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PERSPECTIVE

# Pharmacogenetics in developing countries and low resource environments

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## Abstract

While significant advances have been made in pharmacogenetics (PGx), especially in countries with developed economies, this field remains at its infancy in developing countries and low resource environments. Herein, we provide insights into the gap and challenges of PGx at the research and clinical fronts, and some perspectives to bridge the gap and move forward with PGx in the developing world. We show that developing countries fall behind in PGx research, evidenced by a lower number of researchers, citations, and research output. In addition, the implementation of PGx in the clinic has been progressing at a much slower pace than research, and more so in developing countries. To bridge this gap, we recommend fostering regional and multinational collaborations to secure funds for high-throughput genotyping and local capacity building while preserving individual countries' identity, implementing next-generation sequencing, and organizing specialized training and exchange programs to move PGx research and clinical applications forward in developing countries.

## Introduction

Studying how genetic variations might influence the individual's response to treatment has always been of interest, it stretches as far back as 510 B.C. with the work of Pythagoras on the ingestion of fava beans. Since then, this research field has significantly evolved to become Pharmacogenetics (PGx), a discipline which ensures that every patient receives the right drug at the right time and at the right dose (Maronas et al. 2016). While significant advances have been made in PGx, especially in countries with developed economies, this field remains at its infancy in developing countries and low resource environments (Zgheib et al. 2020). Herein, we provide insights into the gap and challenges of PGx at the research and clinical fronts, and some perspectives to bridge the gap and move forward with PGx in the developing world.

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## Gap and challenges

### Research

Similar to other biomedical and genomic research areas, there is currently a significant gap between developed and less developed countries in PGx research. A search for "pharmacogenetics" or "pharmacogenomics" researchers on Google Scholar (2020) revealed the largest number of researchers from countries of very high human development index (HDI) ($N = 590$) when compared to countries of high (118), medium (81) and low (14) HDI (UNDP 2020). In addition, researchers from very high HDI countries were markedly more cited than their fellow researchers: 2547,627 citations vs. 90,475, 319,988, and 3290 for countries of very high, high, medium and low HDI, respectively. This trend remained after adjustment for population size (in millions) (UNDP 2020) with 83.97% of the scholars and 92.04% of their citations belonging to the very high HDI countries (Fig. 1a, b, and Sup. Table 1).

This discrepancy in the numbers of researchers translates into a similar discrepancy in research output. For instance, a PubMed search of original human subjects' research from January 1, 2000 till June 30, 2020 on the PGx of oral anticoagulants (OACs) revealed 373 publications, most of which emanated from countries of very high HDI ($N = 266$) compared to much lower numbers from countries

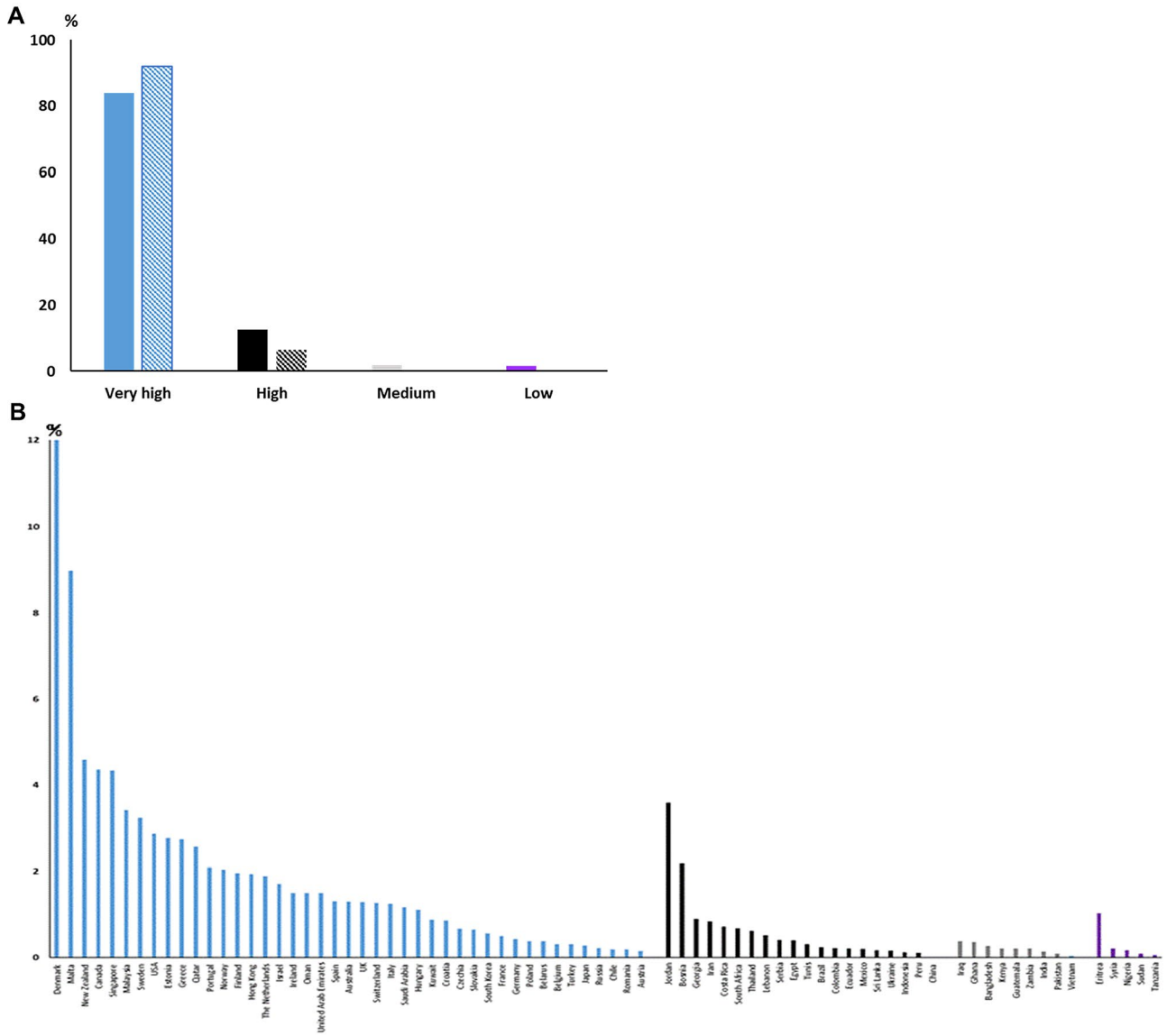


**Fig. 1** Total percentage per million of PGx scholars (full color fill) and citations of PGx scholars (pattern fill) (**a**) and percentage per million of PGx scholars by country (**b**). Data were compiled for "pharmacogenetics" or "pharmacogenomics" researchers on Google Scholar (Sup. Table 1) (https://scholar.google.com/ Accessed on July 6, 2020). Countries are classified based on the United Nations Development Program (UNDP) Human Development Index (HDI, and numbers are corrected for population size (in millions) (http://hdr.undp.org/en/countries)

of high ($N = 84$), medium ($N = 22$), and low (N = 1) HDI (Sup. Table 2). The trend remained after adjustment for population size (in millions), with 86.7% of the manuscripts belonging to very high HDI countries (Fig. 2a). This relatively low research output is not limited to OACs but rather to almost all other drugs (Bilani et al. 2017; Zgheib et al. 2020). Understandably, the main reason is most likely the little investment, support, and funding available for setting up ample infrastructure for systematic phenotype collection and genotyping (Abou Diwan et al. 2019). Accordingly, countries with very high HDI lead PGx research, while others lag behind. For example, and as seen in Fig. 2b, research on the PGx of OACs gradually started in 2000 in very high HDI countries. It peaked and plateaued around a decade later when the rest of the countries started picking up but never reaching numbers as high as developed countries.

Interestingly, while PGx on OACs has currently reached a saturation point in very high HDI countries, such research is still ongoing, and at the same initial rate, in other parts of the world. OACs are probably the most studied drugs in the Western world with a substantial number of original candidate gene evaluations followed by genome-wide association

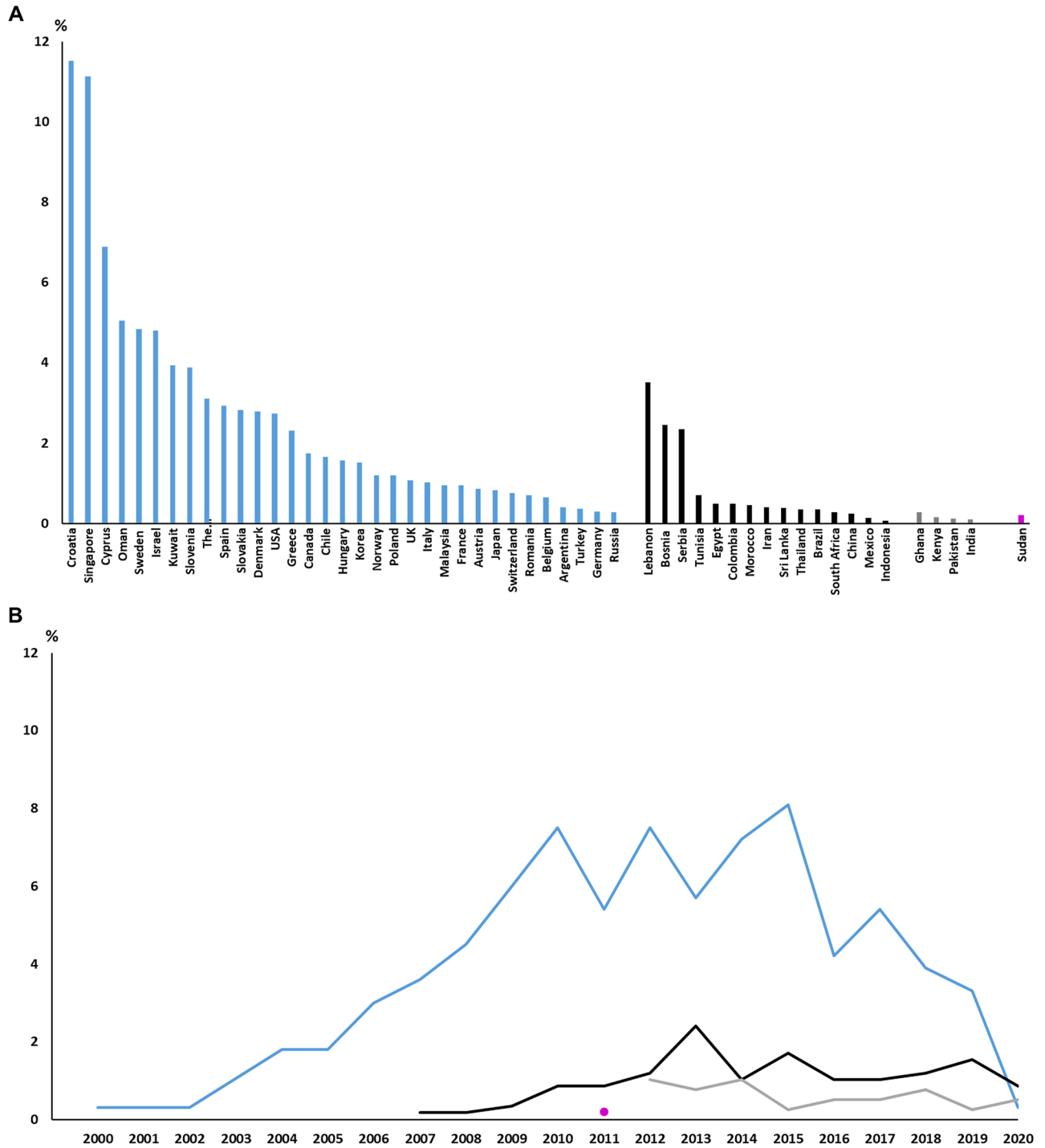


**Fig. 2** Percentage per million of research on the PGx of oral anticoagulants by country (**a**) and year of publication (**b**). Countries are classified based on the United Nations Development Program (UNDP) Human Development Index (HDI, and numbers are corrected for population size (in millions) (http://hdr.undp.org/en/countries): Blue: Very high HDI; Black: High HDI; Gray: Medium HDI; Pink: Low HDI. Data were compiled by a PubMed search of original human subjects' research from January 1, 2000 till June 30, 2020 on the PGx of oral anticoagulants (Sup. Table 2)

studies (GWAS) to unravel novel SNPs with a significant impact on metabolism and inter-individual variability in toxicity and response to these drugs (Cullell et al. 2018). Notably, most reported genetic variants are specific for populations of European ancestry. In addition, allele frequencies of PGx variants differ considerably between populations,

with considerable differences observed in different ethnic groups such as in African ancestry populations (Hernandez et al. 2020). Therefore, including developing countries in association studies will broaden the ancestral groups in whom PGx variation has been assessed. One additional pitfall of early randomized PGx studies on OACs is that the utilized algorithms were originally based on Caucasians' data and hence failed to predict outcomes in different populations and ethnicities such as African Americans (Hernandez et al. 2020). This observation dictates that every variant should be extensively replicated before being considered a universal PGx variant ready for implementation into clinical practice.

It is worthwhile noting that, at times, the need and, hence, focus of PGx research of countries with lower resources do not necessarily coincide with more developed countries. This fact is evident when comparing individual countries shown in Figs. 1b and 2a whereby several of the lesser developed countries, though perform PGx research, are not among the countries studying the PGx of OACs. This is probably most applicable to African countries that evaluate peculiar diseases and drugs such as antiviral and antituberculosis drugs (Zgheib and Patrinos 2020). In addition, some countries may have joined forces and resources to, as a start, evaluate and compare the frequency distribution of actionable pharmacogenes among different tribes and ethnic groups, while others attempt at discovering potentially novel PGx markers that are peculiar to their people (Zgheib and Patrinos 2020).

### Clinical implementation

Despite the plethora of PGx clinical guidelines and drug-label annotations covering more than 120 and 380 drugs, respectively (Whirl-Carrillo et al. 2012), it appears that the implementation of PGx in the clinic has been progressing at a much slower pace than research, and more so in developing countries. For example, in a recent international survey on the implementation and challenges of PGx in clinical practice, academic institutions from the U.S. and Canada reported offering almost all of the well-studied PGx tests, while not all other countries with very high HDI, and very few from countries with low, medium and high HDI do so (Abou Diwan et al. 2019). Universal challenges include test cost and reimbursement, insufficient knowledge, lack of interest, skepticism of health care providers and the community, unclear test interpretation, and a perceived lack of clinical guidelines or sufficient evidence for some PGx applications' clinical utility. The latter being especially relevant for the lesser developed countries since most of the data are from different populations. Notably, the most compelling evidence for PGx implementation is for older generic and inexpensive drugs such as warfarin, clopidogrel, thiopurines, irinotecan, abacavir, and carbamazepine, that are more likely to be used in low resource settings rather than newer versions for which PGx is likely less relevant. Thus implementation of PGx for these drugs are likely to have an even greater impact for patients in low resource countries than in high resource settings (Abou Diwan et al. 2019).

While most developed countries are presently busy figuring out and optimizing the integration of PGx tests within electronic medical records with decision support systems and evaluating the utility and potential benefit of preemptive PGx testing (Roden et al. 2018; Rugevics and Schumann 1987), less developed countries may be still at earlier stages of clinical PGx implementation. For instance, in that same survey, the topmost perceived challenges currently facing these countries include the lack of infrastructure, technology, workforce, and experts. Respondents also reported insufficient administrative and regulatory bodies coupled with a lack of legislative mandate or endorsement of PGx testing and suboptimal ethical regulations to protect private patient information (Abou Diwan et al. 2019).

## Bridging the gap

Despite the above-described lag in PGx research and clinical implementation in countries with low resources, there have been several efforts to bridge the gap.

### Multinational and regional collaborative initiatives

International and regional cooperation is a vital feature for the advancement of any scientific endeavor. Accordingly, there have been major multinational and regional collaborations aiming at local capacity building, securing funds, and performing high-throughput genotyping to improve PGx in low resource environments. See Zgheib et al. (2020) for a detailed description of some of these initiatives, many of which have already contributed to the PGx literature with multi-genetic data on much larger, multiethnic, and more representative populations. The institution of multidisciplinary consortia has also helped bridge the gap since they provide stronger evidence for the clinical utility of PGx variants in multiple different populations. A successful example is the International Warfarin (one of the most commonly prescribed OACs) Pharmacogenetics Consortium (IWPC) that comprises 21 research groups from 9 countries spanning 4 continents (International Warfarin Pharmacogenetics et al. 2009). Nevertheless, such consortia are rarely inclusive, with low resource countries being typically excluded. In addition, many of the resulting dosing algorithms do not necessarily perform equally well in different populations (Roper et al. 2010), making it difficult to implement Western clinical PGx guidelines into drug labels of countries from other

parts of the world. It is important to note that, with the demand for new cooperation forms in the fast-evolving global context of PGx research and innovation, and based on the "fast-second winner" strategy, one should contextualize an individual country's disease burden and public health priorities. One should also strategically streamline efforts while building on developed countries' achievements and know-how instead of repeatedly starting from scratch with a full investment of the whole PGx framework from gene discovery to clinical implementation (Mitropoulos et al. 2017).

### Next-generation sequencing

Because of the complexity of drug response and toxicity, the initial candidate gene studies approach focusing on the implication of single genes in drug metabolism showed limited success, a fact that led developed countries to search further for multi-genetic and genomic information and additional molecular mechanisms or pathways implicated in drug action (Visvikis-Siest et al. 2018). The development and availability of high-throughput genotyping at an affordable cost allowed GWAS to provide an unbiased or 'hypothesis-free' method of interrogating the genome for novel genetic markers. Moving on, and since 2008, next-generation sequencing (NGS) has become a powerful new tool for the identification of many rare genetic variants responsible for a significant part of the heritability in drug response (Ingelman-Sundberg et al. 2018). At the clinical practice level, the translation of NGS is still underway with many challenges ahead, especially in developing countries where the implementation will depend on the available resources and infrastructure (Giannopoulou et al. 2019). Nevertheless, and since 2015, substantial technological advancements have been made in NGS throughput and speed coupled with an exponential decrease in cost, contributing to NGS applications' rapid diffusion into clinical settings in countries with very high HDI (van Dijk et al. 2014). Suppose the OACs' scenario also applies to NGS with an estimated time lag of 10 years. In that case, it may take only five more years until 2025 for it to be widely available in developing countries. By then, the sequencing costs will also further decrease paralleled with streamlined bioinformatics. At the research level, the use of NGS will allow the identification of transethnic variants. If previously identified variants are not replicated, NGS would still decipher novel variants (in known and novel genes) specific to developing countries' populations. NGS's incorporation is expected to generate affordable genetic testing at the clinical practice level, increasing the chances for reimbursement by third-party payers, and therefore will hopefully pave the way for PGx implementation in clinical practice (Ingelman-Sundberg et al. 2018; van Dijk et al. 2014).

### Education and training

As noted above, one of the most prominent challenges for the uptake of clinical PGx is healthcare providers' scepticism and insufficient knowledge. Developing clinicians' and pharmacists' skills is, hence, a critical aspect for the advancement of PGx worldwide, including in developing countries. Several educational efforts are currently available, most notably the Pharmacogenomics Knowledgebase (PharmGKB), a publically available tool with curated information on clinically actionable drug-gene relationships and an updated listing of drug-label annotations and prescribing guidelines (Whirl-Carrillo et al. 2012). Nevertheless, healthcare providers, especially those from developing countries with little exposure to PGx, need to be primed on such resources. This can be achieved by attending educational conferences such as the Pharmacogenomics days organized by the Golden Helix Foundation (Zgheib et al. 2020) and integrating more PGx teaching at the undergraduate and graduate levels (Ghaddar and Zgheib 2012). Developing countries should also be encouraged to participate in international funding calls for mobility grants and exchange programs such as the EuRopean Action Scheme for the Mobility of University Students (ERASMUS) and the Upward Mobility Program (UMP) of the United States Agency for International Development (USAID).

## Conclusion

Several challenges face scientists in developing countries inhibiting or delaying their ability to contribute to the evolution of PGx research and its clinical application. We recommend fostering multinational and regional collaborations to secure funds for high-throughput genotyping and local capacity building while preserving individual countries' identity, implementing NGS, and organizing specialized training and exchange programs to move PGx research and clinical applications forward in these countries.

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## Compliance with ethical standards

**Conflicts of interest/Competing interest** The authors declare that they have no competing interest.

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