drug targets, compared to about 500 molecular targets used currently.⁴⁵ These new drug targets could lead to the development of new therapies. Nunnally et al conclude that pharmacogenomics will bifurcate the pharmaceutical industry so that large companies continue to produce blockbuster drugs indicated for high percentages of people, but only for people with common genetic variants underlying their disease or drug response, and this narrower focus will result in fewer failed drugs.⁴⁶ These smaller markets would create opportunities for companies in developing countries that are just starting to make significant gains on the global market and if they retain control over intellectual property they will also be able to control pricing in their local markets.² If such ventures were applied in developing countries, then business areas that would grow as a result of the use of pharmacogenomics would include bioinformatics, diagnostics, testing services, and medical management. This industrial growth would, in turn, create jobs that require trained individuals thereby strengthening local economies.¹²

Developing Countries Can Least Afford to Waste Limited Health Resources on Ineffective Therapy*

Governments in developing countries are interested in the potential of the pharmacogenomics approach to reduce overall healthcare costs. According to the Director of Mexico's national institute of Genomic Medicine, "New strategies for prevention, early diagnosis, and more effective treatment are essential to meet the mid- and long-term healthcare costs in Mexico".⁴¹ Preliminary studies of the cost-effectiveness of genotyping to guide dosing of some drugs are crucial to understanding how best to use pharmacogenomics. Marra et al found that pretesting for thiopurine-S methyltransferase (TPMT) status to guide azathioprine dosing resulted in some direct reduction in costs.⁴⁷ Another study found that prospective genotyping for the HLAB*5701 allele associated with abacavir hypersensitivity is cost-effective in HIV patients as compared to the costs associated with hospitalization due to occurrence of this adverse event.⁴⁸ Finally, You et al. estimated that the cost of a major bleeding event associated with warfarin sensitivity (~\$6000 US) could be averted with prospective CYP2C9 genotyping based on a simulated decision tree over a twelve month period.⁴⁹ These types of cost-saving measures are an important incentive to developing countries, especially those with very small health budgets; some sub-Saharan African countries have annual per capita healthcare expenditures that can be as low as 10-15 \$US. However drug development is influenced by over-arching regulatory frameworks. Although niche-market companies of all sizes should have more manageable regulatory functions compared to companies following the blockbuster approach, the context in which they operate is crucial for their success and the impact of regulation and intellectual property protection should be considered.⁵⁰

Regulatory Frameworks and Intellectual Property Protection Play a Role

Although intellectual property (IP) protection and regulatory frameworks will impact the implementation of pharmacogenomics in developing countries, these issues are complex and a comprehensive discussion of them is beyond the scope of this chapter. While one concern is that the price of pharmacogenomics drugs might increase as a consequence of market segmentation, the implementation of pharmacogenomics could also widen the gap between rich and poor by encouraging researchers in developing countries who are conducting human genomic variation studies to patent their findings and adversely affect access to patented products. As discussed in the 2005 WHO report on "Genetics, genomics and the patenting of DNA" patents can influence access to genomics products by "improving incentives to develop useful tests; increasing the cost of available services; imposing transaction costs and inconvenience on research and development; impeding the transfer of existing tools and technologies".⁴⁰ However, patenting itself may not lead to expensive therapeutics or increases in health inequities, because the licensing practice adopted, rather than the patenting itself, will influence its effect. For example, following the SARS outbreak in 2002, a series of laboratories around the world sequenced the genome of this virus. As a result, many patents on the genomic sequence of SARS were filed. In an attempt to ensure that social benefits accrue from them, these patent rights may be placed into a pool to be licensed on a nonexclusive basis.⁵¹

Alternatively, earning fees or royalties on patents on an exclusive basis can be seen as an incentive for investing in research and development (R&D) in developing countries. For example, patents can provide opportunities for out-licensing to firms that exist in more profitable markets, thus leading to financial gain via fees or royalties which can be reinvested by the patent holder. In addition, patents can be traded in exchange for other technologies or services.⁴⁰ Patenting may also facilitate collaboration between the developed and the developing

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world, since industrialized countries are more willing to transfer technology when they know it will be protected. In fact, technology transfer has often been accompanied by forced reforms designed to strengthen domestic patent protection.⁵² Also, patents for drugs withdrawn from the market may have expired, or be near expiry, thus presenting opportunities for biotechnology and pharmaceutical companies in developing countries to license these compounds and target local populations or other markets in the developing world.² Ultimately, developing countries need to strengthen intellectual property protection to take their place in a knowledge-based economy. If they build S & T capacity and retain IP rights for their own research, they will have more control over prices downstream for the products they develop, and can ensure that their citizens have access to these products. For example, INMEGEN has partnered with the Mexican Institute of Industrial Property (IMPI) to ensure control over their innovations and ensure that their products will be accessible to Mexicans.

Strengthening IP protection at a national level may not be easy, but the international community is driving a trend towards increasing intellectual property rights (IPR) capacity by requiring developing nations to comply with the Agreement on Trade-Related Aspects of Intellectual Property Rights. TRIPS offers mechanisms to use patents that would be generated from pharmacogenomics research strategically to reduce costs and control drug prices. For example, TRIPS allows researchers in developing countries to use patented products freely for research purposes without infringing the patent. TRIPS also provides an option for compulsory licensing so that governments in developing countries may authorize the use of a patented product without the patent holders' consent. Further research into how developing countries can benefit from these mechanisms, in the field of pharmacogenomics specifically, is necessary to determine how intellectual property protection and regulation can drive or hinder the implementation of pharmacogenomics in the developing world.

Conclusion

As human genomic variation projects in the developing world emerge and grow, careful examination of ethical, social and cultural issues is necessary to guide policy and maximize success of future initiatives in genomic medicine that these countries undertake. We have reviewed the difficulties attendant to the use of race and ethnicity, and explored how economic barriers such as implementation costs and market segmentation may be overcome or transmuted into opportunities. Developing countries have compelling reasons to harness pharmacogenomics to improve the health of their populations. In the global movement to increase access to essential medicines in the developing world, genomics is a useful tool to help determine which medicines are essential for a given country. In particular, a model which focuses on using geographical ancestry as a tool to understand drug response and disease susceptibility offers an opportunity for developing countries to meet their local health needs without depending on knowledge derived in industrialized countries. Pharmacogenomics can generate substantial cost-savings in drug development, reduce healthcare costs, stimulate the private sector, and uncover genetic diversity relevant to drug response or disease predisposition. How they choose to integrate pharmacogenomics into their healthcare systems will depend on their domestic health needs, and different strategies may arise from these efforts. To our knowledge, there are no empirical studies that have looked at exactly how the emerging knowledge of human genomic variation can be practically applied to improving the health of people in the developing world. We are currently conducting a case study of the Mexican National Institute of Genomic Medicine (INMEGEN) and are planning studies of the other four large-scale genomic variation research projects in India, Thailand, South Africa, and Asia. The purpose of our research is to understand the factors driving the adoption of genomic medicine in developing countries and to help create conceptual frameworks for the integration of pharmacogenomics into the health sector in the developing world. Comparing experiences and facilitating cross communication among these developing world programs would be useful in this regard. We hope that our research will produce specific policy recommendations that will assist these countries as they spearhead the adoption of pharmacogenomics to improve global health.

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