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REVIEW

Pharmacogenomics Tools for Precision Public Health and Lessons for Low- and Middle-Income Countries: A Scoping Review

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Abstract: Pharmacogenomics is the integration of genomics and pharmacology to optimize drug response and reduce side effects. In terms of personalized or individualized medicine, PGx is defined as the identification and analysis of specific genetic variants associated with particular drug treatments for each patient. Under a precision public health (PPH) approach, population-level data are analyzed to generate public health strategies. The objective of this study was to conduct a scoping review of technological tools, examining their evolution, the predominance of high-income countries in their development, and the gaps and needs for genomic data and advances in low- and middle-income countries (LMICs). This review was conducted in accordance with the ScPRISMA guidelines. A search was conducted in PubMed, Web of Science and Embase until January 2024. A total of 40 documents were selected, which revealed the continuous evolution and progressive development of pharmacogenomic tools. The technological tools developed come from high-income countries, particularly the United States, Canada, China, and several European nations, where international collaboration has been essential to maintain and expand these tools, which have evolved to keep pace with the rapid generation of genomic data. This trend shows a scarce development of technological tools for public health precision in LMICs, which evidences the need to increase investment in genomic research infrastructure in this aspect and in the development of capacities to guarantee global accessibility and boost PPH for all populations.

Keywords: personalized medicine, pharmacogenomics, precision public health, technological tools

Introduction

The completion of the Human Genome Project at the turn of the twenty-first century constituted a significant milestone for the healthcare system, generating substantial quantities of data.[1,2] This development has created a need for technological tools to store, organise, and analyse valuable information, facilitating decision-making related to diagnosis, prognosis, and treatment for a number of different stakeholders, including health professionals, private sector companies, public sector organizations, and academics.[3,4]

Pharmacogenomics PGx is the developing discipline on the borderline between genomic medicine and pharmacology. This area of research is focused on optimizing drug prescription with the help of knowledge and data about genomic variations. This discipline will progress based on studies demonstrating that genetic polymorphism is associated with variations affecting enzymes related to drug transport and metabolism. These polymorphisms affect the way in which organisms absorb, distribute, metabolize, and eliminate drugs, leading to significant differences in drug response, efficacy, and safety.[5,6]

Accordingly, genomic variations have the potential to significantly affect enzyme function.[5,6] Such variations can result in complete loss of enzyme function, a reduction in enzyme activity, or even a gain of function. Individuals carrying some types of variations in their genes are more prone to side effects or receiving less effective dosifications when taking specific medications.[7] Among those variations, genomic differences can create phenotypes associated with

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drug metabolism, grouping those people into four metabolism rate groups: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers.[5]

Precision medicine is a medical approach utilizing genomic information to diagnose, treat, and prevent diseases.[8] In terms of personalized or individualized medicine, PGx is defined as the identification and analysis of specific genetic variants associated with particular drug treatments for each patient.[9] Alternatively, under a PPH approach, PGx is considered to be a process that focuses on identifying and analyzing population-level data toward developing strategies that benefit public health for groups of people having similar.[10,11] This latter population-based approach leverages data to analyze genetic differences associated with drug responses, with the goal of developing more accurate treatments for public health decision-making.[11]

Thanks to technological advances and innovations in genotypic and phenotypic characterization, the field of pharmacogenomics has made great progress through the analysis of large amounts of data and the optimization of drug selection and dosing with technologies such as Genome-Wide Association Studies (GWAS) and Next-Generation Sequencing (NGS).[12,13] This progress has identified important benefits in several therapeutic areas. For example, in cardiology, 25 studies it has been demonstrated that individuals with loss-of-function alleles in CYP2C19 treated with clopidogrel have a higher incidence of secondary vascular events (HR 1.72; 95% CI: 1.43 to 2.08; 18 studies), stroke (HR 1.46; 95% CI: 1.09 to 1.95; 5 studies) and ischemic stroke (HR 1.99; 95% CI: 1.49 to 2.65; 12 studies), than those without such alleles.[14] On the other hand, a higher risk of death from toxicity related to cancer treatment with fluoropyrimidine use has been demonstrated in oncology studies for carriers of DPYD variants (OR = 34.86, 95% CI 13.96–87.05; $p < 0.05$).[15] These technological innovations have resulted in improvements in the quality of prescribing practices, increased effectiveness of drug use, reduced adverse reactions, improved clinical outcomes, and lower costs of drug interventions and treatments for the healthcare sector.[7]

This population-based public health approach is crucial for implementing technological advances in PGx derived from precision medicine in low- and middle-income countries. The frequencies of pharmacogenomic variants may vary between populations due to ancestry, however the lack of genomic data on diverse ancestral populations could exacerbate existing health inequalities.[7,16,17] Accordingly, initiatives such as the Human Heredity and Health in Africa Consortium (H3Africa) have sought to promote research in 51 projects in 30 African countries, with the aim of developing infrastructure and identifying genetic factors related to health.[18] Similarly, in the Republic of Congo, studies have focused on polymorphisms associated with adverse drug responses to HIV/AIDS, malaria, and tuberculosis.[19] In the latter, pharmacogenetics has enabled the selection of more effective and less toxic drugs, which could reduce resistance and optimize resources in limited health systems.[20]

In Asia, countries such as India are also making important advances in the development of pharmacogenomic databases that address genetic diversity in drug metabolism. The IndiGen initiative has sequenced more than 1000 genomes, identifying that on average, each individual carries eight variants that influence drug selection and dosing, which underlines the relevance of orienting pharmaceutical public policies to seek more effective therapeutic results according to the specificities of the population.[21]

Similarly, in Latin American countries, extensive admixture between African, European, and Native American populations creates a particular genetic diversity,[22,23] as evidenced by studies in Colombian,[24,25] Brazilian,[26] and Chilean[27,28] populations. These countries often lack data on local and regional variations in key pharmacogenes, which could exacerbate health disparities and hinder the application of precision medicine and PGx.[29,30]

The implementation of PGx in clinical practice, tailored to the priorities of each subpopulation structure in every country, is essential to address populations' specific needs for better outcomes and fewer adverse reactions.[30] By adopting this population-based approach, low- and middle-income countries (LMICs) can harness the potential of PGx to tailor medical treatments and interventions more effectively to the needs of groups of individuals, thereby generating a more cost-effective solution for health systems, but also offering a practical pathway to address the unique care challenges encountered in these settings.[24]

The diverse application and potential of PGx in LMICs will, therefore, help in the optimization of strategies for PPH. Moreover, technological tools have high potential to enhance development in medical, personalized treatments, considering health care challenges unique to developing better health outcomes with reduced side effects. Availability and applicability of

available technological tools of PGx in LMICs are still vague. For this reason, a scoping review was conducted to trace an overview of the evolution of pharmacogenomic technological tools, discussing dominance by high-income countries in their development, and highlighting gaps and needs in genomic data and technological advancements in LMICs.

Methods

Search Strategy

The procedure for this scoping review follows the ScPRISMA guidelines;[31] see Supplementary Material 1. An Excel spreadsheet with a defined taxonomy was determined to be the ideal instrument for collecting information, outlining the review step-by-step, and integrating analysis variables based on the following question: ¿What is the evolution and geographical distribution of technological tools in pharmacogenomics? And ¿what are the gaps in low- and middle-income countries?

The search focused on scientific articles emphasizing technological tools for analyzing PGx information that could be useful for decision-making via a population-based approach. The search was conducted via scientific databases such as PubMed, Web of Science and Embase. The combination of keywords and boolean operators used in this study are pharmacogenetics, pharmacogenomics, PGx, drug response, drug metabolism, drug efficacy, variant, polymorphism, biomarker, SNP, database, web, platform, public health, community, population, ancestry, personalized, individual, and precision.

Inclusion and Exclusion Criteria

The search for articles was conducted up to January 2024 and was limited to human-related articles, with no date restrictions. Articles written in English, Spanish, or any other language that could be translated into any of these languages were included. Excluded where articles were studies conducted in animals or in vitro or without full text; articles focused on general or conceptual aspects of PGx and technological tools; technological tools unrelated to PGx; papers on methods or techniques that did not include a technological tool for PGx data storage, organization, and analysis. Subsequently, duplicate papers were excluded.

Three rounds of review were conducted. In the first round, the titles of the documents were examined. The second round involved reviewing the keywords and abstracts of the remaining documents. Finally, a screening of the full texts of the articles was carried out to eliminate those that did not meet the inclusion and exclusion criteria.

Data Extraction

The relevant information from the selected documents was extracted via an Excel form. This form included specific fields for capturing key details such as the document title, year of publication, year of tool development, geographical region, and functionalities of the technological tool. This data extraction ensured a thorough and organized collection, which facilitated the subsequent analysis of the information obtained. This approach ensured that all essential elements were covered in accordance with the stated objectives and that the required data were accurately collected.

Results

PRISMA Flowchart

The search in PubMed, Web of Science and Embase returned 902 documents (see Supplementary Material 2). Of these, 285 duplicates (31,59%) were removed. After the title and abstract review, 438 studies whose topic did not correspond to the aim of this study were excluded. Full-text review of 88 documents was done whose content was assessed for suitability. In the end, 48 documents were eliminated, while 40 at 45.45% documents met all the criteria for information analysis. The flow chart is shown in Figure 1.

Timeline and Geographical Origin

Table 1 lists the articles related to technological tools in PGx, categorized by their year of publication and the country of origin of the authors of the 40 identified manuscripts with 34 technological tools. These documents span nearly two decades, illustrating the chronological evolution of technological innovations and developments in the field.

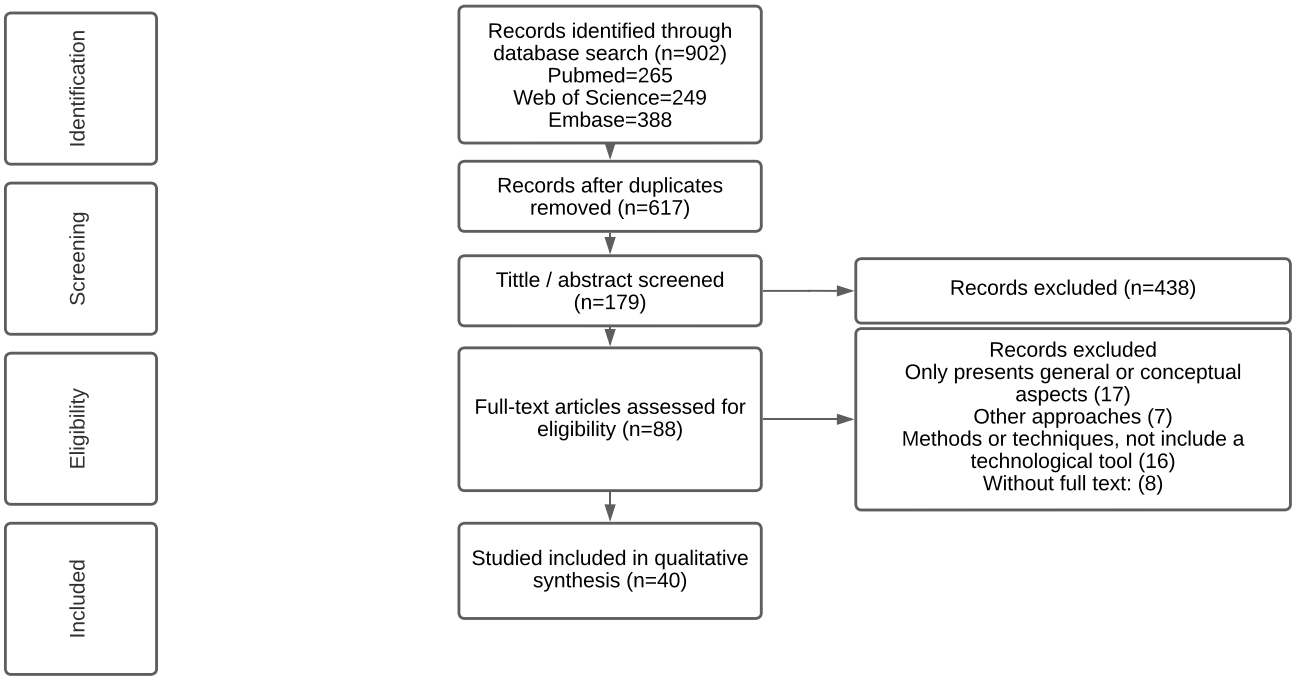

Figure 1 PRISMA flowchart.

Two peaks in publication activity were found in 2013 and 2020, with six and five articles, respectively, presenting new tools in the field. However, the year of publication might not reflect the year of development of the tool, as the identified articles could refer to further improvements and advances in developments.

Table 1 Technological Tool Included in the Analysis

Tool Name	Country of Origin	First Author's Last Name And Year Of Publication	Reference
PharmGKB	USA	Sangkuhl et al, 2008; Thorn et al, 2005, 2013	[32–34]
PharmGED	Singapore	Zheng et al, 2007	[35]
Drugbank	Canada	Wishart, 2008	[36]
KPD	South Korea	Kang et al, 2008	[37]
Nameless "Gamazon tool"*	USA	Gamazon et al, 2009	[38]
The Human Cytochrome P450 (CYP) Allele Nomenclature Database	Sweden	Sim & Ingelman-Sundberg, 2010, 2013	[39,40]
PACdb	USA, Singapore	Gamazon et al, 2010	[41]
SNPshot	USA	Hakenberg et al, 2012	[42]
FINDbase	Greece	Georgitsi & Patrinos, 2013	[43]
DIRECT	USA	Yeh et al, 2013	[44]
DEER Database	China	Q. Yu & Huang, 2013	[45]

(*Continued*)

Table 1 (Continued).

Tool Name	Country of Origin	First Author's Last Name And Year Of Publication	Reference
SPP	Singapore	Wong et al, 2013	[46]
DruGeVar	Greece	Dalabira et al, 2014	[47]
Virtual Pharmacist	China, USA	Cheng et al, 2015	[48]
Nameless "Funk tool"*	USA	Funk et al, 2014	[49]
GWASdb	China, USA	M. J. Li et al, 2016	[50]
SPHINX	USA	Bush et al, 2016	[51]
ePGA	Greece; Greece and Arab Emirates	Lakiotaki et al, 2016, 2017	[52,53]
FDALabel	USA	Fang et al, 2016; Mehta et al, 2020	[54,55]
PharmacoDB	Canada; Canada and USA	Smirnov et al, 2018; Feizi et al, 2022	[56,57]
PreMedKB	China	Y. Yu et al, 2019	[58]
PGxLOD	France, USA	Monnin et al, 2019	[59]
Nameless "Guin tool"*	India, Germany and Italy	Guin et al, 2019	[60]
PharmVar	Austria, USA, Spain, New Zealand and Canada	Nofziger et al, 2020	[61]
PGxMine	USA	Lever et al, 2020	[62]
Pg-path	South Korea	Hong & Kim, 2020	[63]
Nameless "Zarei tool"*	USA and Puerto Rico	Zarei et al, 2020	[64]
PharmVIP	Thailandia	Piriyapongsa et al, 2021	[65]
MTBP	Sweden, Spain, United Kingdom, France, Netherlands, Germany, Italy, USA.	Tamborero et al, 2022	[66]
PharmaKoVariome	South Korea	Kim et al, 2022	[67]
CREAMMIST	Thailand and Singapore	Yingtaweesittikul et al, 2023	[68]
IMOPAC	China	G. Li et al, 2023	[69]
PharmCAT	USA	B. Li et al, 2023	[70]
PancanQTL	USA	Chen et al, 2024	[71]

Notes: *Unnamed tools that to facilitate their identification have been named using the name of the first author of the manuscript "Gamazon tool", "Funk tool" * "Guin tool" and "Zarei tool".

Other results obtained in these 40 documents are the analysis of the geographical distribution of the authors. Authors affiliated with institutions located in the United States represent 52.5% of the articles.[32–34,38,41,42,44,48–51,54,55,57,59,61,62,64,66,70,71] Furthermore, an analysis of the authors' country of origin revealed that 92.5% of the articles came from high-income countries with a GNI per capita of $13,846 or more,[72] such as the United States, Canada, Singapore, Greece, Sweden, the United Arab Emirates, Germany, Italy, Austria, Spain, New Zealand, South Korea, and Puerto Rico.

Similarly, multiple technological tools were developed through collaboration among researchers from several countries (32.35% of the tools identified). Collaboration among multidisciplinary teams was also observed, highlighting its importance. For example, PACdb was a joint effort between authors from institutions in the USA and Singapore;[41] Virtual Pharmacist[48] and GWASdb[50] between authors from China and the USA; ePGA between authors from Greece and the United Arab Emirates;[53] PharmacoDB between authors from Canada and the USA;[57] PGxLOD between authors from

France and the USA;[59] PharmVar between authors from Austria, the USA, Spain, New Zealand, and Canada;[61] MTBP with authors from Sweden, Spain, the United Kingdom, France, the Netherlands, Germany, Italy, USA,[66] and CREAMMIST between authors from Thailand and Singapore.[68] In addition, two tools with no names were identified. The first tool, formed by authors from organizations in India, Germany, and Italy, was mentioned in the paper Guin et al 2019, as included in Table 2, the "Guin tool".[60] A second tool was identified in the paper by Zarei et al 2020, as included in Table 2, "Zarei tool".[64] The tool was showcased in an article by authors affiliated with institutions in the USA and Puerto Rico.

Table 2 Main Characteristics of Technological Tools for Pharmacogenomics Identified

Name	Characteristics
PharmGKB	A well-known resource for pharmacogenomics research, it collects, manages, and shares data on genetic variation impacts on drug responses. It enables searches for genes, variants, drugs, and diseases, and is closely linked to CPIC's dosing guidelines.
	Access: https://www.pharmgkb.org/
PharmGED	Provides information on protein polymorphisms, splicing alterations, expression variations, noncoding region mutations, and their effects on drug response.
	Access: Currently unavailable.
Drugbank	It provides biochemical and pharmacological data on drugs involving mechanisms, targets, and pharmacokinetics, pharmacodynamics, interactions, metabolism, enzymes, and polymorphisms represented through networks and graphs.
	Access: https://www.drugbank.com/
KPD	Tool designed to facilitate access to genetic information on the Korean population. Collects data on single nucleotide polymorphisms of 154 genes related to drug metabolism and compares SNP and haplotype frequencies among different ethnic groups. Provides educational materials and links to other global databases.
	Access: Currently unavailable.
"Gamazon tool"	Developed to show information on key pharmacogenes and utilize data from the 1000 Genomes Project to enhance predictive accuracy of drug response based on genetic variability.
	Access: Currently unavailable.
The Human Cytochrome P450 (CYP) Allele Nomenclature Database	It aims to harmonize the allele nomenclature of the CYP genes and provides a database with gene-specific pages about alleles and variations. Users can search for alleles by name or symbol, for genes, variants, rs, or amino acid changes.
	Access: Currently unavailable.
PACdb	Tool designed to analyse connections between genetic variations, gene expression, and cellular responses to drugs, focusing on cancer treatment. It examines differentially expressed genes in HapMap samples of European and African ancestry and summarizes correlations between gene expression and pharmacological phenotypes.
	Access: Currently unavailable.
SNPshot	Database developed by mining PubMed for genotype-phenotype associations, focusing on SNPs and their impact on drug response. It includes information on genetic variants, their drug relationships, frequency in subpopulations, and disease associations.
	Access: Currently unavailable.

(*Continued*)

Table 2 (Continued).

Name	Characteristics
FINDbase	This tool presents the distribution of genetic variants in different populations around the world, focusing on diseases and pharmacogenomic biomarkers. It was developed by researchers who also created Drugevar and ePGA.
	Access: http://www.findbase.org
DIRECT	Clinical database designed to assist physicians in making therapeutic decisions in oncology based on the mutational status of tumor genes of individual patients. It provides information on rare and common mutations. Allows prioritization of genetic treatments in real time and at the point of care.
	Access: Currently unavailable.
DEER Database	Developed to interpret the chemical effects of genetic and environmental factors on drug responses, including data on ecotoxicity, biodegradability, and persistence.
	Access: Currently unavailable.
SPP	It allows exploring the allelic architecture of genetic regions in selected populations using allele frequency plots. It also provides haplotype diversity maps (HDM) to visualize inter-population differences in haplotype patterns. It aims to facilitate comparisons of genetic diversity across ethnicities for genes related to drug response.
	Access: Currently unavailable.
DruGeVar	Provides pharmacogenomic biomarkers for FDA- and EMA-approved drugs; it serves as a tool to translate research in pharmacogenomics into practice. It is possible to search via genes, variants, drugs, and diseases.
	Access: Currently unavailable.
Virtual Pharmacist	Enables analysis of genetic variations, providing information on drug effectiveness, dosage, and toxicology using PharmGKB, dbSNP, and Drugbank. Accepts data from SNP array, FASTQ, and VCF, and calculates drug response in population.
	Access: Currently unavailable.
"Funk tool"	It is a machine learning-based classifier for predicting pharmacogenes on a genome-wide scale, using Gene Ontology annotations and features extracted from the biomedical literature. The system separates pharmacogenes from background genes, demonstrating significant functional differences between the two.
	Access: Currently unavailable.
GWASdb	A resource centred on human variation data from genome-wide association studies investigating the genetic basis for common human diseases. It collects and curates GWAS data by further adding knowledge through annotation and prediction of disease-causative genes.
	Access: https://www.ebi.ac.uk/gwas/
SPHINX	Analyses genetic variation in pharmacogenes from samples sequenced at nine US sites. Users can consult information by gene, pathway, or drug, including variant frequency by location and ancestry.
	Access: http://www.emergesphinx.org/

(*Continued*)

https://doi.org/10.2147/PGPM.S490135

Table 2 (Continued).

Name	Characteristics
ePGA	Enables personalized analysis, translating genotype to phenotype per clinical guidelines. Analyses pharmacogenomic biomarkers across different populations.
	Access: http://www.epga.gr/.
FDALabel	This database contains complete information on the FDA-approved drug labeling for indications, dosages, warnings, interactions, and clinical pharmacology. It also comprises pharmacogenomics information with data on genetic variants and correlations in drug response.
	Access: https://nctr-crs.fda.gov/fdalabel/ui/search
PharmacoDB	Compiles published cancer pharmacogenomic studies and curates data from in vitro experiments with cancer cell lines, including dose–response testing of approved and investigational drugs.
	Access: https://pharmacodb.ca/
PreMedKB	Integrates information on diseases, genes, mutations, and medications to understand the clinical significance of genetic variants. Generates semantic networks and dynamic graphs illustrating mutations, protein expression, gene positions, and drug molecular structures. Interprets genetic profiles, recommends therapies, designs genetic testing panels, and matches patients for clinical trials.
	Access: http://www.fudan-pgx.org/premedkb/index.html#/home
PGxLOD	It allows representing pharmacogenomic relationships between genetic factors, pharmacological treatments and phenotypes, integrating information from various sources such as databases (PharmGKB), biomedical literature and EHR studies with biobanks.
	Access: https://pgxlod.loria.fr/
"Guin tool"	Uses semiautomated text mining to create a comprehensive pharmacogenomic resource, integrating disease-drug-gene polymorphism relationships for a global perspective on therapeutic approaches.
	Access: Currently unavailable.
PharmVar	Provides nomenclature and cataloging of genetic variants related to drug metabolism and transport proteins. Identifies variant information, frequencies, gene function, and drug response associations.
	Access: https://www.pharmvar.org/
PGxMine	Uses text mining to gather pharmacogenomic associations from published literature, aiding PharmGKB curation. A supervised machine learning pipeline extracts associations between genetic variants (DNA, protein changes, star alleles, dbSNP) and specific chemicals.
	Access: https://pgxmine.pharmgkb.org/
Pg-path	Visually represents the interaction between drugs and genes using data from DrugBank 5.0.1. Maps networks of interactions, providing a dynamic view of the pharmacological process at the molecular and genetic level.
	Access: Currently unavailable.
"Zarei tool"	Provides a list of pharmacogenetically relevant drugs, classified by specialty and perioperative stage. Includes information on drugs, genetic variants, population frequencies, and their impact on drug response, particularly in anaesthesia and surgery.
	Access: https://pharmacogenomics.github.io/pharmacogenetics/

(*Continued*)

Table 2 (Continued).

Name	Characteristics
PharmVIP	It allows the analysis and interpretation of genomic variants derived from NGS platforms. Consists of three main modules: 1. Guidelines, which provides dosing recommendations based on CPIC data; 2. Reports on HLA genotypes and potential adverse drug reactions; and 3. Prioritizes variants according to their impact on gene function. Provides detailed, customizable and exportable reports.
	Access: https://pharmvip.nbt.or.th
MTBP	Integrates genomic and clinical data to support precision oncology decision making from the capture and analysis of sequencing data. Facilitates interpretation of cancer variants and linkage of molecular profiles to clinical actions.
	Access: https://mtbp.org/
PharmaKoVariome	Provides information on gene variations in 12 ethnic groups worldwide, aiding the development of national precision medicine guidelines. Users can retrieve information by gene, drug, or disease name and analyse ethnically diverse SNV frequencies for each locus.
	Access: http://www.pharmakovariome.com/#/.
CREAMMIST	The database provides an integrative dose–response curve. Specifically, this curve is based on five cancer cell-line drug-response datasets.
	Access: https://creammist.mtms.dev
IMOPAC	Simplifies complex pharmacogenomic profiles from cell lines into genetic, epigenetic, transcriptional, proteomic, metabolomic, and pharmacological events. Identifies biomarkers for drug response in cancers by linking multiomics gene and pathway alterations with drug responses.
	Access: http://www.hbpding.com/IMOPAC
PharmCAT	Technological tool to identify and analyze PGx alleles and diplotypes in large genetic datasets. This tool standardizes and normalizes genomic data, providing accurate results on genetic variations and prediction of drug responses.
	Access: https://pharmcat.org/
PancanQTL	Expression quantitative trait loci (eQTL) analysis tool for the study of cancer. It allows the mapping of causal variants, linking eQTL with drug response and immune infiltration.
	Access: https://hanlaboratory.com/PancanQTLv2

Characteristics of Technological Tools for PGx

We reviewed the functionality of the various technological tools involved by studying in detail their characteristics. Where possible and available, tools were accessed to know how they function. Details of these are shown in Table 2. It was also established from the review if these tools make use of information harvested or data from other PGx tools or databases.

We noted that 41.1% of tools are no longer accessible: PharmGED,[35] KPD[37] "Gamazon tool",[38] The Human P450 (CYP) Allele Nomenclature Database,[39,40] PACdb,[41] SNPshot,[42] DIRECT,[44] DEER Database,[45] SPP,[46] DruGeVar,[47] Virtual Pharmacist,[48] "Funk tool",[49] the "Guin tool",[60] and Pg-path.[63] This reflects the dynamic nature of the PGx field, which evolves rapidly. Newer technologies often replace older ones, whereas some tools evolve by incorporating functionalities or datasets from their predecessors.

In reviewing functionalities and information sources, many tools rely on data from previously developed databases through links or data integration. For example, the Human Cytochrome P450 (CYP) Allele Nomenclature Database was used by

PharmGKB and was later replaced by PharmVar.[61] DrugBank is also frequently utilized by other tools, including PharmGKB,[34] SNPshot,[42] the DEER Database,[45] SPP,[46] Virtual Pharmacist,[48] GWASdb,[50] PharmacoDB,[56] PreMedKB,[58] PGxLOD,[59] PGxMine,[62] Pg-path,[63] PharmVIP,[65] and PharmaKoVariome.[67] Finally, PharmGKB serves as a foundation for tools such as the "Gamazon Tool",[38] PACdb,[41] SNPshot,[42] SPP,[46] Drugevar,[47] Virtual Pharmacist,[48] "Funk tool",[49] SPHINX,[51] ePGA,[52,53] PreMedKB,[58] PGxLOD,[59] "Guin tool",[60] PharmVIP,[65] PharmCAT.[70]

PGx Technological Tools for PPH: Addressing Gaps and Needs in the Context of LMICs

Among these results, population and ancestry analysis emerges as a particularly notable functionality that is especially relevant for LMICs. Tools such as KPD,[37] PACdb,[41] SNPshot,[42] FINDbase,[43] SPP,[46] Virtual Pharmacist,[48] SPHINX,[51] ePGA,[52,53] PharmVIP[65] and PharmaKoVariome[67] offer the ability to analyse population- and ancestry-specific pharmacogenomic data. Specifically, these tools aim to detail how genetic variants, in the context of ancestral diversity and population-specific genetic background, influence the efficacy, dosing, and potential side effects of drugs. This is particularly relevant in low- and middle-income countries, where such tools could be used to deepen the analysis of genetic variations in diverse populations. In this way, they will contribute to optimizing drug therapies in these countries, closing the gaps in technological advances.

Another valuable functionality we found is the ability of users to upload their own data, notably with the Virtual Pharmacists tool,[48] ePGA,[52] PharmVIP,[65] MTBP,[66] and PharmCAT.[70] This feature enables the integration of various types of PGx data, including SNP genotyping results from microarrays, as well as FASTQ and variant call format files. This capability not only facilitates the collection and organization of data from new studies so that the tool provides up-to-date information but also makes it possible to include data from diverse sources and populations, including genetic data from LMICs.

Discussion

Mapping the Timeline and Geography

Our results show a steady increase in the literature related to technological tools for PGx. This trend coincides with statistics from the Centers for Disease Control and Prevention (CDC), which indicate an increase in the number of PGx study publications, from 12 in 2012 to 333 in 2021.[73] This kind of growth probably reflects the demand due to the need for tools to store, organize, and analyze PGx data generated by these studies. This underlines the growing interest and investment in a data-driven approach for integrating PGx information to translate theoretical research into practical clinical applications.[74]

This evolutionary trend is also consistent with the increasing interest in genomic databases, which have grown from 88 in 2013 to more than 700 in 2022, including different data types such as whole-genome sequences, whole-exome sequences, genome-wide genotypes, RNA-Seq, and epigenomic information, and includes the management of population data and PGx research practices.[75] This confirms the importance of implementing technological innovations to utilize PGx data.

Furthermore, through the documentary review of the articles, it was found that several technological tools were developed years before the publications. For example, PharmGKB, with articles from 2005, 2008, and 2013,[32–34] was initially established in 2000. Subsequent publications have highlighted additional functionalities integrated into the tool. Similarly, the Human Cytochrome P450 (CYP) Allele Nomenclature Database originally was developed in 1999, with publications in 2010 and 2013 article detailing updates.[39,40] The FindBASE article, published in 2013,[43] reflects a development that occurred in 2007. GWASdb, developed in 2012, introduced its version 2.0 in a 2016 publication.[50] The SPHINX is a 2016 publication[51] but reflects a tool developed in 2013. PharmacoDB, developed in 2017, has two associated articles: one dating from 2018 and another from 2022.[56,57] The latter describes version 2.0, emphasizing new data and the adoption of advanced technologies to ensure scalability. PharmVar, established in 2017, was the subject of a 2020 article focused specifically on the CYP2D6 gene,[76] the identified publication of PharmCAT[70] of the year 2023, but whose development took place in 2018 and finally PancanQTL[71] whose publication corresponds to a second version PancanQTLv2.0 in 2024 but whose initial version was in 2018. Therefore, these publications suggest the continuous evolution and progressive development of technological tools and databases for PGx over the last two decades.

Another relevant result is the origin of the authors of the publications analyzed. The results show that academic production is concentrated in developed countries, with few exceptions. Only in Asia was the participation of low- and middle-income countries identified, such as Thailand and India, whose authors participated in three articles. In Latin America and Africa, no technological tools developed by authors from low- and middle-income countries were found. This concentration highlights the critical role played by leaders in PGx research and underlines the need for greater representation from other regions in pharmacogenomics research, as well as its applicability to diverse populations.[73] This demonstrates that the development of PGx technologies is a critical area that requires resources, skills, experience, and the training of professionals, as well as specialized facilities and laboratories, which are lacking in many low- and middle-income countries in Latin America and Africa, representing a significant gap in access to PGx due to the lack of technology and financing in these countries, which, added to political and fiscal factors, can represent additional barriers to the implementation of PGx databases and technological tools.[77–79]

The need to implement pharmacogenomics (PGx) technologies is especially important in contexts where information on ancestral genomic variants is lacking. In Africa, a recent genome-wide study of 426 individuals from 13 African countries revealed more than 3 million new genomic variants, highlighting the knowledge gap on the genetic diversity of these populations and the urgency of prioritizing PGx research in Africa.[80,81]

According to Kuguyo,[82] biorepositories could be an alternative in advancing pharmacogenomics and translational research, and a cancer biobank has now been established in Zimbabwe to collect and analyze genomic data, which is essential to overcome barriers in that country, where a lack of representative studies and limitations in storage and analysis infrastructure complicate the progress of PGx. Other initiatives are focused on implementing preventive pharmacogenetic screening programs in South Africa, which they claim could reduce adverse drug reactions by 30%, reflecting the enormous potential of these technologies to improve public health outcomes, but caution that African genetic diversity and socio-economic challenges require specific local approaches.[83] This approach could also serve as a model for other under-represented regions, which could leverage Pgx technology tools such as those shown in this article. Meanwhile, initiatives such as CÓDIGO-Colombia in Latin America underline the importance of strengthening local infrastructures that facilitate the large-scale use of existing population data.[84]

Kanhaiya[85] emphasized that building healthcare informatics systems require synergy between healthcare information components and highly qualified multidisciplinary teams comprising physicians, biomedical researchers, computer scientists, and data scientists. Such teams play essential roles in effectively managing, integrating, analyzing, and interpreting data to advance PGx. Further, there is a requirement for computational and collaborative data management infrastructures, with investment in state-of-the-art omics technology and other digital tools in high-performance computing and multistorage facilities based on the cloud.[85] This highlights the importance of having sufficient resources to maintain these technological tools. Many of the reviewed tools herein still exist, but ensuring continuity in maintenance and upgrades is important in sustaining initiatives in PGx implementation.

PGx Technological Tools for PPH: Addressing Gaps in the Context of LMICs

These 34 tools underscore the commitments of the scientific community toward the advancement of PGx analysis. From enzymatic variation to text mining, through studies of genetic variations having an impact on the prediction of response to drugs and treatment optimization, these tools enhance clinical practice. It makes it easier and more accessible for researchers and clinicians alike to do their job with the help of online resources and applications that provide ease in medication selection and administration while contributing to the prevention of adverse reactions and improving the efficacy of therapeutic interventions.[86]

The use of technological tools for PPH in low- and middle-income countries is crucial to the translation of pharmacogenomics advances to help respond to global health challenges. According to Magavern,[87] the application of population-level PGx is critical in harnessing the power of genomic knowledge that has not yet been fully tapped in genomic diversity-rich regions like Oceania, Africa, and Latin America. However, this review revealed a lack of options for capturing, organizing, and analyzing pharmacogenomic data in these regions.

In this review, 11 identified tools—KPD, PACdb, SNPshot, FINDbase, SPP, Virtual Pharmacist, SPHINX, ePGA, PharmVIP, and PharmaKoVariome—provide specific functionalities to analyze population- and ancestry-specific

pharmacogenomic data, helping to address biases and optimize drug therapies for diverse populations. Ancestry plays a crucial role in PGx by mitigating biases that arise in studies predominantly involving majority groups. Therefore, ancestry should be taken into account in these various populations living in LMICs for both equitable and safe practices.[88,89]

The advancement of a range of technological instruments was made possible through the collaborative efforts of researchers from a multitude of nations. The differences in technological advancement in population genomics are sharp reminders of why collaboration between nations would be needed, especially within those countries with no kind of pharmacogenomic tools, to help narrow the gap—underscoring capacity-building activities within underrepresented regions. Population genomics offers significant potential to increase initiatives worldwide by enhancing the understanding of specific populations' genetic profiles for drug policies and dosage recommendations.[90]

Online tools and resources are invaluable for conducting a variety of analyses. Often, access to multiple sources is necessary to gain comprehensive insights. In countries lacking their own tools, health professionals and researchers can use online resources or adapt existing resources to analyze available data as an initial step in population analysis for resource-limited regions. The ability to upload data to technological tools and conduct population and ancestry analyses helps narrow the technology gap for low- and middle-income countries, enhancing their capacity to utilize pharmacogenomic insights effectively.

Conclusions

In this review, we identified groups of tools and discussed how their functionalities can support population analyses in LMICs where PGx has not yet been widely implemented. The use of these tools created by international experts in PGx gives valuable resources that allow for prioritization of candidate genes and promotes PPH interventions for diverse populations.

Development of technological tools for storing, organizing, and analyzing generated PGx information has been a basic pillar about understanding, harmonizing, dissemination, and definition of key factors related to the impact of genetic variations on drug absorption, distribution, metabolism, and elimination. This review highlights the significant advancements in technological tools and their role as fundamental sources of information for precision health decision-making.

Collaboration is essential for collecting, organizing, and analyzing genomic information from diverse populations. Such collaborative efforts enhance the accuracy of public health decision-making and effectively address specific PGx gaps in LMICs. By leveraging these technological tools and fostering international cooperation, we can advance the implementation of PPH and improve health outcomes globally, which would enhance the accuracy of public health decision-making and effectively address specific PGx gaps.

Limitations and Future Work

This review examined technological tools capable of capturing, storing, and analysing PGx data; however, it may be that the number of existing tools is bigger than that reviewed here. It is recommended developing services facilitating large-scale use of data existing populations and multiple population inclusions, as is currently being developed at CÓDIGO-Colombia[85] and Africa.

There is also an urgent requirement for the development and strengthening of such technological tools in LMICs. Future research has to evaluate not only the possibility of implementing PGx technologies in these regions but also strategies elaboration concerning public health initiatives targeting underrepresented populations.

Abbreviations

LMICs, Low and Middle-Income Countries; PGx, Pharmacogenomics; PPH, Precision public health; PRISMA ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its Supplementary Material.

Ethics Approval

Ethics approval was not required for this scoping review.

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