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Opinion Paper

Relevance of pharmacogenomics for developing countries in Europe

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Abstract

Pharmacogenomics holds promise of personalized treatment for patients suffering from many common diseases, particularly those with multiple treatment modalities. Owing to recent advances in the deciphering of the human genome sequence, high throughput genotyping technology has led to the reduction of the overall costs of genetic testing and allowed the inclusion of genotype-related dosing recommendations into drug package inserts, hence enabling the integration of pharmacogenomics into clinical practice. Although pharmacogenomics gradually assumes an important part in routine clinical practice in developed countries, many countries, particularly from the developing world, still do not have access either to the knowledge or the resources to individualize drug therapy. The PharmacoGenetics for Every Nation Initiative (PGENI) aims to fill this gap, by making pharmacogenomics globally applicable, not only by defining population-specific pharmacogenomic marker frequency profiles but also by formulating country-specific recommendations for drug efficacy and safety. This article aims to highlight the PGENI activities in Europe in an effort to make pharmacogenomics readily applicable in the European healthcare systems, particularly those in developing countries.

Keywords: allele frequencies; developing countries; marker; pharmacogenomics; single nucleotide polymorphisms.

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Introduction

Availability of drugs in countries around the world is overseen by national health authorities, often in conjunction with recommendations issued by regional agencies, such as the European Medicines Agency (http://www.ema.europa.eu) or international authorities, such as the World Health Organization (http://www.who.int). In 1977, the WHO established the essential medicines list (EML; http://www.who.int/medicines/services/essmedicines_def/en/index.html) in an effort to provide a list of safe, effective, and cost-effective therapies for the treatment of diseases worldwide, taking into consideration criteria, such as drug quality, efficacy and safety, and total cost of the therapeutic intervention. This list is employed by the Drug Regulatory Agencies of each country to establish a list of drugs for use by the respective population.

However, there are often bottlenecks when attempting to establish such drug lists in various countries. In most cases, drug safety, efficacy, and dosing information is based on White European-based studies that involve subjects from, e.g., the US, Canada or Europe and hence very little is known on how these drugs will function in other populations worldwide. Instead, there is often anecdotal evidence on drug efficacy and toxicity in these populations (1).

The genomic revolution holds promise to lead to better diagnosis of disease and selection of therapy (1, 2). To date, significant amounts of data exist for DNA variations that are predictive for risk of toxicity or lack of effectiveness for commonly used medications. Hence, pharmacogenomics can enhance the assessment of drug efficacy and safety to the current systematic process for rational use of medicines and may play a significant role in the evaluation of the overall cost-benefit for competing therapies (3). Consequently, genome-guided therapy is gradually being introduced in Western countries to a greater or lesser extent and several national pharmacogenomic networks are being formed, e.g., the UK Pharmacogenetic and Stratified Medicine Network. Similarly, genomic information may be equally useful to other countries around the world to offer a way to better integrate medications into national formularies in a safe and effective manner.

However, despite much research over the past decade, the clinical application of pharmacogenomics is still lagging behind for the majority of the underdeveloped and developing world. Many consider genetic testing and pharmacogenomics as luxury items in countries where the supply of electricity and fresh water is not guaranteed and modern healthcare infrastructure is missing, but this does not imply that the

application of genetics is not useful for the developing world to stratify public healthcare decisions.

This article aims to outline the efforts to implement pharmacogenomics in developing countries in Europe and the various obstacles that should be overcome to reach the maximum benefit in national healthcare systems.

Pharmacogenomics for developing countries

The PharmacoGenetics for Every Nation Initiative (PGENI; http://www.pgeni.org) aims to incorporate pharmacogenomics into the national formulary decision-making process for medication selection in developing countries, providing improved rational drug selection (2, 3). The PGENI aims to: (i) promote the integration of genetic information into the public health decision-making process, (ii) enhance the understanding of pharmacogenomics in the developing world, (iii) provide guidelines for medication prioritization for individual countries using pharmacogenetic information, and (iv) help build infrastructure for future pharmacogenetic research studies (2, 3).

There are several examples of drugs whose efficacy and/or toxicity is correlated with genomic variants, for which the relevant pharmacogenomic information is available in different sections in the drug label (Table 1; for a complete list of pharmacogenomic biomarkers in drug labels, please visit http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). HLA-B*5701 screening is highly recommended prior to treatment with Abacavir to prevent drug-related hypersensitivity reaction. This marker has variable allele frequency worldwide, from <1% in sub-Saharan Africa to up to 20% in India, whereas in European populations HLA-B*5701 frequency varies between 1% and 7% (4). The same is true for the allele frequency of many other pharmacogenomic markers, currently being documented in dedicated repositories, such as the Frequency of Inherited Disorders database (FINDbase; http://www.findbase.org) (5, 6). The study plan includes screening for the most common pharmacogenomic markers in 50–500 healthy volunteers from various populations and ethnic groups worldwide and the formulation of recommendations for genome-based prioritization of medication selection. Targeted countries are characterized by moderate to good healthcare system infrastructure, which is nevertheless insufficient to integrate individual patient genotyping into routine clinical practice. Pharmacogenomic markers include variants in CYP450 enzymes (e.g., CYP2D6, CYP2C9, CYP2C19, CYP4F2, etc.), Phase II enzymes (e.g., NAT1, NAT2, DPYD, UGT1A1, etc.), drug transporters (e.g., MDR1, ABCC1, SLCO1A1, etc.), transcription regulators, and other enzymes that have been shown to be relevant to drug metabolism (e.g., RXRA, AHR, PPARD, PPARG, etc.) (7). PGENI populations span 104 countries, coordinated by the Institute of Pharmacogenomics and Individualized Therapy of the University of North Carolina (Chapel Hill, NC, USA) and eight Regional Centers in the Americas (Mexico, Brazil), Africa (Ghana, South Africa), Asia (China, Jordan, India), and Europe (Greece). These entities are established Centers of Excellence to promote pharmacogenomics education from the ground up, integrating into healthcare worker education and serving as a resource to the respective Ministries of Health (8). Also, these regional centers will be responsible to advance the research capabilities in developing nations with regional experts, so that the necessary research infrastructure for advancing pharmacogenomics research in these populations is efficiently built. Ultimately, the population- and ethnic group-specific pharmacogenomic marker allele frequency information will assist the development of country- and population-specific national recommendations for various therapeutic modalities (8).

Table 1 Examples of the most common drugs for which a pharmacogenomic test is recommended (approved by the US Food and Drug Administration; http://www.fda.gov).

Drug	Gene	Package insert information	Approved device
Imatinib	bcr/abl or 9:22 translocation	Y	N
Trastuzumab	HER2-neu	Y	N
Imatinib	C-kit	Y	Y
Mercaptopurine, Azathioprine	*TPMT*	Y	N
Irinotecan	*UGT1A1*	Y	Y
Warfarin	*CYP2C9*, *VKORC1*	Y	Y
Carbamazepine	HLA-B*1502	Y	N
Abacavir	HLA-B*5701	Y	N
Clopidogrel	*CYP2C19*	Y	Y
5-HT3 receptor antagonists	*CYP2D6*	Y	Y
Antidepressants	*CYP2D6*	Y	Y
ADHD drugs	*CYP2D6*	Y	Y
Codeine derivatives	*CYP2D6*	Y	Y
Tamoxifen	*CYP2D6*	Y	Y

For a complete list, please visit http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). Y, yes; N, no.

Pharmacogenomics in Europe: challenges and pitfalls

Contrary to the US, Europe has some unique features that influence the integration of pharmacogenomics in the healthcare systems of the various European countries (9). First, not all European countries are European Union member states, indicating that they are not subject to European Union (EU) guidelines and recommendations, e.g., European Medicines Agency directives. Second, even among the 27 EU member states, the implementation of the various EU guidelines, particularly related to healthcare and education, is not uniform and relies on their adoption of the local governments. Third, even though certain countries belong to the EU, they are likely to resemble more (e.g., culturally, religiously) with others that are non-EU member states. Finally, contrary to the initial planning, the Eurozone member states differ substantially in

Table 2 The PGENI-related activities of the Golden Helix Institute of Biomedical Research.

1. Recruitment of healthy volunteers from various developing European countries that participate in the PGENI project.
2. Organization of education activities in the PGENI European countries to disseminate information pertaining to pharmacogenomics to achieve knowledge transfer to society.
3. Documentation of the pharmacogenomic markers allele frequencies in the FINDbase database.
4. Surveying the pharmacogenomic environment in PGENI European countries.
5. Establishment of guidelines and recommendations for integrating pharmacogenomics in healthcare systems of developing countries.

fiscal terms, which directly impacts available healthcare and national insurance spending. These facts make the implementation of pharmacogenomics in developing European countries an even more challenging task.

The European Regional center of the PGENI initiative is the Golden Helix Institute of Biomedical Research (http://www.goldenhelix.org), an international non-profit scientific organization with interdisciplinary research and educational activities in the field of genome medicine. The PGENI-related activities of the Golden Helix Institute of Biomedical Research (summarized in Table 2) are:

- Recruitment of healthy volunteers from various developing European countries that participate in the PGENI project. So far, DNA samples from Malta, Serbia, Greece, and Poland have been processed and are currently being analyzed, whereas other countries, such as Slovenia, Turkey, Czech Republic and Georgia, have lined up and will start soon.
- Organization of education activities in the PGENI European countries to disseminate information pertaining to pharmacogenomics to achieve knowledge transfer to society. These educational activities, known as the Golden Helix Pharmacogenomics days (http://www.goldenhelixsymposia.org), are organized in major cities with large academic hospitals, aiming to provide timely updates on the field of pharmacogenomics and personalized medicine to the local biomedical scientists and healthcare providers, to inform them on the application of pharmacogenomics in various areas of medical practice, and to network faculty members from universities and research institutes from the local scientific arena working in the field of pharmacogenomics to initiate collaborative projects in this field to the benefit of society. Such educational events are likely to be expanded soon to other countries outside Europe as one of the main PGENI educational activities.
- Documentation of the pharmacogenomic markers allele frequencies in the FINDbase database (http://www.findbase.org) (5, 6), as part of the Golden Helix Server, where a number of National/Ethnic Genetic databases that record the incidence of genetic diseases and the corresponding mutation spectrum in various populations and ethnic groups are developed and hosted. As part of the effort to incentivize genomic variation data submission, the microattribution approach is currently being tested to provide credit to unpublished pharmacogenomic marker allele frequency data submitters (9), to expand the existing data collection in this publicly available structured repository.
- Surveying the pharmacogenomic environment in PGENI European countries, particularly pertaining to genetic laboratories, the general public, and healthcare professionals. Such efforts in Greece have already revealed both opportunities and weaknesses (10, 11), such as the poorly regulated direct-to-consumer (pharmaco)genomic testing (12). These findings need to be exploited to their full extent by all interested parties and policy makers to enhance the impact of pharmacogenomics in public health.
- Establishment of guidelines and recommendations for integrating pharmacogenomics in the healthcare systems of developing countries (Table 3). These guidelines for medication prioritization will emerge as valuable tools for integrating genetic information into the public health decision-making process, usually at the National Health Authority/Ministry of Health level. Given that genome-based medication prioritization can contribute towards the reduction of the National Healthcare spending, by rationalizing medical treatment and reducing hospitalization due to the various adverse drug reactions, this need is more than ever urgent, particularly in EU countries who have a vast fiscal deficit, such as Greece, Ireland, and Portugal. In Germany, adverse drug reactions cause the death, hospitalization, or serious injury of over 2 million people each year, of which up to 30% of cases are preventable. Direct treatment costs of adverse drug reaction in internal medicine total € 434 million annually; base models including all medical specialties have extrapolated this figure to be upwards of € 816 million. Using a more conservative

Table 3 Proposed recommendations for integrating pharmacogenomics in healthcare systems of developing countries.

1. Establish national networks of clinicians and researchers involved in pharmacogenomics in developing countries.
2. Encourage communication and research interactions with healthcare systems and pharmacogenomics networks in developed countries.
3. Create international networks between (closely related) developing countries to enhance communication, interaction, pursue funding, and initiate joint research projects.
4. Develop a framework to catalyze knowledge transfer between the regional center, national healthcare authorities, and international agencies.
5. Ensure that all legal, ethical, social, and religious issues are thoroughly addressed.

preventability estimate of 20%, this would amount to approximately €163 million in savings for the German health insurance funds on an annual basis (13, 14).

These activities contribute to the generation of new knowledge and its dissemination to the various stakeholders, which address, in part or fully, several of the issues that are currently considered as hurdles that hold this field back, such as healthcare costs, education of healthcare professionals, proper regulation of (pharmaco)genomic tests, data collection, storage, and retrieval (15).

Conclusions

As more pharmacogenomic information becomes available from data collection and analysis from the PGENI countries in Europe, this will not only enable integration of pharmacogenomics in healthcare decision-making at the country level but will also support new research initiatives in areas with low research potential. Also, targeted educational efforts will also prepare the Ministry of Health staff from participating countries to better integrate genetic information into many areas of healthcare, including disease management and therapeutic interventions.

Overall, individualization of therapy for each patient is the ultimate goal, providing the rationale for implementing pharmacogenomics in healthcare provision in developing countries in Europe and worldwide.

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