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REVIEW ARTICLE

A systematic review on the cost effectiveness of pharmacogenomics in developing countries: implementation challenges

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The major challenges that delay the implementation of pharmacogenomics based clinical practice in the developing countries, primarily the low- and middle-income countries need to be recognized. This review was conducted to systematically review evidence of the cost-effectiveness for the conduct of pharmacogenomics testing in the developing countries. Studies that evaluated the cost-effectiveness of pharmacogenomics testing in the developing countries as defined by the United Nations were included in this study. Twenty-seven articles met the criteria. Pharmacogenomics effectiveness were evaluated for drugs used in the treatment of cancers, cardiovascular diseases and severe cutaneous adverse reactions in gout and epilepsy. Most studies had reported pharmacogenomics testing to be cost-effective (cancers, cardiovascular diseases, and tuberculosis) and economic models were evaluated from multiple perspectives, different cost categories and time horizons. Additionally, most studies used a single gene, rather than a gene panel for the pharmacogenomics testing. Genotyping cost and frequency of risk alleles in the populations influence the cost-effectiveness outcome. Further studies are warranted to examine the clinical and economic validity of pharmacogenomics testing in the developing countries.

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INTRODUCTION

Pharmacogenomics is the study of how an individual's genetic variants influence drug responses, including the variants associated with adverse drug reaction (ADR) and treatment efficacy. The variable drug responses are due to polymorphisms of genes encoding the enzymes, transporters and receptors underlying the pharmacokinetic and pharmacodynamics pathways [1]. The term "pharmacogenomics" was introduced in 1959 by Friedrich Vogel [2] and the first pharmacogenomics test, namely AmpliChip CYP450, was approved by the US Food and Drug Administration in 2004 [3]. Since then, pharmacogenomics testing has been applied in personalizing drug treatment of various diseases, including cardiovascular disease [4], cancer [5], gout [6], autoimmune diseases [7], and infectious diseases [8] to personalize the therapy with the aim of achieving maximum efficacy while reducing the ADR that attributes to a high economic burden, high mortality and morbidity, and higher hospitalization costs globally [9–12].

In the developing countries, ADRs are estimated to contribute to 1.8% mortality rate [13]. The WHO ADRs database, Vigibase reported that African populations experienced more ADRs than the rest of the world populations [14]. In developed countries the implementation of pharmacogenomics guided use of medicines has been shown to reduce risk for ADRs at individual and population level [15] hence better health outcomes and better use of clinical resources. The high throughput next-generation sequencing platform has made it possible to identify almost all the genetic variants (known and unknown functional implication) in an individual and those associated with variable drug response [16]. Identification of the genetic variants helps the healthcare practitioners and relevant parties to predict the outcome of a particular drug selected in the treatment strategy. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe cutaneous hypersensitivity reactions with clinical presentations including keratoconjunctivitis, blisters, macules, and finally sloughing of skin that exposes erythematous skin. Factors that contribute to development of SJS/TEN include drug reaction, infection and graft vs host disease [17].

Although pharmacogenomics practice has been well conducted in developed countries [18], the practice is still lagging or at infancy in most developing countries. The major challenges to establish pharmacogenomics practice in the developing countries include lack of clinical trials which validate genomics biomarkers of interest, low resources in clinical settings, cultural issue that complicates medical ethics, and less enthusiasm among investors and stakeholders to invest in the developing countries [19]. Skepticism arises whether implementing pharmacogenomics testing in the developing countries would be good value for money. The adoption of pharmacogenomics in the healthcare system has economic consequences to patients, payers, and the pharmaceutical industry due to the cost of pharmacogenomics

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test, cost of drugs, and additional costs to conduct clinical trials to validate the biomarkers. Therefore, the economic impact of pharmacogenomics testing should be critically evaluated before the practice can be implemented [20]. Cost effectiveness is an economic evaluation that compares the costs and health outcomes which differ in different countries. In case of pharmacogenomics practice, the cost effectiveness compares economic evaluation of genotype-guided therapy and standard therapy. Pharmacogenomics-guided therapy is considered as cost-effective if it is superior compared to that of standard therapy. Health outcomes can be measured according to life years gained, lives saved and avoidance of incidences and hospitalizations. To be cost-effective, pharmacogenomics-guided therapy should be dominant, in which the guided therapy must be cost saving and give higher quality adjusted life per year than that of standard therapy. However, the pharmacogenomics-guided therapy can also be deemed as cost-effective if the quality of life that results from the guided treatment gives significantly better quality of life although the cost is more expensive than that of standard care. Incremental cost-effectiveness ratio (ICER), a ratio of net cost of implementing genotype-guided therapy to net of health effect, is usually adopted to assess the cost-effectiveness of genotype-guided therapy. Health effect is measured using quality-adjusted life-year (QALY) that can be expressed in the range of 0 (death) to 1 (healthy) in subjects with genotype-guided therapy to that of subjects with standard therapy. In order to evaluate whether the outcome of medical intervention is cost-effective or not, a concept of 'willingness to pay' threshold, maximum cost the subject willing to pay, is usually adopted. The threshold varies from country to country, but the threshold is usually set at three time of the gross domestic product (GDP) of the country [21]. Cost utility is a part of cost effectiveness analysis, in which instead of adopting ICER as the parameter, it adopts QALY as the parameter in the analysis [22]. Economic evaluation of cost-effectiveness can be evaluated from different perspectives, namely societal, healthcare payer, and healthcare sector. For instance, healthcare perspective evaluates the impact of cost-effectiveness based on health costs while social perspective evaluates all costs including medical and non-medical costs. The perspectives chosen for the economic evaluation will impact resource allocation, policymakers, insurance body (healthcare payer), costs borne by patients from 'out-of-pocket' money, and society as a whole [23].

A recent systematic review conducted on the cost-effectiveness of pharmacogenomics-guided treatment in cardiovascular disease reveals that most studies performed in the developed and developing countries were cost-effective [24]. However, the study perspective, cost of drugs and cost inputs varied across studies, and the study design elements pertinent to economic models were obscure [24]. The objective of this study was to perform a systematic review on the cost-effectiveness of pharmacogenomics in developing countries to update present knowledge and gaps on the implementation of pharmacogenomics in developing countries.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched through the database, namely PubMed, SCOPUS, MEDLINE, and Science Direct for previous literature published on the cost-effectiveness of pharmacogenomics in developing countries using the procedure as described in the supplementary file (Table S1). Furthermore, we also searched the articles through manual processes and the reference lists from relevant articles were identified using electronic databases. Studies that examined the cost-effectiveness of pharmacogenomics practice in the developing countries were included according to the PICO guidelines:

1) Population: studies conducted on populations in developing countries based on the criteria from United Nations (Table S1). We follow the UN classification of developing countries according to the World Economic Situation and Prospects published in 2021 [25]. Based on this report, the countries are classified into three categories: developed economies, economies in transition and developing economies. Developed economies that include 36 countries were excluded from our analysis as they are categorized as developed countries. The countries categorized under economies in transition and developing economies are classified as developing countries, and hence were included in our literature search. Regions of developing countries were divided into the Caribbean, Mexico and Central America, South America, South Asia, East Asia, Western Asia, North Africa, Central Africa, East Africa, Southern Africa, and West Africa, and the economic status of the developing countries were classified into economies in transition, developing economies, and the least developed countries (Table S1).

2) Intervention: studies that screened for the host's genetic variant(s) or genomes to study drug response.

3) Context: studies that applied pharmacogenomics (assessment of drug-gene interaction) in their studies were included in this review.

4) Outcome: studies that evaluated the cost-effectiveness of pharmacogenomics in their studies were included in this review.

Meanwhile, exclusion criteria included studies that (1) did not evaluate the cost-effectiveness of pharmacogenomics, (2) were not conducted in the developing countries, (3) did not screen the genetic variants of the subjects, and (4) did not examine the interaction between drug and the genetic variant of the hosts. Reviews, letter to the editor, chapter in book, conference proceedings, and studies not published in English were also excluded from our systematic review. Critical appraisal of the articles was conducted as described previously [26], with scores given to evaluate quality of the articles using Quality of Health Economics Studies (QHES) criteria [27]. The QHES scores range from 0 to 100, with 100 indicating a perfect score. Three independent reviewers were tasked to critically review all the articles to be included in this systematic review. Disagreement on the suitability of the articles to be included in the systematic review was resolved through discussion and consensus among three independent reviewers. Compilation of articles and data extraction were conducted using MS Excel 2016.

Presentation of results

Results were synthesized narratively due to the variability of study design across the included studies. The results include study characteristics (i.e., year, country, disease and drugs studied), study strategies applied, a summary of cost-effectiveness in implementing pharmacogenomics practice and conclusion on cost-effectiveness.

RESULTS

Study selection process

The systematic search of the electronic database captured 1699 articles published from 2000 to March 2021 and three articles from hand-searching (Fig. 1). We excluded 929 articles during the initial screening process because they were not relevant to the research question. After title and abstract screening, 72 articles were eligible for full-text review. After applying exclusion criteria, 28 articles met the inclusion criteria as stipulated in the Methods section. However, a study conducted by Jiang et al. [28] was excluded because it was conducted based on the USA healthcare provider and the origin of the population used in their study was unclear. Finally, 27 articles were included in our systematic review. A list of studies included in this systematic review is available in Table 1 [29–55].

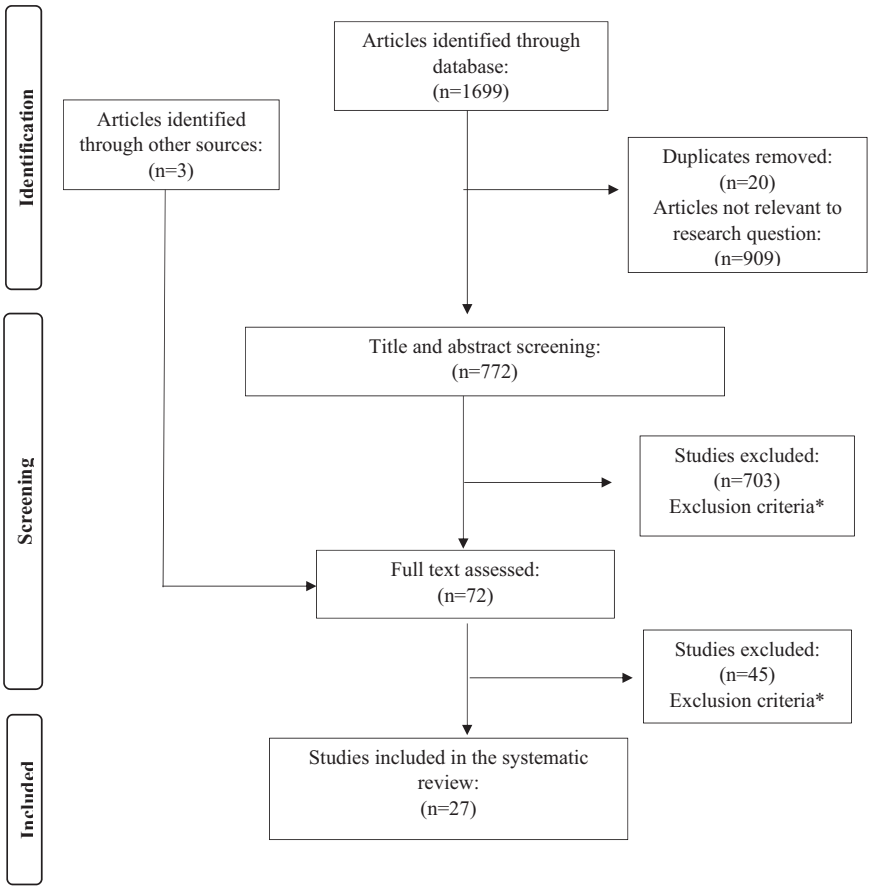

Fig. 1 Study overview. Flowchart of article screening *Exclusion criteria: (1) the study did not evaluate the cost-effectiveness of pharmacogenomics, (2) the study was not conducted in developing countries, (3) the study did not screen genetic variants of subjects, and (4) the study did not examine the interaction between drug and the genetic variant of hosts, (5) reviews, letter to the editor, chapter in book, conference proceedings, and studies published not in English.

Summary of study characteristics

The characteristics of the studies included in the systematic review are summarized in Table 2. Most studies were single center study conducted in the respective country: China ($n = 10$), Singapore ($n = 7$), South Korea ($n = 3$), Thailand ($n = 3$), Malaysia ($n = 2$), and Taiwan ($n = 1$). One recent study involved 3 countries of Brazil, India and South Africa [48]. All studies ($n = 27$) were conducted in Asian countries with one study including Brazil and South Africa. Twenty-five studies were published from 2012 onwards, while two studies were published in 2004. The most common disease group studied was cancers ($n = 6$), namely breast cancer, lung cancer, and colorectal cancer, followed by cardiovascular diseases ($n = 5$), and gout and severe cutaneous adverse drug reactions (both groups, $n = 4$). The other studies focused on epilepsy ($n = 3$) and thromboembolic events ($n = 2$), and one study each focused on HIV, tuberculosis, and autoimmune diseases. Meanwhile, most studied drugs include urate-lowering agents and uricosuric acid ($n = 7$), followed by anticoagulant agent ($n = 4$), anticancer agent ($n = 4$), antiplatelet agent ($n = 3$), and anticonvulsant agent ($n = 4$). The remaining studies covered antiestrogen ($n = 2$), antibiotic ($n = 1$), antiviral ($n = 1$), and immunosuppressant ($n = 1$). All studies employed a pharmacogenomics approach after the treatment plan was made rather than a pre-emptive strategy. Most of the studies ($n = 24$) employed the single gene test in their tests; two studies employed two genes in their studies [31, 37], while one study employed next-generation sequencing to analyze patients' genomes in their pharmacogenomics-guided strategy [44]. The funding source was reported in 12 studies, 14 studies had no statement regarding their research funding, and one study [49] had no funding source. Of the 12 studies with funding sources, 10 were funded by public organizations, while private organizations funded two [40, 42].

Summary of study strategies

Most of the studies ($n = 17$, 63%) used hypothetical cohorts as their economic models, while the remaining studies used observational studies ($n = 7$, 25.9%) and randomized controlled trials ($n = 3$, 11.1%). The studies that employed hypothetical cohorts in their models derived model parameters from randomized controlled trials, hospital database, government records, and published literature. Most studies were conducted based on the perspective of the healthcare system ($n = 8$, 29.6%) and societal ($n = 8$, 29.6%), followed by the payer's perspective ($n = 5$, 18.5%). The remaining studies employed both the perspective of the healthcare and societal ($n = 1$, 3.7%) and healthcare providers' perspectives ($n = 2$, 7.4%). Three studies (11.1%) did not state what perspective was used in their studies [29, 33, 45]. Time horizons used in the cost-effectiveness studies varied, in which nine studies employed lifetime assessment, five studies employed 20-30 years assessment, four studies employed 7-20 years assessment, eight studies employed ≤1-year assessment, and one study did not state the time horizon used [42]. Majority of the studies ($n = 15$, 57.7%) did not specify patients' age in their models, while four and eight studies enrolled patients aged ≥60 years and <60 years, respectively. Most studies used quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) to measure effectiveness ($n = 25$, 92.6%) (Table 3). Cost categories included in cost-effectiveness evaluation were pharmacogenomics test cost,

Table 1. List of studies included in the systematic review.

Authors [Ref]	Year	Country	Drug/disease	Gene variant	Parameters of cost-effectiveness evaluation
Fu et al. [29]	2020	China	clopidogrel and ticagrelor/ acute coronary syndrome	CYP2C19 loss of function	PGx test; daily cost of clopidogrel; daily cost of ticagrelor; non-fatal MI; non-fatal stroke; non-fatal intracranial bleeding; CVD death; post MI; cost of event free
Teng et al. [30]	2020	Singapore	allopurinol and febuxostat/gout patients with chronic kidney disease	HLA-B*58:01	PGx test; annual cost allopurinol; annual cost febuxostat; cost per admission; cost of SJS; cost of SJS/TEN; cost of TEN; annual long term sequelae of SJS/TEN
Chong et al.[31]	2014	Thailand	warfarin/thromboembolism and bleeding	CYP2C9 and VKORC1 A	PGx test; cost of drugs; costs of TE, major bleeding/episode and sequelae; cost of transportation and additional food cost per visit (relatives); daily productivity loss per age group
Wei et al. [32]	2019	China	irinotecan/colorectal cancer	UGT1A1*6/*28	PGx test; Cost of FOLFIRI, full doseand 50% dose of irinotecan; cost of grade 0–4 neutropenia; cost of routine examination and testing
Chen et al. [33]	2016	Hong Kong/China	carbamazepine/epilepsy	HLA-B*15:02	Current, ideal and extended screening policy of PGx tests; annual CBZ cost; cost of non-fatal death of SJS/TEN
Wei et al. [34]	2020	China	tamoxifen and toremifene/breast cancer	CYP2D6*10	PGx test; cost of TOR and TAM; cost of non-fatal death (disease-free survival and recurrent disease); direct non-medical costs due to disease-free survival and recurrent disease
Wang et al. [35]	2017	Hong Kong/China	clopidogrel or ticagrelor/acute coronary disease	CYP2C19*2	PGx test; costs of clopidogrel and ticagrelor; costs of non-fatal events including MI, major bleeding, stent thrombosis, and stroke; cost of fatal death; costs of post MI and post stroke; cost of event free
Ke et al. [36]	2017	Taiwan	allopurinol/severe cutaneous adverse drug reaction	HLA-B*58:01	Annual cost of PGx test; annual allopurinol, annual febuxostat, and annual benzbromarone; costs of non-fatal death including gout- or hyperuricemia-related medical cost and survived with SCAR; cost of death with SCAR
Kim et al. [37]	2017	South Korea	warfarin/cardiovascular disease	CYP2C9 and VKORC1	PGx test; cost of warfarin; costs of non-fatal death including hospitalization fee for initial anticoagulation, valve replacement surgery, intracranial hemorrhage, extracranial hemorrhage, transient ischemic attack, stroke, and sequelae
Dong et al. [38]	2015	Singapore	allopurinol/gout	HLA-B*58:01	PGx test; annual allopurinol and annual probenecid; Cost of per case SJS–TEN overlap treatment; cost per case SJS; cost per case TEN
Kim et al. [39]	2021	Singapore	clopidrogel and ticagrelor/acute coronary syndrome	CYP2C19 loss of function	PGx test; annual clopidogrel and annual ticagrelor; non-fatal events including MI, non-CABG major bleeding, and CVA; post event including post ACS management
Lu et al. [40]	2016	China	crizotinib/lung cancer	ALK gene rearrangement	PGx testing using either Ventana, IHC, qRT-PCR, and FISH; costs of pemetrexed, traditional chemo, and crizotinib per day; costs of non-fatal death including follow-up, salvage chemo, palliative end of care life, supportive care per cycle, and cost of SAE
You et al. [41]	2004	China	warfarin/thromboembolic events	CYP2C9	PGx test; costs of non-fatal events including standard service at clinic, major bleeding and TE
de Lima et al. [42]	2012	Singapore	gefitinib/advanced lung carcinoma	mutation in EGFR	PGx test; cost of gefitinib for patients with activating EGFR mutation, cost of gefitinib for patients without activating EGFR mutations, cost of chemotherapy for patients with and without activating EGFR mutations; costs of non-fatal death including fixed BSC cost and monthly BSC cost

Table 1. continued

Authors [Ref]	Year	Country	Drug/disease	Gene variant	Parameters of cost-effectiveness evaluation
Wei et al. [43]	2020	China	tamoxifen/breast cancer	CYP2D6*10 T/T	PGx test; costs of TAM and AI; non fatal events including disease-free survival and recurrent disease; non-medical costs related to disease-free survival and recurrent disease
Lu et al. [44]	2018	China	crizotinib/lung cancer	ALK gene rearrangement	PGx tests using multiplex PCR or NGS; costs of pemetrexed, traditional chemo, and crizotinib per day; follow-up, salvage chemo, palliative end of care life, supportive care per cycle, and cost of SAE
Kapoor et al. [45]	2015	Singapore	abacavir/HIV	HLA-B*57:01	PGx test; cost of drugs; cost non-fatal death including intolerable side effects; cost of fatal death
Saokaew et al. [46]	2014	Thailand	allopurinol/Stevens-Johnson syndrome and toxic epidermal necrolysis	HLA-B*58:01	PGx test; annual allopurinol and annual probenecid; costs of non-fatal events including annual cost SJS/TEN, gout, and DES; non-medical costs of foods and transportation for relatives
Dong et al. [47]	2012	Singapore	carbamazepine and phenytoin/ newly diagnosed epilepsy	HLA-B*15:02	PGx test; annual CBZ, annual VPA, and hypothetical therapy; costs of non-fatal events including SJS, TEN and SJS/TEN
Rens et al. [48]	2020	Brazil, South Africa and India	isoniazid/ tuberculosis	NAT2	Cost of PGx test; costs of antibiotics; costs of non-fatal events including toxicity and healthcare management
Pruis et al. [49]	2020	Singapore	allopurinol, febuxostat, and probenecid/ gout	HLA-B*58:01	PGx test; costs of drugs in primary and secondary care; non-fatal events costs including chronic phase and acute flare; cost of fatal events including chronic phase and acute flare
You et al. [50]	2012	Hong Kong/China	dabigatran and warfarin/atrial fibrillation for stroke prevention	CYP2C9	PGx test; costs of baigatran and warfarin; costs of non-fatal events; cost of fatal event
Park et al. [51]	2015	South Korea	allopurinol/gout, adverse drug reaction	HLA-B58:01	PGx test; costs of allopurinol and febuxostat; non-fatal events including admission cost and other lab tests; cost of fatal event
Oh et al. [52]	2004	South Korea	azathioprine/SLE and rheumatoid arthritis	TPMT	PGx test; cost of non-fatal event (admission cost)
Chong et al. [53]	2017	Malaysia	allopurinol/Stevens-Johnson syndrome	HLA-B*58:01	PGx test; costs of drugs including allopurinol, probenecid, indomethacin, and febuxostat; costs of non-fatal events including gout management, acute gout flare, and SJS/TEN treatment; cost of post event including follow up for DES; costs of direct non-medical costs clinic, food and hospital
Chong et al. [54]	2017	Malaysia	sodium valproate/adverse drug reaction	HLA-B*15:02	PGx test; costs of drugs including CBZ, VPA and TPM; cost of non-fatal events including SJS/TEN treatment and follow up for DES; direct non-medical costs including clinic, hospital and foods
Rattanavipapong et al. [55]	2013	Thailand	carbamazepine/epilepsy and neuropathic pain	HLA-B*15:02	PGx test; costs of drugs including CBZ and GBP; direct medical costs and indirect medical costs

PGx pharmacogenomics, *CBZ* carbamapezine, *GBP* gabapentin, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis, *VPA* valproate, *TPM* topiramate, *DES* exposure to diethylstilbestrol, *TAM* tamoxifen, *AI* aromatase inhibitor, *MI* myocardial infarction, *CVD* cardiovascular disease, *TE* thromboembolism, *TOR* toremifen, *FOLFIRI* folinic acid, fluorouracil and irinotecan, *EGFR* epidermal growth factor receptor, *BSC* best supportive care, *IHC* immunohistochemistry, *FISH* fluorescence in situ hybridization, *CABG* coronary artery bypass grafting.

Table 2. Summary of study characteristics and strategies.

Study characteristics	Total studies included, $N = 27$
Year	Number of studies, *n*
2004–2008	2
2009–2013	4
2014–2018	13
2019–2021	8
Country	
China	10
Singapore	7
South Korea	3
Thailand	3
Malaysia	2
Taiwan	1
India[a]	1
Brazil[a]	1
South Africa[a]	1
Disease diagnosis	
Cancers	6
Cardiovascular disease	5
Severe cutaneous adverse drug reactions	4
Gout	4
Epilepsy	3
Bleeding and thromboembolic events	2
HIV	1
Tuberculosis	1
Autoimmune disease	1
Drug category	
Urate lowering agent and uricosuric agent	7
Anticancer	4
Anticoagulant	4
Antiplatelet	3
Anticonvulsant	4
Antiestrogen	2
Antiviral drug	1
Immunosuppressant	1
Antibiotic	1
Genes studied[c]	
HLA-B	12
Cytochrome P450	9
ALK	2
UGT1A1	1
EGFR	1
NAT2	1
Thiopurine methyltransferase	1
VKORC1	2
Funding support	
No statement	14
Public	10
Private	2
No funding	1
Study strategies	
Hypothetical	17
Observational	7
Randomized controlled trial	3
Perspective	
Healthcare system	8
Societal	8
Payer[b]	5
Healthcare system and societal	1
Healthcare provider	2
No statement	3
Time horizon	
Lifetime	9
20–30 years	5
10–15 years	3
7 years	1
1 year	6
<1 year	2
No statement	1
Patient age range	
≥60 years old	4
<60 years old	8
Not specified	15

HLA-B human leukocyte antigen B, *ALK* anaplastic lymphoma kinase, *UGT1A1* UDP glucuronosyltransferase family 1 member A1, *EGFR* epidermal growth factor receptor, *NAT2* N-acetyltransferase 2, *VKORC1* vitamin K epoxide reductase complex subunit 1.

[a]A tuberculosis study that involved three countries i.e., India, Brazil and South Africa.

[b]Payer's perspective includes public and private payers.

[c]Two studies employed more than one gene in the pharmacogenomics test.

patients' management in case of non-fatal and fatal events, costs of drugs, and non-medical costs. Different cost categories were included in the economic models. All the studies included costs for the pharmacogenomics test that varied based on the countries and targeted genetic variants (Fig. 2). Similarly, all studies also included one-time event costs such as bleeding events, stroke, toxicity, and intolerable side effects. The cost of drugs was also included in most studies ($n = 26$, 96.3%), with the cost of drugs, pharmacogenomics tests, and patients' management varied across countries. Seven studies included indirect medical costs (e.g., transportation cost, additional food cost, cost of being accompanied by at least one relative to the healthcare facility, and daily productivity loss based on age group). Only 75% of the studies were conducted based on societal perspective which included indirect medical costs in their analyses. Furthermore, 23 studies (85.2%) used one-way sensitivity analysis to account for uncertainties in their model parameters (Fig. 2). Twenty-one studies included 'willingness to pay' costs according to their respective countries' gross domestic product (GDP) (Table 3), and they explored the parameter using probabilistic sensitivity analysis.

Comparison of cost-effectiveness results

Sixteen studies (69.2%) reported pharmacogenomics practice to be cost-effective, eight studies found pharmacogenomics practice

Table 3. Outcomes of cost-effectiveness analysis.

Author [Ref]	Outcomes	ICER	Willingness to pay	Conclusion
Fu et al. 2020 [29]	QALY and ICER	84118 yuan per QALY relative to universal clopidogrel	178980 yuan per QALY as the threshold	Ticagrelor was more cost-effective compared to PGx-guided therapy, but PGx-guided therapy was more cost-effective than universal clopidogrel
Teng et al. 2020 [30]	QALY and ICER	USD 269147 per QALY	USD 50000	Not cost-effective due to increment in costs (i.e., genotyping and annual febuxostat)
Chong et al. 2014 [31]	QALY and ICER	USD 49234 per QALY (healthcare) and USD 49128 per QALY (societal)	160,000 THB (5,333 USD; 1.2 GNI) per QALY	Not cost-effective due to higher cost in PGx-guided therapy than that of standard therapy
Wei et al. 2019 [32]	QALY and ICER	Dominant compared to treatment strategy without genotyping	USD 26,508 (3X GDP in China in 2017)	Cost-effective and cost saving
Chen et al. 2016 [33]	QALY and ICER	USD 85697 per QALY in the current situation; USD 11090 per QALY in the ideal situation and USD $197158 per QALY in the extended situation.	USD 50000 per QALY	Not cost-effective due to turnaround time, cost of PGx and low incidence of ADR among the drug response gene carriers
Wei et al. 2020 [34]	QALY and ICER	USD 5055.74 per QALY	USD 26508 per QALY	Cost-effective
Wang et al. 2017 [35]	QALY and ICER	USD 418 per QALY	USD 42423 per QALY	Cost-effective
Ke et al. 2017 [36]	QALY and ICER	NT$17,378,777 per life-year and NT$230,925 per QALY	NT$ 400000 (USD 12,800 in 2015) per QALY	Cost-effective
Kim et al. 2017 [37]	QALY and ICER	USD 1356.2 per QALY	USD 50000 per QALY	Cost-effective
Dong et al. 2015 [38]	QALY and ICER	USD 85630 per QALY	USD 50000 per QALY	Not cost-effective due to lower quality of life, higher costs of drug and genotyping, and treatment than that of standard care. However the authors concluded that PGx-guided treatment can be cost-effective if cost of genotyping is lower than that of standard care.
Kim et al. 2021 [39]	QALY and ICER	SGD 72158 per QALY	SGD 88991 per QALY	Cost-effective
Lu et al. 2016 [40]	QALY and ICER	USD 16820 to USD 254668	USD 32000	Cost-effective
You et al. 2004 [41]	QALY and ICER	USD 155700 per 100 patients	N/A	Cost-effective
de Lima et al. 2012 [42]	QALY and ICER	SGD 77160 per QALY (dominant)	N/A	Cost-effective
Wei et al. 2020 [43]	QALY and ICER	USD 5015.69 per QALY	USD 26508 per QALY	Cost-effective
Lu et al. 2018 [44]	QALY and ICER	USD 14384 to USD 13740 per QALY gained	USD 32000 per QALY	Cost-effective
Kapoor et al. 2015 [45]	QALY and ICER	USD 44 649 per QALY in Singaporean Indian with genotype testing prior to administration of abacavir; USD 114068 to USD 757 270 for Singaporean Malays and Chinese at early stage of HIV and all ethnicities at late stage of HIV.	USD 50000 per QALY	Not cost-effective except for Singaporean Indians at early stage of HIV who underwent genotype testing prior to administration of abacavir
Saokaew et al. 2014 [46]	QALY and ICER	THB 156937 (USD5062) per QALY per 1000 patients	THB 160000 (USD 5161) per QALY gained	Cost-effective
Dong et al. 2012 [47]	QALY and ICER	USD 37030 per QALY) for Singaporean Chinese patients, USD 7930 per QALY for Singaporean Malays, and USD 136 630 per QALY for Singaporean Indians	USD 50000	Cost-effective for Singaporean Malays and Chinese, but not for Singaporean Indians due to difference in frequency of PGx biomarker tested
Rens et al. 2020 [48]	QALY and ICER	USD 476 per QALY (Brazil); USD 1780 per QALY (South Africa); USD 546 per QALY (India)	GDP for Brazil (USD 8921), South Africa (USD 6340), and India (USD 2016)	Cost-effective in all countries examined
Pruis et al. 2020 [49]	QALY and ICER	Dominated by standard care without genotyping testing	SGD 1620 to SGD 16500 per QALY	Not cost-effective due to genotyping cost and low incidence of SJS/TEN in Singapore

Table 3. continued

Author [Ref]	Outcomes	ICER	Willingness to pay	Conclusion
You et al. 2012 [50]	QALY and ICER	Dabigatran 150 mg dominated genotype-guided therapy	USD 50000 per QALY	Not conclusive, only dabigatran 150 mg was cost-effective
Park et al. 2015 [51]	Total expected cost and ICER	N/A	N/A	Cost-effective
Oh et al. 2004 [52]	Total expected cost and ICER	N/A	N/A	Cost-effective
Chong et al. 2017 [53]	QALY and ICER	Standard care dominated PGx-guided therapy	USD 8695 per QALY	Not cost-effective due to low incidence of allopurinol-induced SJS/TEN in Malaysia
Chong et al. 2017 [54]	QALY and ICER	Standard care dominated PGx-guided therapy	USD 8695 per QALY	Not cost-effective due to low prevalence of PGx biomarker tested in Malaysia
Rattanavipapong et al. 2013 [55]	QALY and ICER	Genotype screening prior to treatment: THB 222000 per QALY (epilepsy patients) and THB 130000 per QALY (neuropathic pain)	THB 130000	PGx-guided therapy was cost-effective for neuropathic pain patients, but not epilepsy patients

QALY (quality-adjusted life years); ICER (incremental cost-effectiveness ratio); GDP (gross domestic product); PGx (pharmacogenomics); N/A (not available); Ref (Reference).

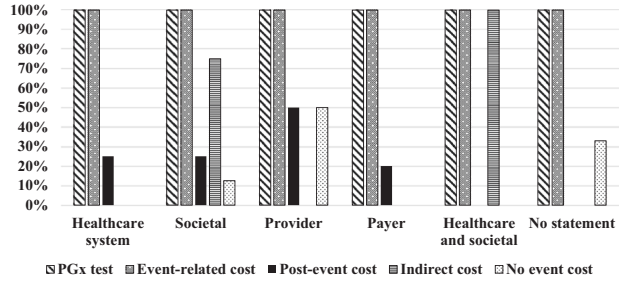

Fig. 2 Cost categories included in the studies based on study perspectives. All studies reported cost categories. Categories were divided into cost of pharmacogenomics (PGx) test, event-related costs (according to disease type), post-event cost (follow up and management of patients at long-term duration), indirect costs such as foods and transportation, and no event costs (medical costs for patients without adverse effects).

was not cost-effective compared to standard care, and three studies found the result was not conclusive. For three studies with uncertain conclusions regarding the cost-effectiveness for the practices [47, 50, 55], one study reported that cost-effectiveness relied on the quality of life of the patients and time taken to achieve the therapeutic target using the genotype tests [50]. Meanwhile, another study conducted in a multi-ethnic country in Singapore reported pharmacogenomics practice to be cost-effective in specific ethnicities, i.e., cost-effective in Singaporean Chinese and Malays, but not among the Indians [47]. A study conducted in Thailand showed that pharmacogenomics test before carbamazepine treatment was cost-effective in patients diagnosed with adverse drug reaction with neuropathic pain, but not epilepsy [55]. Of 16 studies that found pharmacogenomics test to be cost-effective compared to standard treatment, 14 studies (88.2%) found pharmacogenomics test to be cost-effective compared to all other treatment options in their studies. However, another two studies conducted on clopidogrel and ticagrelor in patients with cardiovascular disease found pharmacogenomics test to be cost-effective compared to standard care of clopidogrel, but not cost-effective compared to ticagrelor [29, 39]. Five studies found pharmacogenomics test to be dominant, in which pharmacogenomics-guided therapy was found to be lower in cost and higher quality adjusted life per year than that of standard therapy [35, 42, 51, 52].

We summarized the results on cost-effectiveness according to drugs studied. All pharmacogenomics-guided strategies were cost-effective in the management of anticancer and antiestrogen drugs ($n = 5/5$, 100%), namely irinotecan (colorectal cancer), crizotinib (lung cancer), gefitinib (advanced lung cancer), tamoxifen and toremifene (breast cancer). For cardiovascular diseases, the most frequently examined genotype-guided drugs were clopidogrel and ticagrelor. All studies ($n = 4/4$, 100%) conducted on clopidogrel found that genotype-guided treatment was more cost-effective than standard clopidogrel treatment. In a study that compared genotype-guided warfarin to that of standard care using dabigatran in cardiovascular disease treatment, the cost-effectiveness finding was inconclusive [50]. Of four studies conducted on genotype-guided allopurinol therapy for the treatment of gout, three studies found the results were not cost-effective [30, 38, 49]. Reasons for the lack of cost-effectiveness of genotype-guided treatment included higher cost of drugs and genotyping test [38, 49], low incidence of SJS/TEN in Singapore [49], higher lifetime cost of gout management if forgoing urate-lowering agent treatment due to concern of SJS/TEN [38] and non-responders to allopurinol for gout treatment can move on to febuxostat rather than get genotyped and skipped allopurinol [30]. Nevertheless, one study found screening of the *HLA-B*58:01* allele before initiation of allopurinol treatment

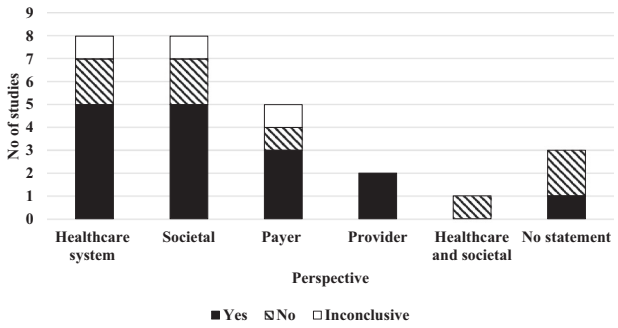

Fig. 3 Cost-effectiveness based on study perspective, including healthcare system, societal, payer, provider, and a study conducted based on both healthcare and societal perspectives. Studies with no clear statement on perspective were classified under "No statement".

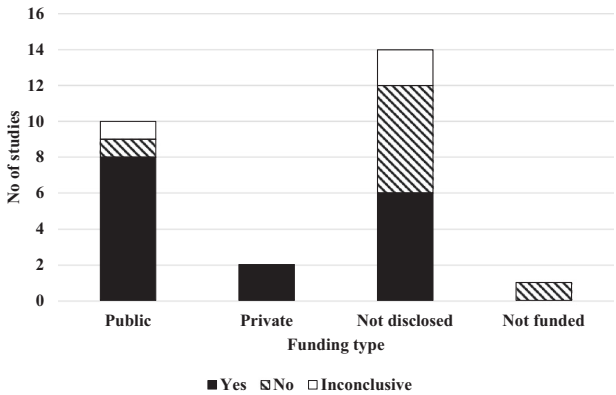

Fig. 4 Cost-effectiveness according to funding type. Most studies did not disclose the funding type they received for their studies. Study without funding was classified under 'Not funded'.

in gout patient with chronic renal insufficiency to be cost-effective [51]. In pharmacogenomics-guided practice to prevent severe cutaneous adverse drug reactions using allopurinol, it was found that the guided therapy was cost-effective compared to standard care [36, 46]. In contrast, the remaining study found the guided therapy was not cost-effective because of the low incidence of SJS/TEN and low frequency of biomarker tested [53].

The genotype-guided carbamazepine treatment in epilepsy for the Singaporeans was found to be cost-effectiveness in Singaporean Malays and Chinese, but not in Indians mainly because of different risk allele frequency in these 3 ethnic populations, in which the frequency of HLA-B*1502 is high in the Malays and the Chinese (more than 5%) while it is low in the Indians (less than 2.5%) [47]. In contrast, genotype-guided carbamazepine treatment in China failed to observe cost-effectiveness [33] due to genotyping cost, turnaround time of the test, and low incidence of adverse drug reaction among the genetic carriers while the study conducted in Thailand was inconclusive [55].

In Thailand, pharmacogenomics-guided warfarin treatment in patients with thromboembolism and major bleeding was not cost-effective based on societal and healthcare perspectives [31]. The reasons include higher cost in genotype-guided treatment than that of usual care; while in China, it was cost-effective based on the healthcare perspective [41]. A study conducted on genotype-guided azathioprine treatment in autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis) found the strategy to be cost-effective as it is less costly and resulted in less adverse drug reaction [52]. Genotype-guided tests before anti-tuberculosis treatment was cost-effective in Brazil, South Africa, and India [44], while a study on genotype-guided antiviral therapy (abacavir) in Singapore found it was not cost-effective because of high genotyping cost, low frequency of biomarker (*HLA-B*57:01*) and low mortality rate due to hypersensitivity reaction in Singaporean populations [45].

The review on the cost effectiveness of genotype-guided antimicrobial treatment found that the parameters that affect the outcome are genotyping cost, cost of patient management, and cost of hospitalization associated with adverse drug events, and risk allele frequency in specific population. Low genotyping cost and cost of patients' management due to hospitalization caused by adverse drug reaction are linked to cost-effectiveness of genotype-guided therapy. In addition, robustness and clinical validity of variant examined as biomarker in genotype-guided therapy also influence the outcome of cost-effectiveness.

Heterogeneity across study characteristics

High proportion of studies which were evaluated from the perspectives of healthcare system, societal, payer, and provider had concluded that implementing pharmacogenomics-guided therapy were cost-effective ($n = 5/8$, 63%; $n = 5/8$, 63%, 71%; $n = 3/5$, 60%; $n = 2/2$, 100%, respectively). In contrast, a low proportion of studies with no statement on economic perspective concluded that pharmacogenomics-guided therapy was cost-effective ($n = 1/3$; 33%). One study conducted based on the healthcare system and societal perspective concluded that pharmacogenomics-guided therapy was not cost-effective due to a higher cost of pharmacogenomics-guided therapy than that of standard therapy [31] (Fig. 3). For funding type, studies funded by the public and private organization had a high proportion of studies concluded that implementing pharmacogenomics-guided therapy was cost-effective ($n = 8/9$, 89% and $n = 2/2$, 100%, respectively). In contrast, studies with no clear statement regarding funding support were not conclusive whether pharmacogenomics-guided therapy were cost-effective (Fig. 4). One study without funding support did not find pharmacogenomics practice to be cost-effective [49].

We also analyzed the result of cost-effectiveness according to the country where the study was conducted. A high proportion of studies from China and South Korea reported that pharmacogenomics practice was cost-effective ($n = 8/10$, 80% and $n = 3/3$, 100%, respectively). Meanwhile, two studies (100%) conducted in Malaysia [53, 54] reported that pharmacogenomics-guided practice was not cost-effective, while in Singapore, most studies also found that the practice was not cost-effective ($n = 4/7$, 57%). One study conducted on populations in Brazil, India and South Africa found that pharmacogenomics practice was cost-effective [48], while a study conducted in Taiwan had reported similar result [36] (Fig. 5). In Thailand, pharmacogenomics-guided therapy was cost-effective in one study [46], while another two studies conducted in the same country found it was not cost-effective [31] or inconclusive [55]. Our analysis revealed that the type of drugs examined, frequency of risk allele in the population, genotyping cost and economic perspective influenced the outcome of cost-effectiveness in the respective country (Table 1).

Quality of reporting based on QHES

The quality of articles included in this systematic review was assessed using the QHES guideline. All articles scored in the range of 70 to 100. Twelve articles had a score of 100, while eight articles had a score that ranged from 90 to 97. All articles clearly stated their objectives (criterion 1) and primary outcomes (criterion 10) of the studies. However, most articles did not employ subgroup analysis (criterion 4) in their studies. Some studies failed to mention their source of funding, and some of them did not explicitly state the method of data analysis employed. Although most studies discussed the limitation of their studies, some failed to discuss the magnitude and direction of study bias. Elements

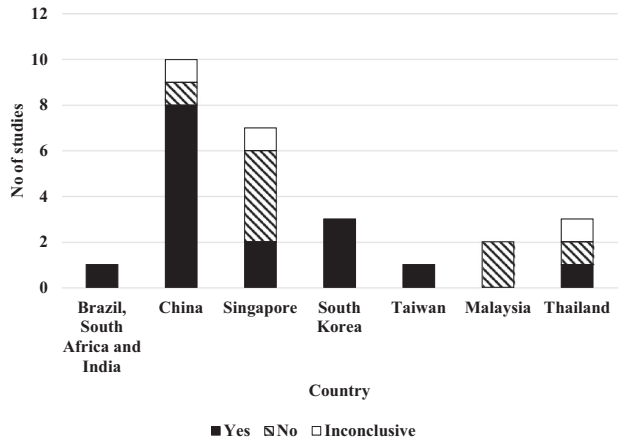

Fig. 5 Cost-effectiveness and the countries where the studies were conducted. One study on tuberculosis was conducted in populations from Brazil, South Africa and India.

essential in economic design, namely time horizon, parameter uncertainty, and discounting, were highly reported among the included studies.

DISCUSSION

In this systematic review, we evaluated the cost-effectiveness of implementing pharmacogenomics-guided therapy in developing countries. Our analysis reveals that cost-effectiveness of implementing pharmacogenomics-guided in developing countries varies according to diseases, medical costs, and types of drugs evaluated. To our knowledge, this study is the first systematic review performed to evaluate cost-effectiveness of pharmacogenomics practice in the developing countries. Most studies were published in Asian countries, particularly in the East Asian region compared to that of countries in other continents, suggesting the increasing growth of this field in Asian continent. Most publications were published last decade (from 2012 to 2019), indicating the infancy of the practice in the developing countries and recent growing interest in this field as more biomarkers with clinical validity are discovered [56]. Most of the studies targeted cancer, cardiovascular diseases, gout, and severe adverse drug reactions, with some studies also targeted infectious diseases in the developing countries such as HIV and tuberculosis. Given the high economic, morbidity and mortality burden associated with cancer [57] and cardiovascular diseases [58], it is not surprising that these two diseases were the most frequently studied. However, we observed a lack of studies that examined the cost-effectiveness of pharmacogenomics-guided therapy in three common infectious diseases in the developing countries i.e., malaria, HIV and tuberculosis. More pharmacogenomics studies on these diseases should be conducted in the future, particularly in the regions where the diseases are prevalent i.e., sub-Saharan countries. Cost categories included in the studies differed according to the country, drug and disease type examined, which may have affected the conclusion on cost-effectiveness. We also found that the validity of biomarker tests used in the pharmacogenomics study and the magnitude and direction of study bias was frequently underreported. In addition, the pharmacogenomics tests have not been adequately standardized in the developing countries.

Our findings are consistent with findings from previous systematic reviews conducted to evaluate the cost-effectiveness of pharmacogenomics testing. Zhu et al. [25] systematically reviewed the cost-effectiveness of pharmacogenomics testing in cardiovascular disease drugs from an economic perspective. Although they found that most studies reported cost-effectiveness of pharmacogenomics testing for cardiovascular diseases, there were variability in cost categories, economic evaluations and study design elements employed in the methodology. Similarly, another systematic review performed on the cost-effectiveness of pharmacogenomics testing showed that most studies reported the practice to be cost-effective. However, the critical analysis of the magnitude of study bias and the robustness of the biomarker was frequently missing [59]. Furthermore, a systematic review conducted by Wong et al. [60] reveals that only a few biomarkers employed in pharmacogenomics testing demonstrated clinical utility and validity, suggesting the urgency to evaluate the utility and validity of the biomarkers used in the testing procedure. Recent systematic review conducted on cost-effectiveness of genotype-guided psychiatric disorders revealed that half of the studies examined found genotype-guided therapy to be cost-effective although the economic perspective, cost inputs and study design elements were poorly reported in the studies [61].

Most of the studies employed a single gene in the pharmacogenomics testing, only a few studies employed panel testing (testing multiple genes for one drug) and one study employed whole genome sequencing testing. Although pharmacogenomics testing with multigene panel is desirable as it provides data for any future treatment or if patient is on polypharmacy of different drug-gene pairs, testing a targeted single genetic variant for pharmacogenomics-guided therapy is preferable as it is more economical than testing multiple genetic variants particularly in developing countries where genotyping cost can go higher as more genetic variants are added to the testing panel. However, testing a single genetic variant is limited by low sensitivity and would be useful if the variant is present at a high frequency in the specific population. To improve its practicality, a pilot study is required to profile the common risk alleles before a specific targeted single variant can be applied as biomarker for pharmacogenomics-guided therapy. This will indeed reduce the cost of testing particularly in low-and –middle income countries. As the medical community moves towards precision medicine, pharmacogenomics testing using targeted robust drug response gene is preferable than that of low specificity biomarkers. The application of pre-emptive treatment strategy, in which the genome or targeted genetic panel of patients which are already available in the database at the point of care, is more attractive compared to that of reactive genotyping because it reduces drug exposure and toxicity and increases patients' satisfaction [62]. However, no study was conducted based on pre-emptive treatment strategy due to a higher testing cost. Additionally, pre-emptive treatment strategy was thought to have limited value as the tested subjects might never develop the disease that requires treatment with the drugs although they might possess the high-risk drug response variants. Furthermore, the lack of funding to conduct fundamental research and clinical trials on the utility of genetic panel in the developing countries further complicates the success of pre-emptive pharmacogenomics testing in the low- and middle-income countries. We found only one out of 28 studies mentioned patients' gender in their studies. A study conducted by Planelles et al. [63] reveals difference in adverse drug reactions of opioid therapy between men and women, in which women experience more headache, loss of appetite, insomnia, nausea and dizziness than that of men. Given the importance of gender in pharmacogenomics-guided therapy, it is pertinent for future study to examine cost-effectiveness of pharmacogenomics-guided therapy to include patients' gender in their studies.

Studies on the implementation of pharmacogenomics test on anticancer and antiestrogen drugs for various cancer treatments were reported to be cost-effective. This result was supported from a healthcare system and societal perspective. A similar result was found in cardiovascular diseases, in which most

studies from multiple perspectives (payer, healthcare and provider) showed that pharmacogenomics testing was cost-effective. Although the number of studies was small, our analysis suggests that the establishment of pharmacogenomics testing in cardiovascular diseases and cancers in the developing countries may be cost-effective compared to standard care. Contrary to these 2 diseases, most studies showed that implementing pharmacogenomics testing for treatment of gout, or severe adverse drug reaction (i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis) was not cost-effective. Again, multiple factors contribute to this result, including different countries where the study was conducted, different cost categories, patient management, post-event costs, and study perspectives examined.

The strength of this study includes evaluation of the cost-effectiveness of pharmacogenomics-guided treatment in developing countries with multiple gene-drug interaction and diseases examined. We targeted different ethnic groups in each country for a broad spectrum of economic analysis of the populations resided in the countries that are primarily low and middle-income with diverse genetic backgrounds, cultures, and government policies. Furthermore, current knowledge and gaps on cost-effectiveness of implementing pharmacogenomics testing in the developing countries were highlighted, and the result will be beneficial for clinical practitioners and policymakers for decision making especially in developing countries where the resources and funding for healthcare research, knowledge on patients' management and healthcare costs are limited.

However, this study also has several limitations. First, while the quality of most studies included in this systematic review had a high score, a few studies failed to report on essential elements such as economic design, perspectives, and cost categories. This would inadvertently result in an inaccurate synthesis of the findings. Second, most studies employed hypothetical cohorts in their economic models. Although the hypothetical modeling is usually conducted to examine the cost-effectiveness of pharmacogenomics testing, the results may differ if applied to real cohorts. Third, we restricted our systematic review to studies published in English and might miss the studies published in other languages.

In conclusion, pharmacogenomics testing is a promising practice for the developing countries for selected drug and diseases, namely cancers and cardiovascular diseases. The evidence for pharmacogenomics testing such as gout, severe adverse drug reaction and epilepsy may not be supportive, perhaps due to different cost categories, perspectives, and prevalence of risk genetic variants in the diverse populations in the developing countries. The application of genetic panel for pharmacogenomics testing and the genotype-phenotype are still limited in the developing countries. These are constraints towards the implementation of a pre-emptive treatment strategy for precision medicine.

While the notable interest of pharmacogenomics application in East Asian countries is increasing, remarkable absence of studies to evaluate cost-effectiveness in other regions, specifically in African countries and low-income countries in South and South East Asian countries with increasing incidence of emerging infectious diseases and non-communicable diseases, was noted. The paucity of studies in those regions can be attributed to underrepresentation of genome-wide association studies in the populations resided in those regions. Thus, more fundamental genomic and clinical studies to respectively evaluate the presence of drug response variants and clinical validation in these disadvantaged communities in low-and middle-income countries should be conducted to improve healthcare and reduce the economic burden associated with the diseases. Gaps persist in methodology used to evaluate cost-effectiveness of pharmacogenomics-guided therapy in developing countries, in which perspectives, cost categories, groups of patients' cohorts, and time horizon used were distinct across studies examined. We recommend standardized methodology for economic evaluation of pharmacogenomics-guided cost-effectiveness as current approach used was variable across different countries. We also noted the cost of genotyping that varied from USD 20 to USD 277 and frequency of risk allele in populations, particularly in ethnically diverse countries such as Malaysia and Singapore, affected the cost-effectiveness of genotype-guided therapy. Therefore, reduction in genotyping cost and biomarker discovery in drug response are two essential key elements to economically implement pharmacogenomics-guided therapy in the developing countries. This review updates current knowledge and gaps of pharmacogenomics testing in the developing countries and will be helpful in implementing pharmacogenomics-guided therapy to improve patient care.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization, LKT and MZS; methodology, AS; validation, LKT, MZS, and CM; formal analysis, AS; data curation, AS; writing—original draft preparation, AS; writing—review and editing, LKT, MZS, and CM; supervision, LKT and MZS. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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