Economic evaluations of pharmacogenetic approaches in infectious diseases: a review of current approaches and evaluation of critical aspects affecting their quality

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Abstract

Pharmacogenetics holds great potential for improving the effectiveness of treatment modalities in infectious diseases by taking into account the genetic determinants of both the host and infectious agents' individuality. Better utilization of resources and improved therapeutic efficiency are the expected outcomes of personalized medicine using pharmacogenetic and pharmacogenomics information made available by technological advances. However, there has been growing concern in the clinical community regarding the evaluation of the true benefits of these approaches. This perception is partly due to the limited number and perceived poor quality of economic evaluations in this field, and initiatives aimed at harmonizing and communicating strategies improving the quality of these studies and their acceptance by the clinical community are greatly needed. This paper reviews current literature of economic evaluations of pharmacogenetics interventions guiding pharmacotherapy in infectious diseases. PubMed and the NHS Centre for Reviews and Dissemination databases were searched using a combination of five broad research terms related to pharmacogenetic approaches, and papers relative to economic evaluations of pharmacogenetic interventions in infectious diseases retained for further analysis. Using these criteria, a total of 14 papers were included in this review. The area of economic evaluation of pharmacogenetic interventions in infectious diseases remains understudied and would benefit from greater harmonization. The main weaknesses of evaluations reviewed in this paper seem to be represented by poor evidence of pharmacogenetic marker validation, inconsistencies in the selection of costs and utility included in the economic models and the choice of sensitivity analysis. All these factors limit the overall transparency of the studies, greater acceptance of their results and applicability to diverse and possibly resource-limited environments where these approaches could be expected to have the greater impact.

Introduction

Infectious disease remain one of the leading causes of death worldwide, and it has been estimated that out of the 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are somehow related to infectious diseases.¹ Infectious diseases are the second largest cause of death² and the emergence of novel and/or resistant strains is a continuous threat to global health.³ While a relative decrease in the proportion of death by communicable diseases is currently being observed,⁴ these diseases still account for a significant number of deaths, especially in resource-limited countries.

The wide use of antimicrobials to treat patients without bacterial infection is thought to be associated with an increasing rate of resistance which complicates treatment.⁵ This phenomenon has led to the appearance of many initiatives to limit the use of antibiotics.

A more targeted use of anti-infectives has been traditionally associated with microbiology procedures assessing the infectious agents' susceptibility to different therapeutic agents. However, the slowness of these growth dependent tests and the limited access to cell culture facilities and sample management logistics in resource-limited environments limits significantly their use in current clinical practice, so that the prescription of antibiotics remains largely empirical.

In comparison, pharmacogenetic or pharmacogenomics analysis (PGA) of the genetic makeup of infectious agent, as well of the host (patient) holds the promise to deliver fast and accurate information about the infectious organism susceptibility to drug treatment as well as on the presence of patient's factors potentially affecting the effectiveness of the treatment.^{6,7} Identification of microbial and viral genetic signatures associated with drug susceptibility could represent an effective, rapid and information rich method effectively guiding the prescription of the most effective therapy against given diseases. Similarly, identification of the host metabolic enzymes or other proteins associated with adverse events or idiosyncratic reactions could significantly reduce the number of complications and therapeutic failures.

While various examples exist of the usefulness of PGA approaches in infectious diseases,^{8,9} a limited number of economic evaluations have validated the positive impact of these approaches on the utilization of economic resources, particularly in resource-limited countries.

The main aim of economic evaluations of health technologies is to highlight factors leading to a better allocation of resources. These

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methods have become increasingly important and frequent due to the rising costs of the healthcare⁷ and are critical to the evaluation of the impact of new technologies on healthcare budget utilization. However, to this moment, no review has specifically focused on the characteristics and outcomes of economic evaluation of therapeutic interventions for infectious diseases.

While published economic evaluations have to some extent included PGA testing for conditions including infectious diseases, no review considered the specificities of this therapeutic area. As an example, a recent literature review¹⁰ excluded economic evaluations looking at genetic tests on the infectious organism, an essential component of PGA interventions in infectious disease.

This paper, based on the review of relevant literature will determine the current status of Economic Evaluation of PGA interventions in infectious diseases and highlight factors currently preventing a wider adoption of these evaluations in support of health policy development.

Methods of research

Study selection

A literature search was performed over the month of April 2012 using PubMed and the

NHS Centre for Reviews and Dissemination (CRD) databases.

The search was performed using a combination of five broad research terms related to PGA approaches (*pharmacogenetics, genetic screening, sequencing, isoform, SNP*) and three terms related to economic evaluations (economic evaluations, cost-effectiveness, economics).

To be included, studies had to i) meet the definition of being a PGA study (defined as use of information on human genetic variation to target drug therapy) ii) describe an economic evaluation (defined as an evaluation of both costs and clinical outcomes) and iii) concern a therapeutic intervention for an infectious disease (modified from¹¹).

Searches were limited to studies with abstracts and written in the English language. Only original publications meeting inclusion criteria were considered.

To maximize the chances of including all relevant and published papers, bibliographies quoted in the retrieved papers were also examined for papers meeting the inclusion criteria and identified review papers were also searched for relevant studies that may have

been missed through the keyword-based search.

Applying these search criteria, a total of 1509 papers were identified from Medline, and 302 from CRD. After evaluation of the abstracts for meeting of the inclusion criteria, a total of 14 original papers were included in this review.

Data extraction

Based on previous reviews of PGA and pharmacogenomics interventions published in the literature,^{10,12} a Microsoft Excel extraction template was created to include the following dimensions: i) disease, ii) population, iii) gene analyzed, iv) cost of genetic test, v) drug affected by gene, vi) analytical validity of the test, vii) clinical validity of the test, viii) variation of genetic marker of interest, xi) population ethnicity, x) type of economic analysis, xi) perspective, xii) source of data for utility assessment, xiii) detail of cost data, xiv) sensitivity analysis used, xv) indication of software package used, xvi) time window, xvii) discounting rate, xviii) use of decision tree, xix) modeling techniques used, xx) outcome measures used, xxi) base case economic outcome, xxii) outcome of study.

Results

Fourteen papers were identified as responding to the inclusion criteria for this review, and are listed in Table 1¹³⁻²⁶ in the first author's alphabetical order.

A summary of the data extracted from the papers selected is reported in Table 2, along with an explanation of the acronyms used.

Disease and population considered in the studies

Economic evaluations of PGA interventions could only be identified for a few therapeutic indications within infectious diseases. The therapeutic area most frequently considered in the studies qualifying for this review was HIV infection. All of the studies looking at the host genetic information in HIV-infected patients considered the *HLA-B*5701* gene as a marker connected to Abacavir hyper sensitivity reaction, while those looking at the genome of the HIV virus followed the genotypic antiretroviral resistance testing (GART) protocol to assist decision making in the definition of the most suited antiretroviral therapy.

Table 1. Papers from Medline and Centre for Reviews and Dissemination identified as responding to the inclusion criteria for this review.

Title	Journal	Authors, Reference
Clinical significance of the cytochrome P450 2C19 genetic polymorphism	Clin Pharmacokinet. 2002;41:913-58.	Desta <i>et al.</i> ¹³
Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of <i>H. pylori</i>	Clin Pharmacol Ther 2007;81:521-8	Furuta <i>et al.</i> ¹⁴
Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity	Pharmacogenetics 2004;14:335-42.	Hughes <i>et al.</i> ¹⁵
Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV	Pharmacoeconomics 2010;28:1025-39	Kauf <i>et al.</i> ¹⁶
Will genetic testing alter the management of disease caused by infectious agents? A cost-effectiveness analysis of gene-testing strategies for prevention of rheumatic Fever	Clin Infect Dis 2002;34:1491-9	King <i>et al.</i> ¹⁷
Polymorphisms and the pocketbook: the cost-effectiveness of cytochrome P450 2C19 genotyping in the eradication of <i>Helicobacter pylori</i> infection associated with duodenal ulcer	J Clin Pharmacol 2003;43:1316-23	Lehmann <i>et al.</i> ¹⁸
Should resistance testing be performed for treatment-naïve HIV-infected patients? A cost-effectiveness analysis	Clin Infect Dis 2005;41:1316-23.	Sax, <i>et al.</i> ¹⁹
The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV	AIDS 2008;22:2025-33	Schackman, <i>et al.</i> ²⁰
Cost-effectiveness of genotypic antiretroviral resistance testing in HIV-infected patients with treatment failure	PLoS One 2007;2:e173.	Sendi <i>et al.</i> ²¹
Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines	Pharmacoeconomics 2009;27:341-54	Siebert <i>et al.</i> ²²
Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes	Genet Med 2007;9:695-704.	Veenstra <i>et al.</i> ²³
Use of genotypic resistance testing to guide HIV therapy: clinical impact and cost-effectiveness	Ann Intern Med 2001;134:440-50.	Weinstein <i>et al.</i> ²⁴
Cost impact of prospective HLA-B*5701-screening prior to abacavir/lamivudine fixed dose combination use in Germany.	Eur J Med Res 2010;15:145-51	Wolf <i>et al.</i> ²⁵
Cost Effectiveness of Interferon a2b Combined With Ribavirin for the Treatment of Chronic Hepatitis C	Hepatology 1999;30:1318-23	Younoussi <i>et al.</i> ²⁶

Table 2. Summary of data extracted from the studies included in this review.

Disease	Younoussi 1999	Weinstein 2001	Desta 2002	King 2002	Lehmann 2003	Hughes 2004	Sax 2005	Furuia 2007	Sendi 2007	Veenstra 2007	Schackman 2008	Siebert 2009	Kauf 2010	Wolf 2010
Hep C	Simulated	Simulated	Simulated	Simulated	Simulated	Simulated	Simulated	HPV	HIV	CF Secondary infection	HIV	HepC	HIV	HIV
Population	Simulated	Simulated	Simulated	Simulated	Simulated	Patients with Abacavir HSR	Simulated	H. Pylori positive patients	Simulated	Simulated	Simulated	Simulated	Simulated	Simulated
Gene analysed:	HCV genotype	GART	CyP450 2C19	HLA, HLB	CyP450 2C19	HLA-B*5701	GART	CYP4502C19 2S2142/43	GART	A1555G	HLA-B*5701	HCV genotype	HLA-B*5701	HLA-B*5701
Cost of genetic test	NR	400 USD	30 USD	150 USD	89.2-119 USD	43.4 Euros	400 USD	NR	625 USD	345 USD	68 USD	NR	87.92 USD	86 euros
Test Technology	NR	NR	Restriction frag. analysis	NR	PCR	NR	Serial invasive signal amplification reaction	NR	NR	NR	NR	NR	NR	NR
Treatment affected by gene(s)	IFV/RBV	HAART	Omeprazole, amoxicillin	Antibiotics	PPI	Abacavir	HAART	Lomeprazole, Chloritromicin	HAART	Aminoglycosidic antibiotics	Abacavir	IFV/RBV	Abacavir	Abacavir
Analytical validity of the test	NR	NR	NR	NR	NR	Primary	NR	NR	NR	References	NR	NR	NR	NR
Clinical validity of the test	References	References	References	References	References	References	References	Primary data	References	References	References	References	References	References
Variation of genetic marker of interest	NR	References	References	References	References	Yes	References	Yes	References	References	References	NR	NR	References
Ethnicity Indicated	NR	Yes	Yes	NR	Yes	Yes	NR	Yes	NR	NR	Yes	NR	Yes	NR
Type of economic analysis	CE	CE	CI	CE	CE	CE	CE	CI	CE	CE	CE	CE	CI	CE
Perspective	HP	S	HP	S	HP	HP	S	HP	S	S	HP	S	HP	S+HP
Source of data for utility assessment	Listed	Listed	NA	References	NA	NA	References	NA	Listed	Listed (Primary & References)	NR	Listed	Listed	NA
Cost data detailed	Listed	Listed	Listed	Listed	Listed	Listed	Listed	Listed	Listed	Listed	NR	Listed	Listed	Listed
Sensitivity analysis	Det.	Det.	NR	Prob.	Det.	Det.	Det.	NR	Prob.	Det.	Det.	Prob. + Det.	Det. + Scenario	Det. + Prob.
Software package mentioned	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Time window	LT	LT	3 months	LT	1 year	6 wks	LT	3 months	LT	LT	LT	LT	LT	6 wks
Discounting	3%	3%	NA	3%	NA	NA	3%	NA	2-4%	3%	3%	3%	3%	NA
Decision trees	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes
Modeling techniques	Markov	Simulation	NA	Markov	Simulation	Decision Tree	Simulation	NA	Simulation	Decision Tree	Simulation	Markov	Simulation	Decision Tree
Outcome measurements	ICER	LE, QA-LE, ICER	Cost of therapy	ICER, LVG, QALY, Cost of care	CER	ICHSR	LE, QA-LE, Cost of care, CER	Cure Rate	LE, QALY, Cost of Care, Prod. Costs	ICER, QALY, Cost of Care, SAE incidence	QALY, Cost of Care, CER	LE, QA-LE, Cost of Care, ICER	ICER	Cost Saving/Patient
Base Case economic outcome or ICER	ICER of 7500 USD/QALY	CER of <25,000 USD/QALY	Cost saving of 50 USD per asian patient screened	7900 USD/ QALY gained	647 USD/ Ulcer prevented	Dominant ICER of 22,811 euros/HSR avoided	ICER of 23,900 USD/QALY	Higher eradication on rates vs similar costs of treatment	ICER of 35,000 USD/QALY gained	ICER 79,300 USD/QALY	CER of 36,700 USD/QALY	Dominant ICER 1500 euros/QALY	Dominant	Dominant
Outcome	+	+	+	+	+	+	+	+	+	-	+/-	+	+/-	+

CE, cost-effectiveness; CER, cost-effectiveness ratio; CF, cystic fibrosis; CI, cost impact; Det., deterministic; GART, genotypic antiretroviral resistance testing; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; Hep C, hepatitis C virus; Hep C, hepatitis C virus; HP, *Helicobacter Pylori* infection; HSR, hypersensitivity reaction; IC/HSR, incremental cost per HSR avoided; ICER, incremental cost-effectiveness ratio; IFV/RBV, interferon/ribavirin treatment; LE, life expectancy; LT, life time; NR, not reported; LVG, life years gained; NA, not applicable; PPI, proton pump inhibitors; Prob., probabilistic; Prod. costs, productivity costs; QA-LE, quality-adjusted life expectancy; QALY, QALY gained; RP, rheumatic fever (following *Streptococcal* infection); S, societal; SAE, severe adverse event.

The remainder of the studies was almost equally split between *Helicobacter Pylori* infection, Hepatitis C (HepC) infection and bacterial infections associated/linked to other diseases. Only 35% of studies used infectious organisms' genetic information defining viral resistance, mainly in HIV and HepC infection.

Prevalence, ethnic variation, clinical relevance and validation of the PGA marker considered mostly relied on previously published data that may not have included these as primary objectives of the study and therefore present different levels of quality.

Genetic test

The technology and cost of the genetic test used were not described or assessed in the majority of the papers. While the type of technology being used for the determination of the biomarker was indicated only in 20% of studies, 86% of the studies did not mention the analytical validation of the assay used, making all specific consideration on the analytical validation as well as comparison between different technologies impossible.

Economic evaluation

This is the dimension where most of the studies had the majority of information. Of the fourteen studies, 11 were defined as cost-effectiveness studies, while the remaining three were defined by the author as cost-impact studies. Interestingly, the majority of the cost-effectiveness studies included utility assessment and had quality-adjusted outcomes (QALY, quality adjusted life-years gained, quality-adjusted life expectancy, etc.) and could also be considered as cost-utility studies. Only 40% of studies took a societal perspective in the estimation of costs and benefits relative to the PGA intervention, and of the seven assuming a health provider or third party payer perspective, a significant number only included direct costs (cost of treatment, cost of genetic tests) in the model.

The source of data for cost and utility assessment was not consistently reported. While the absolute majority of studies listed the cost data used in the model, only six out of the nine studies evaluating utilities listed the utility values and information included in the model. Methodologies used in the original papers to obtain utility values were also not listed and this information could only be retrieved by obtaining the original referenced papers.

The majority of the studies (85%) performed sensitivity analysis that was mainly deterministic in nature (60%). Quite interestingly, very little information could be found on the statistical tests and approach followed in most cases, and few studies mentioned explicitly whether their approach could be considered truly probabilistic (*i.e.* whether the interrelations

between variables were considered in the analysis). In comparison, the software package used for modeling and/or stat analysis was indicated in the majority of the cases.

Decision trees were presented in half of the studies, while most common modeling techniques to extrapolate data were simulation techniques associated with decision trees and Markov models. The majority of the models extended to life time (at least thirty years), and applied a discounting rate of 3% per annum.

Outcomes

Outcomes measures most frequently used were cost of care (50% of studies) and incremental cost-effectiveness ratio (42% of studies). Cost-effectiveness ratio, life expectancy and quality-adjusted life expectancy were also found in 20-30% of the studies, while the remaining used a number of other indicators (life years gained, quality adjusted life years gained, others).

While almost 80% of the studies reported a positive outcome following the evaluation of the PGA intervention, and only one study in the sample had a completely negative evaluation of the intervention, economic benefits deriving from the use of PGA interventions and the thresholds used to assess the acceptability of the intervention varied greatly across studies.

Considering the difference in gross domestic product, the WHO-Choice initiative²⁷ suggested differential cost-effectiveness thresholds. Using average cost-effectiveness thresholds for African countries (5700 USD - 4380 Euros, WHO-CHOICE), only 42% of interventions remained cost effective.

Discussion

One of the first findings of this review is represented by the fact that economic evaluations of PGAs in the field of infectious diseases remain limited. This finding is all the more surprising as these diseases disproportionately affect resource limited countries where an efficient use of healthcare resources is vital.

More generally, while the number of PGA biomarkers have grown over the years,²⁸ many authors feel that a number of challenges prevent the assessment of the value of PGA markers and a wider use of this information.

Swen²⁹ attempted a classification of these challenges, and reported six main hurdles on the way to the use of PGA testing in clinical practice. Clinical utility, analytical and clinical validation and transparency of data sources were all identified as areas of concerns.

While challenges identified by Swen²⁹ emerge from extensive literature surveys,

recent stakeholder consultations^{30,31} reiterate some of the factors highlighted by Swen²⁹ but specifically point to two large areas of concern also in line with arguments used by other authors:³² i) The true value of new PGx information and products for patients, physicians and the medical care delivery system at large; ii) the transparency of the studies, quality of the data they relied upon and their capacity to be fully understood by the users.

Many clinicians are still concerned about the relevance of economic evaluation studies and the use of QALYs as a measure of the utility associated with a specific treatment.³⁰ As a result, properly founded economic considerations are often not taken into account in selecting a particular treatment strategy. This skepticism may be further reinforced by the perception of poor transparency and insufficient quality of studies lacking critical information on the genetic markers or the poor relevance of economic data and assumptions used in these economic evaluations.

Within this review, we have tried to address these two broad areas of concern by carefully selecting critical information to be extracted from studies meeting inclusion criteria.

Studies were evaluated looking specifically at two clusters of information: the first one related to the characterization and validation of the genetic marker and parameters associated with it (disease area, the population considered as a basis for the evaluation, the gene analyzed and its frequency in the different ethnic groups, the type and cost of the genetic assay used, the analytical and clinical validation of the gene as a PGx marker), and the second related to the way these data was analyzed in the context of an economic evaluation of PGA interventions (type of economic analysis, the perspective assumed in the evaluation, the source of data for utility and cost evaluation, the timeframe and discounting used, the model used for predictions, the kind of sensitivity analysis and the outcomes measures and results). When we look at the characterization of the marker used in the PGA intervention and using criteria set out in previous reviews,^{10,11,33,34} we can see that very little detail could be found on the clinical validation of the PGA tests. In the absolute majority of studies, this aspect was normally dealt with in the introduction and with reference to other publications (association studies, prospective clinical studies etc). Often, details of how validation was approached in the quoted study were not provided. Besides, the main objective of the quoted publication was often not the proper validation of the gene as a biomarker in accordance with published guidelines and consensus papers,^{35,36} but rather its generic association with specific outcomes in clinical studies. The analytical validation of the test can be considered even more neglected as most of the

studies identified no reference could be found to the way that the test was validated nor to the sensitivity and specificities proper to the technology. The technology used for the genetic test was also not indicated, further limiting possible generalizations of the conclusions.

As suggested by Beaulieu,¹⁰ analytical characteristics of the test used have repercussions on the model assumptions and their ignorance is not devoid of consequences.

Relatively to the second cluster of data mentioned earlier (namely the characteristics of the economic evaluation and its effect on the value of the studies), one of the main concerns raised in previous reviews was the identification of data used for the definition of the utility associated with different pathological states. The majority of the studies used data obtained in separate, published studies and the original paper was effectively listed only in two thirds of the papers using utility outcomes. However, this often included QALY values for the different disease states but did not provide details on the methodology used for deriving QALY and the applicability to the study conducted, thus making the interpretation of the relevance of the study to different situations and realities extremely challenging.

The preponderance of cost-effectiveness and cost-utility evaluations in this pool of studies is indicative of a trend towards the improvement in the quality of economic evaluations¹² in line with international guidelines³⁷ and expert consensus.

Parameters used in economic modeling were also of good standard and in line with recent recommendations.

The perception of value associated with economic evaluations can also be affected by conflicting results of different studies related to the same marker and technology. Heterogeneity in outcomes measure and base case economic outcome or ICER was reported in previous reviews^{10,11,12} as some of the factors making comparisons between studies and generalization of the findings difficult.

If we take the example of studies dealing with HIV infection identified in this review, ICER/CERs reported for HLA-B*5701 testing went from 31-37.000 USD/QALY gained^{15,20} to be a dominant strategy in two more recent studies.^{16,25}

In comparison, GART genotyping was associated with much more homogeneous ICER/CERs of between 23,900 and 35,000 USD/QALY.

Choice of comparator, therapeutic strategies and choice of primary data are most likely reasons for the variability in these results, but details provided in the studies makes it difficult to assess the true causes and the transferability of the results to specific contexts such as those found in developing and resource-limited countries.

Everything considered, the analysis of studies included in this review shows that concerns expressed by some authors on the value of economic evaluation of PGA interventions are in this case not related to the type of economic methodology applied (that probably capitalizes on a more widespread use of pharmacoeconomic evaluations), but rather to the analytical and clinical validation of the genetic marker examined in the study.

When we looked at the second area of concern mentioned earlier, namely the transparency of the studies, the data they relied upon and their capacity to be fully understood by a wider public, it becomes obvious that the area is still open to improvement.

Beside the lack of transparency in how the utility values were obtained in some studies, the justification of the costs associated with genetic testing and the inclusion of a limited number of costs (often limited to the cost of the therapeutic agents used and the direct medical costs associated with the treatment) was sometime limited. The inclusion or exclusion of certain costs from the societal and/or third part payer perspective was certainly not consistent between studies, making it difficult to evaluate the relevance of the studies to specific realities in the health care systems of different countries. Furthermore, the frequent use of data from literature studies without the inclusion of the actual value in the text did not facilitate the knowledge of the actual inputs to the adopted models and made the interpretation of the study quality and relevance difficult to the reader.

Overall, it was clear to see why the transparency, comparability and user-friendliness of the studies is considered to be a major hurdle in the use of these results by clinicians and decision makers not specifically trained in economic evaluations and/or pharmacoeconomy.

The feeble proportion of economic evaluations of PGA of infectious agents deserves a final consideration. One of the main challenges in the therapeutic management of infectious diseases remains the soaring phenomenon of antibiotic and antiviral resistance. The advent of effective genotyping techniques has created many expectations for the development of multiple rapid diagnostic opportunities that will slowly replace classical phenotypic methods for identifying microbes and determining their antimicrobial susceptibility pattern.³⁸ At the same time, the growing burden of chronic viral diseases (such as AIDS, hepatitis C and B) has increased the pressure on the identification of strategies targeting the reduction in adverse drug reactions (ADRs) frequently encountered in a significant proportion of patients treated with antiviral drugs.

These two priorities require access to biomarkers both in the human genome (identification of patients with a higher/lower chance

of response to treatment/ADRs) and in the genome of the infectious organism (to identify the presence of resistance to specific pharmacological agents).

In our review, the majority of studies used biomarkers from the host organism, also reflecting the preponderant position of HLA-B*5701 testing in HIV treatment.

While the potential of nucleic acid testing and sequencing technologies in the identification of bacterial and viral strains resistant to treatment in support of therapeutic decisions has been described a few years ago,⁶ the availability of convenient PGA assays acting at this level and capable of providing answers in a timeframe compatible with the therapeutic imperatives of infectious disease treatment has remained limited.³⁸ This limited availability of assays may partly explain the small number of economic evaluations relative to their implementation in a public health setting.

Conclusions

The present review identified significant gaps that should be filled to increase the perceived value and transparency of economic evaluations of PGA interventions between researchers, users and stakeholders alike.

While the quality of the economic models used in the papers reviewed here could be deemed sufficient, economic evaluations of PGA interventions still lack adequate attention to the analytical and clinical validation of the markers selected and the necessary transparency to communicate the way costs were selected and calculated thus supporting the value of these interventions and their relevance to different health environments.

The poor transferability of study results between different realities is aggravated by the paucity of economic evaluations in relevant populations and add support to views previously expressed^{39,40} suggesting that capacity has to be built in individual countries in order to understand the relevance of published economic evaluation of pharmacological and PGA interventions and their inclusion in clinical practice.

On the positive side, most of the studies identified here show a positive outcome of PGA interventions and 13 out of the 14 studies could identify a positive effect at least in specific populations or therapeutic approaches. This point strongly suggest that the use of PGA interventions in infectious disease may lead to a better resource utilization and could have a great impact in this area of health of particular relevance to developing and resource-limited countries.

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