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REVIEW

One Step Ahead in Realizing Pharmacogenetics in Low- and Middle-Income Countries: What Should We Do?

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Abstract: Pharmacogenetics is a promising approach in future personalized medicine. This field holds excellent prospects for healthcare quality acceleration. It promotes the transition to the precision medicine era, whereby a health treatment is driven by a deeper understanding of individual characteristics by interpreting the underlying genomic variation. Pharmacogenetics has been developing rapidly since the human genome project. Many pharmacogenetics studies have shown the association between genetic variants and therapy outcomes. Several pharmacogenetics working groups have recommended guidelines for the clinical application of pharmacogenetics. However, the development of pharmacogenetics in low- and middle-income countries (LMICs) is still retarded behind. The problems mainly include clinical evidence, technology, policy and regulation, and human resources. Currently, available genome and drug effect data in LMICs are scarce. Pharmacogenetics development should be escalated with evidence proof through research collaboration across countries. The challenges of pharmacogenetics implementation are discussed comprehensively in this article, along with the prospect of pharmacogenetics-guided personalized medicine in developed countries. Stepwise is expected to help the researchers and stakeholders define the problem that hindered the pharmacogenetics application.

Keywords: pharmacogenetics, implementation, LMICs, personalized medicine

Introduction

Every organism has hereditary material called genes. Nearly every human cell has Deoxyribonucleic acid (DNA), which carries genetic information. DNA contains code for development and functioning. As the genetic material, DNA codes for amino acids, the building blocks of protein.[1] Each protein has its function in creating particular anatomical features or physiological processes. Genetic variation may alter the protein function or expression levels.[2] Several studies have discovered the relevance of inter-individual genetic variation with individual drug responses that support therapy decisions, called pharmacogenetics.[3] Even though genetic variations (genotype) influence drug response and the incidence of adverse drug reaction (ADR) phenotypes in an individual is considered the focus of pharmacogenetics study, translations of the available genomic information into actionable clinical recommendations still lagged behind.[4]

The term "pharmacogenetics" was first created by Friedrich Vogel in 1959.[5] In the last decade, the human genome project has accelerated pharmacogenetics discoveries.[6,7] Pharmacogenetics is rapidly evolving in developed countries like the United States of America (USA). Private sectors, educational institutions, and the government significantly increase research and create an adequate bioinformatics environment. Cutting-edge technology has rapidly evolved, including the high throughput sequencing platform.[8] Genetic information in the form of DNA sequences from individual laboratories and large-scale projects worldwide is documented in a database to provide access to the scientific

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community.[9,10] The USA Food and Drugs Administration (FDA) has also offered expanded information related to drug-gene interaction on its website (www.fda.gov) and drug labels.[9,11]

To apply pharmacogenetics knowledge in routine clinical practice, several initiatives of pharmacogenetics implementation in clinical practice have started to emerge. Evidence-based guidelines for specific drug combinations and genotypes or predicted phenotypes are crucial to improve drug safety and enhance clinical effectiveness.[12,13] Globally, evidence-based guidelines have been developed for pharmacogenetics by various committees, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC), the French National Network (Réseau) of Pharmacogenetics (RNPGx), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and The Dutch Pharmacogenetics Working Group (DPWG).[14,15]

Most guidelines highlight the gene-drug pharmacokinetics interaction, particularly cytochrome P450 (CYP). Individuals are categorized based on CYP enzymes: poor, intermediate, average, and ultrarapid metabolizers. This classification describes the pharmacokinetic processes that vary among populations. CYP is highly polymorphic and affects the metabolic rate of certain drugs, for example, warfarin – CYP2C9, clopidogrel – CYP2C19, tricyclic antidepressants (TCA) – CYP2D6 – CYP2C19, and codeine – CYP2D6.[14] In addition, CYP polymorphisms are also known to be associated with the activity of several infectious disease drugs, such as primaquine (malaria) – CYP2D6;[16–18] antituberculosis drugs – CYP2E1;[19,20] and efavirenz and nevirapine (HIV) – CYP2B6.[21,22]

On the other hand, pharmacodynamics interaction happens when a drug target gene polymorphism can alter the pharmacological activities. It includes signal transduction proteins, enzymes, ion channel receptors, and other particular proteins. The guidelines have suggested pharmacodynamic drug-gene interaction, such as warfarin – VKORC1, abacavir – HLA, and thiopurines – TPMT.[14,23] The guideline is crucial since one of the implementation challenges is translating genotype data into clinical information.[12,24] However, currently, guidelines are only available for a few medications, and most working groups are from high-income countries.

Meanwhile, the application of pharmacogenetics in most low- and middle-income countries (LMICs) is still early. Despite the emergence of various research confirming pharmacogenetics' benefits in LMICs, many hurdles make this intervention difficult to implement. This article illustrates the challenges of pharmacogenetics for personalized medicine in LMICs.

Barriers to Pharmacogenetics Implementation

Pharmacogenetics development in LMICs remains in its infancy compared with those in high-income countries (HICs) due to several difficulties.[4] The significant barriers can be classified into four themes: clinical evidence, technology, policy and regulation, and human resources (see Figure 1).

Clinical Evidence

Although there has been a substantial increase in the understanding of how inter-individual genetic variation can impact drug response in the past several decades, the current result must be more robust to quantify the added value of pharmacogenetics testing in several disease groups. The need for translation of the genomics research findings into actionable recommendations is one of the problems.[4,6,25] Randomized clinical trial (RCT) is a gold standard experimental research design for healthcare intervention.[12,26] However, it is only sometimes an ideal design to evaluate the benefit of pharmacogenetics intervention because the number of patients with a clinically significant genetic variant is often too small. Meanwhile, randomizing the treatment to patients with known genetic variants may be considered unethical. In this case, observational studies can be the solution despite the risk of bias.[27]

The number of research outputs can justify scientific progress. The bibliometric data was obtained from PubMed Advanced search with the following query: "pharmacogenetic*" OR "pharmacogenomic*" for "title and abstract" AND "country name" (with modification for accuracy) NOT "review" for "publication type". It showed that HICs are 2.9 times more productive than LMICs in this research field. Among the LMICs, China, India, and Brazil have the highest number of pharmacogenetics and pharmacogenomics research, respectively (Figure 2).

The disparity in research funding may be the root of this problem (see Figure 3). As the UNESCO Institute for Statistics (UIS) reported, the research and development budget (% of GDP) is relatively lower in LMICs.[28] There needs

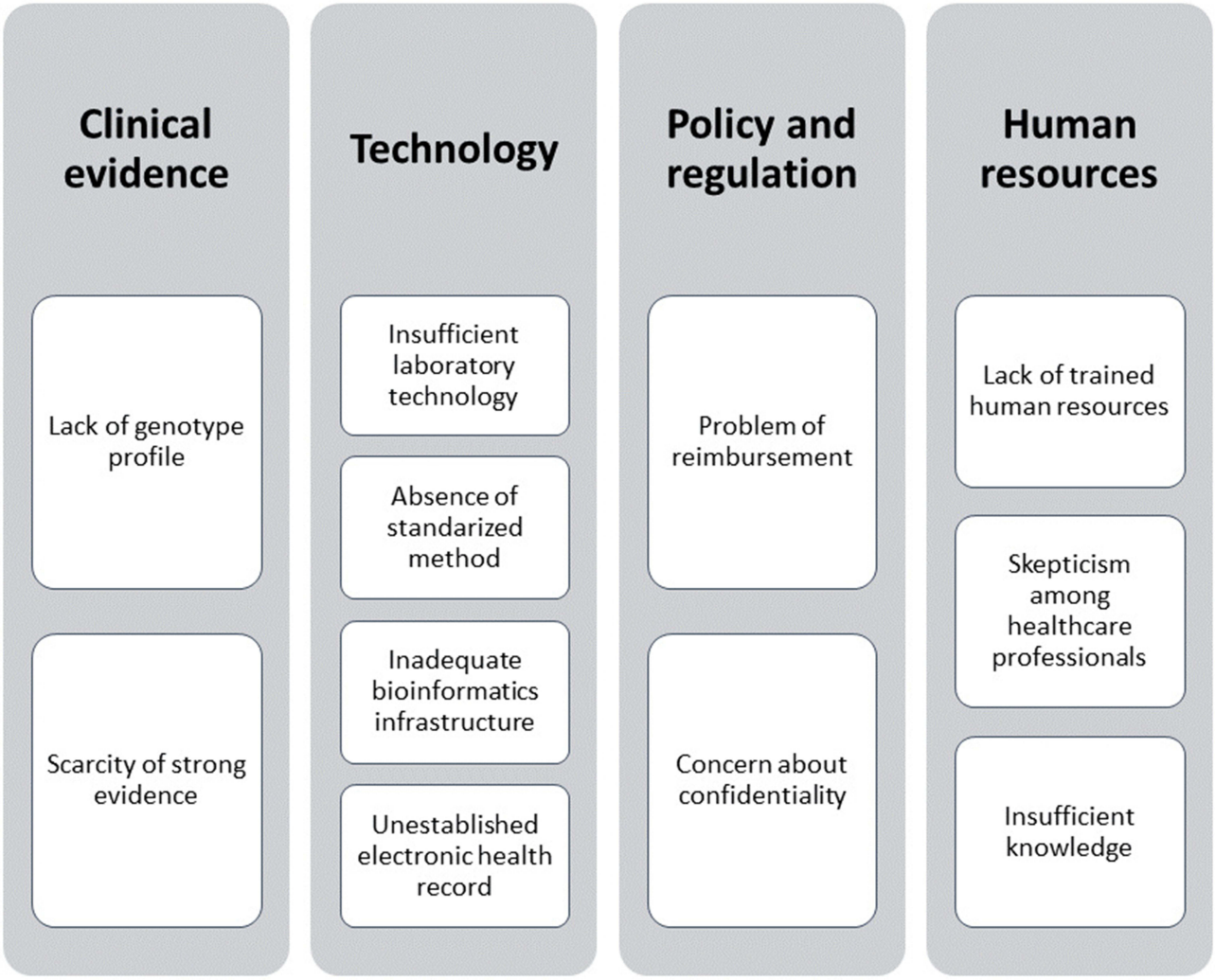

Figure 1 Barriers to pharmacogenetics implementation.

to be more resources between HICs and LMICs, which means that many funding strategies do not prioritize the contribution of researchers in LMICs to the development of global health research priorities and agendas. Moreover, the budget allocation of these countries in health research varies depending on priority and financial capacity.[29]

Technology

More technology support is another major issue. Pharmacogenetics needs a complex technology ecosystem with an efficient genotyping method, appropriate databank, and bioinformatics infrastructure. Regarding the genotyping method, the absence of a standardized genetic testing method disputes the validity of genomic testing. An accurate and precise procedure requires the discovery of the appropriate biomarker. The expensive and inefficient genotyping methods are also considered barriers to integrating pharmacogenetics.[30]

A proper informatics infrastructure is needed for bioinformatics data management and analysis.[31] An ideal expected scenario to be implemented in a clinical setting should be as follows: (i) the test results are available for prescribing and drug dispensing for a lifetime of the patient; and (ii) the test results should be accessible in different healthcare facilities, including general practitioners and pharmacists.[13] Electronic health records should be available to deal with these issues. However, the integration still needs to be improved, especially in LMICs, which have limited information technology resources.

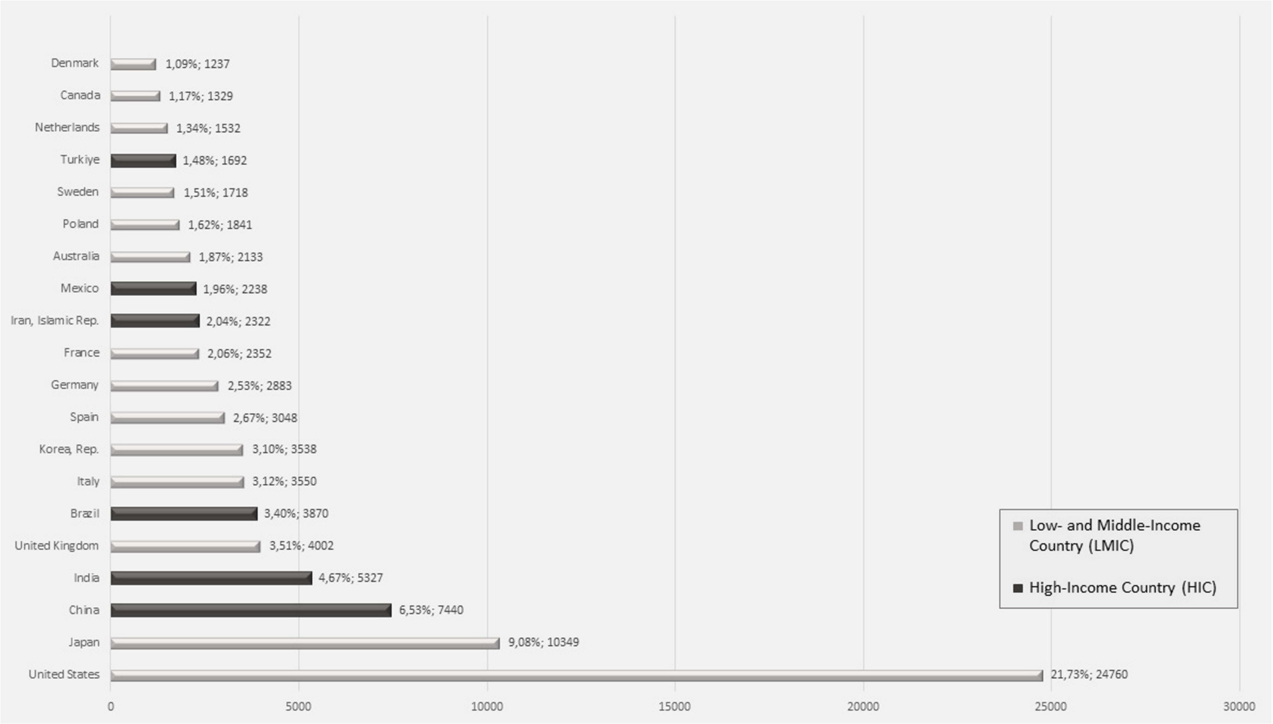

Figure 2 Countries with the highest research outcome based on PubMed Search.
Abbreviations: LMIC, low- and middle-income country; HIC, high-income country; SAR, special administrative region; PDR, People's Democratic Republic; USA, United States of America.

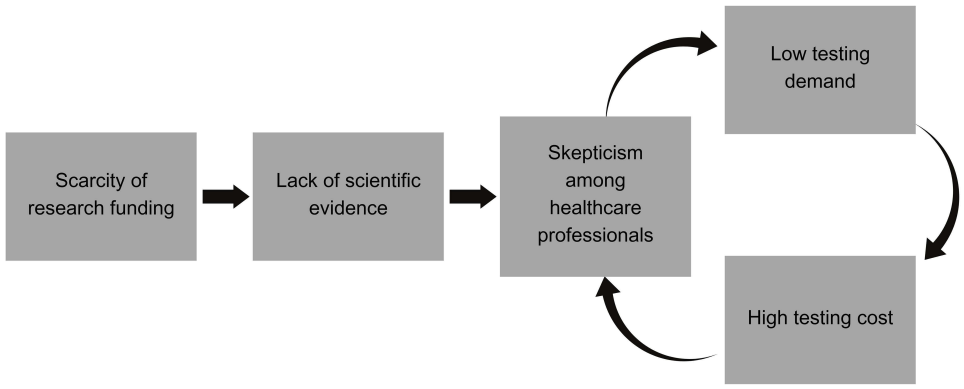

Figure 3 The importance of research funding.

Using biobanks as the reference case, biobanks in HICs are commonly well-established, while they are rapidly evolving in LMICs. According to surveys of biobanks operating in LMICs, the sustainability of the biobanks is threatened by a lack of funding and short-term funding tied to particular projects.[32] It is likewise the constraint of electronic medical records in LMICs.[33]

Policy and Regulation

Policy is needed to ensure data safety and define clinical workflow and reimbursement. Large-scale genetic and clinical data collection raises confidentiality issues. There is a concern about the privacy of genetic information because genetic information is highly personal. Personal and genetic data have the risk of being misused.[34] United Nations Conference on Trade and Development (UNCTAD) in 2021 reported that only 71% of countries worldwide have data protection and

privacy legislation; 9% have draft legislation, 15% have no legislation; and 5% still need to be discovered. Almost all countries that do not have legislation are LMICs.[35]

The delivery of pharmacogenetics services can be through healthcare providers or direct-to-consumer. Integrating pharmacogenetics with healthcare facilities is a crucial issue that needs to be addressed with an appropriate workflow, including testing, translation, interpretation, and transfer procedures. This integration requires standard regulations to ensure its smooth implementation.[36] This concern is not limited to a few countries but is a global issue. However, LMICs face more critical challenges due to their fragile healthcare system.[37] To tackle this, the European consortium has initiated a workflow design and evaluated the cost-effectiveness of implementation through preemptive panel testing, known as Ubiquitous Pharmacogenomics (U-PGx).[6]

Pharmacogenetics includes a variety of technological approaches. Technology is supported by various levels of evidence to optimize genetic-based personalized medicine. These factors and acceptance of clinical guidelines are the decisive factors of reimbursement policy enforcement. Direct-to-consumer marketing for some pharmacogenetics technology has persisted without reimbursement.[38] The difficulty in LMICs is demonstrated by the discrepancy between revenue and expenditure for healthcare, which restricts access for a significant number of the population and forces them to pay for their medical cost out of pocket (OOP).[39]

Human Resources

Besides the lack of clinical guidelines and established workflow, there is also a lack of pharmacogenetics-related education for health care professionals (HCPs) that hinders clinical execution.[4,6,25] Education of HCPs becomes more challenging in low-income settings, like several African countries, with a significant gap in the number of HCPs nationwide and only a small number being educated as specialists.[40]

Skepticism and low confidence also impede the uptake of pharmacogenetics into the clinical setting.[41,42] Nevertheless, physicians and pharmacists need more time to be ready and knowledgeable, even in a developed country like Finland.[43]

In addition, from the physician's perspective, several other issues become barriers to pharmacogenetics application, such as decision-making, concerns with pharmacogenomics adoption, outcome expectancy, provider knowledge of pharmacogenomics, patient attitudes, individualized treatment, and provider interest in pharmacogenomics.[44]

Moreover, the public has not been familiar with pharmacogenetics. A nationwide survey of the USA with 1060 respondents reported that 78.9% of respondents had yet to hear about this intervention.[45] The condition could be more challenging in LMICs with lower health literacy.[46]

Economic Consequences of Pharmacogenetics Implementation

Even though optimizing public health is one of the ultimate goals in the healthcare system, cost is a significant consideration in adopting new health technology due to the finite budget setting.[47] Much investment is needed to establish a good quality genetic-guided clinical practice.

As pharmacogenetics is not a single concept, the actual cost of pharmacogenetics implementation is not only the testing cost itself. When the supporting evidence is adequate, the cost structure of pharmacogenetics from the stakeholder perspective can be identified as the economic consequences of its implementation (see Table 1).[48]

Infrastructure Cost

An excellent investment should cover expenses for testing equipment, including instruments, software, laboratory equipment, and bioinformatics computing systems to analyze and process the data with sufficient genetic data storage.[30,49,50] Developing bioinformatic infrastructure is crucial for genetic research as the starting point for sustainable clinical genetics.[48] The cost of data storage depends on the size of cloud capacity.[51] These facilities will work appropriately with the support of an integrated electronic healthcare system and medical records. Ideally, pharmacogenetics findings and their interpretation should be accessible to all clinicians and other HCPs through the medical record to make it available for clinical use as needed.[52] Maintenance is required to ensure all systems are running well.

Table 1 The Cost Structure of Pharmacogenetics Implementation

Testing cost	Infrastructure cost	Human resources training cost
Sampling technique and preparation	Testing equipment: instrument, software, and laboratory equipment	Pharmacogenetic training for HCP and stakeholders
Gene test	Electronic healthcare systems and electronic medical record	Bioinformatics training for HCP and stakeholders
Operation and administration	Genetic data storage	Health information system and bioinformatics specialists
	Bioinformatics computing system	Laboratory analyst training
	Facilities maintenance	

Notes: Investment should cover testing, infrastructure, and human resources training costs to make pharmacogenetics clinically applicable in the healthcare system.
Abbreviation: HCP, Healthcare professional.

Human Resources Development

Interprofessional collaboration of physicians, pharmacists, and nurses is needed to maximize the potential of patient care.[53] These expenses cover the training cost of HCPs, especially for patient counseling regarding the implications of pharmacogenetics testing and the training and how to interpret and apply pharmacogenetics data in clinical practice.[52] The program can be a short course or an academic credit-based program. However, beyond the structured education program, the skills of accessing pharmacogenetics information in an authentic setting are needed.[54] Therefore, practical modalities such as case studies and clinical rotation can be helpful.[55] Sustainable training for bioinformaticians is required to develop and maintain the system.[56] Moreover, the analyst also should be trained to support the technical laboratory activity.

Testing Cost

Various testing approaches have been discovered, such as Real-time Polymerase Chain Reaction (PCR) with TaqMan probes, Restriction Fragment Length Polymorphism (RFLP), microarray, PCR + Sanger sequencing, and Next Generation Sequencing (NGS). Each method has advantages and disadvantages. NGS is a cost-effective option for sequence verification.[49]

The test can be conducted either using the preemptive or reactive method. Preemptive testing is undertaken before a symptom arises and a drug is prescribed.[57] The results should be integrated into the medical records, allowing access to personalized prescribing and surveillance. Reactive testing, conversely, is conducted before any high-risk medication is prescribed after patients receive the standard medicines. Preemptive testing showed cost-effectiveness compared with standard care, while reactive testing did not. Panel testing is more recommended compared with single gene testing.[58]

This situation is the underlying issue of pharmacogenetics implementation in several countries, especially LMICs since the limited budget must be adjusted strictly based on priority setting. These barriers become more complicated in LMICs. Therefore, clinical effectiveness and cost-effectiveness data are also needed to prepare this advanced technology. An economic evaluation is required to evaluate to what extent pharmacogenetics intervention can be worth the costs paid compared with the existing standard treatment. The outcome of pharmacogenetics could be described in many different ways, such as: (1) effectiveness, the prevented event or specific clinical parameters; (2) utility, measured as quality-adjusted life year (QALY), the expected number of years of life accounting for the quality of life; and (3) benefit, which is represented as monetary unit.[59,60] Pharmacogenetics intervention is considered to dominate the standard treatment if it reduces costs and offers a better outcome than the standard treatment. Otherwise, standard treatment dominates pharmacogenetics intervention if the intervention costs more and has a less effective outcome than the standard treatment.

A systematic review comprising 108 studies that conducted economic evaluations of 39 drugs concluding 71% (n=77 studies) confirmed this intervention was cost-effective (n=48) or cost-saving (n=29), 21 studies (20%; n=21 studies) reported that pharmacogenetics was not cost-effective, and ten studies (9%) were uncertain.[61] The application of

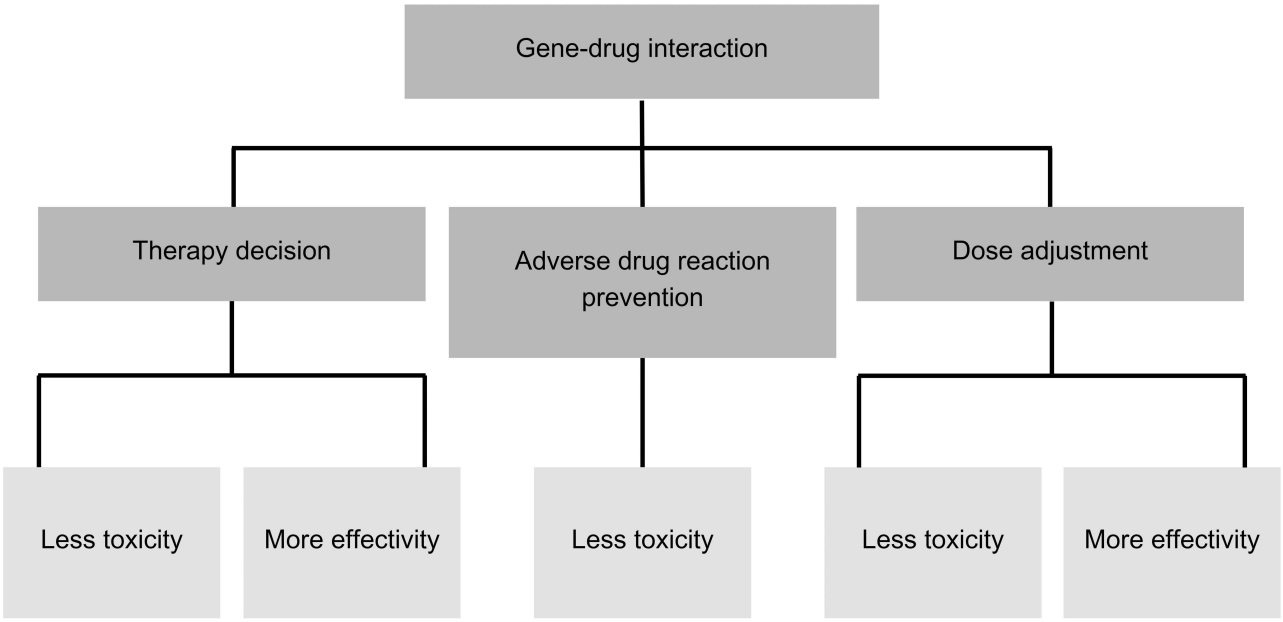

Figure 4 Potential benefits of pharmacogenetics implementation.

pharmacogenetics will be likely to be cost-effective if (1) the genetic polymorphism is common and has a high degree of penetrance in the population; (2) the test has high sensitivity and specificity; (3) the disease state or adverse drug reactions cause significant morbidity or mortality especially when it is untreated; and (4) the therapy leads significant outcomes and cost that can be influenced by genotype-guided therapy (see Figure 4).[62]

Overall, bridging the gaps and barriers needs a considerable capital investment. Globally, pharmacogenetics research depends on private investment (private R&D and Venture Capital (VC)) and government funding. Venture capital is projected to hold the most financing over the next five years. By country, in 2018, the USA had the largest genomic market (~33%). The UK, China, Japan, and Singapore followed it. The USA is also the most significant contributor to global genomics public funding (~35%).[63,64]

Lessons Learned from a Path Forward of Pharmacogenetics in Indonesia

The COVID-19 pandemic caused a shift in the priorities of resources focused on outbreak control. It caused the development of health technology to be reasonably delayed. Nonetheless, the pandemic has stimulated health biotechnology research around the world. During the crisis recovery era, many countries rigorously improve their health systems. The Indonesian government has begun an effort to develop and widespread pharmacogenetics and pharmacogenomics in Indonesia through the Biomedical dan Genome Science Initiative (BGSi) since 2022. According to the Indonesian Health Strategic Plan 2020–2024, it is part of the health transformation support. The Ministry of Health, Republic of Indonesia, proposes using pharmacogenomics as one of the approaches in the national formulary drug selection.[65] By unlocking genomic-based healthcare services, future treatment is expected to be more precise and personalized. BGSi elaborates on essential platforms such as registry, biobank, and bioinformatics service unit to accelerate this goal. The optimization of these facilities allows the increase of data-driven research, clinical trials, or post-market surveillance studies that enhance the maturity of genetic-based personalized medicine in Indonesia. This initiation involves the private sector and international venture capital companies.[66]

However, the bibliometric data showed that the progress of pharmacogenetics research in Indonesia could be faster. Grant aid is substantially desired to optimize research. The amount of the research budget allocated by the Indonesian government is still meager (0.1% of the Gross Domestic Product in 2021) compared to several neighboring countries (0.5% in Thailand, 1.3% in Malaysia, and 2.1% in Singapore).[67] The development of facilities should also be balanced with the development of scientific evidence.

Moreover, education in pharmacogenetics for HCPs should be started to encourage the assimilation of pharmacogenetics into routine practice.[68] A study conducted in Indonesia and Singapore showed that the HCPs need training to prepare for pharmacogenetics adoption.[69]

The Future of Pharmacogenomics: What to Expect in the Next Five Years

Globally, there needs to be more programs and solutions required to empower clinical application pharmacogenetics between countries. Therefore, pharmacogenetics practice in LMICs should be clinically exposed in a stepwise process.[26] Building capacity for technology, especially in terms of education and infrastructure, is a starting path to bridging the gap between pharmacogenetics research and clinical development.[70] The appropriate research and data synthesis must be gathered early, including existing clinical evidence, guidelines, facilities, financial data, and policy. The development of workflow is vital to compile information. In this stage, laboratory facilities and IT infrastructure are also prepared. The availability of testing technology can accelerate the research, education, and biobank data gathering. When genetic data is readily available, primary research findings can be expanded into translational research to increase the clinical implication of gene variance, including the gene-environment interaction.[71]

Despite technology, human capital is an essential asset for healthcare.[72] Optimal integration of pharmacogenetics knowledge in the curriculum will adequately prepare students to manage patients based on clinical and genetic information.[54] Continual development and certification programs can effectively improve the skill and knowledge of HCPs.[54,73]

The pilot initiation can be completed afterward with systematic evaluation to build up more reliable gene-drug pairs information.[71] A powerful way forward to facilitate clinical implementation was the development of clinical guidelines based on gene-drug pairs information.[3,44] Although recommendations and guidelines from other countries can be referenced, the characteristics of the population should be taken into account since the genetic profile is ethnicity- and racially-specific.[3,44,74] The role of pharmacogenetics consortium and networks is needed, not only for genetic data exchange and guideline purposes but also to adopt policies and transfer knowledge. Lessons can be taken from France, which has less pharmacogenetics research than the USA and Japan. However, their application is progressive because they collaborate with other countries.[14]

The Southeast Asian Pharmacogenomics Research Network (SEAPharm) is an example of a pharmacogenetics network that may open a great opportunity for the LMICs in Southeast Asia. Nine countries participated in this project: seven countries from Southeast Asia (Indonesia, Thailand, Myanmar, Philippines, Laos, Malaysia, and Vietnam), one from Europe (Greece), and one from Western Asia (United Arab Emirates).[75] Thailand, Malaysia, Singapore, and Indonesia are Southeast Asian countries that have initiated the implementation of gene testing both for research and clinical purposes. The test is generally available for drug-metabolizing enzyme genes (CYP superfamily – which is associated with various medications including clopidogrel,[9] antipsychotic,[76] antidepressive agent[77,78]); Human Leukocytes Antigen (HLA) genes – which are related to antiepileptic drugs;[79] VKORC – which is associated with warfarin;[80,81] and SLCO1B1 – which is associated with statin.[82] Although the national application is still far from the current condition, this beginning provides a path to national implementation.

Ideally, in a more extensive scope, secure and sufficient data storage and transfer, public repositories, and data processing technologies must be well-developed with integrated clinical decision support systems to deal with such complicated and extensive data.[31,50] Efficient analysis and interpretation of big genomic data allow the researchers to explore molecular biology, physiological and pathological states, leading to a better understanding of diagnostics and therapeutics.[83] The bioinformatics database will provide a space to document the genome profile. Big data could help data-driven research in pharmacogenetics. Tapping large biobanks of therapeutic drug monitoring data allows researchers to conduct high-quality retrospective studies validating the clinical implication of genetic variants currently incompletely characterized.[4] Besides, emerging methods that would enable the high-throughput experimental characterization of genetic variants combined with machine learning-based computational technology hold a promising improvement in the accuracy of drug response predictions.[84] Improving the accuracy of drug response predictions will narrow the gap between variant identification and its utilization for clinical decision support.[4] LMICs can reflect on The Electronic Medical Records and Genomics (eMERGE) network, which brings together experts in genomics, legal and ethics,

informatics, medicines, and statistics in the USA to validate and implement risk assessment system based on genomic data, family history, and clinical characteristics.[85]

Furthermore, robust regulations and policies are needed within the health facilities and national scope, such as data protection, standardization of testing methods and workflow, and reimbursement. Data ownership to protect HCPs' and patients' rights and obligations is critical.[26] The national drug authority should make precise regulations regarding the workflow and qualified biomarkers.[27,52] Reimbursement strategies for stakeholder acceptance, incorporation of pharmacogenetics education in all institutions and clinics, and pharmacogenetics promotion to all HCPs and patients are also crucial. Finally, the proper execution of this idea will support the transformation of health. This workflow can be implemented with periodic review and monitoring.[26]

Conclusion

Pharmacogenetics is a promising approach to optimize patient outcomes and prevent the potential cost and burden of patient therapy. Yet, it takes a long time to achieve the ideal execution. Most countries in the world generally face these hurdles. However, LMICs must put extra effort as early adopters of pharmacogenetics with limited resources. Initiation of infrastructure development, structured pharmacogenetics education, and policy formulation should be enforced together with rigorous research and development. Collaboration across nations and resource sharing can be the solution to minimize the burden of pharmacogenetics implementation in achieving equal healthcare quality worldwide.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work

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Disclosure

The authors report no conflicts of interest in this work.

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