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ARTICLE

Economic evaluation in psychiatric pharmacogenomics: a systematic review

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Nowadays, many relevant drug–gene associations have been discovered, but pharmacogenomics (PGx)-guided treatment needs to be cost-effective as well as clinically beneficial to be incorporated into standard health care. To address current challenges, this systematic review provides an update regarding previously published studies, which assessed the cost-effectiveness of PGx testing for the prescription of antidepressants and antipsychotics. From a total of 1159 studies initially identified by literature database querying, and after manual assessment and curation of all of them, a mere 18 studies met our inclusion criteria. Of the 18 studies evaluations, 16 studies (88.89%) drew conclusions in favor of PGx testing, of which 9 (50%) genome-guided interventions were cost-effective and 7 (38.9%) were less costly compared to standard treatment based on cost analysis. More precisely, supportive evidence exists for *CYP2D6* and *CYP2C19* drug–gene associations and for combinatorial PGx panels, but evidence is limited for many other drug–gene combinations. Amongst the limitations of the field are the unclear explanation of perspective and cost inputs, as well as the underreporting of study design elements, which can influence though the economic evaluation. Overall, the findings of this article demonstrate that although there is growing evidence on the cost-effectiveness of genome-guided interventions in psychiatric diseases, there is still a need for performing additional research on economic evaluations of PGx implementation with an emphasis on psychiatric disorders.

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INTRODUCTION

Mental disorders stand as a significant public health challenge, affecting ~10.7% of the global population, which translates into 792 million people having at least one mental illness in 2017 [1]. The World Health Organization has ranked mental disorders as the leading cause of ill-health and disability globally [2]. Mental disorders comprise various conditions that may vary regarding their severity and which can range from mild and moderate to severe [3]. These conditions include depression, anxiety disorders, bipolar disorder, schizophrenia, and substance use disorder. Moreover, many epidemiological studies have explored the mortality associated with mental disorders. Despite the differences in mortality rates between several studies, most research articles have shown that people with severe mental conditions on average have a lower life expectancy compared to the general population [4, 5].

Given the prevalence of mental health issues, it is not surprising that there is an enormous financial burden for societies. More precisely, mental disorders cost developed countries with established health systems many billion US dollars, both in terms of health expenditures as well as loss of productivity [6, 7] and with large numbers in global direct and indirect costs [8]. Coming to European Union countries with advanced health systems, the economic costs related to mental illnesses were 798 billion EUR in 2010, with estimates projecting that these costs will double by 2030 [8–10].

In addition, several studies have shown that patients with mental disorders do not respond effectively to their first medication trial. Specifically, the proportion of patients that do not respond to their medication ranges from 30% [11, 12] to 50% [13, 14]. The resulting prolonged duration of psychiatric symptoms is often associated with common and potentially very severe adverse reactions, and as a result, increased medical costs and a decreased treatment adherence and hence probability of achieving remission [15, 16].

It has been well documented that genetic variability can account for much of the inconsistency in drug response [17–20]. Pharmacogenomics (PGx) is an emerging discipline that has the potential to significantly improve health outcomes. This can be achieved either by decreasing health costs by tailoring pharmacotherapy to individual's genetic makeup [21, 22] or by providing a personalized approach by predicting both drug response as well as reducing the

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risk of adverse drug events [23, 24]. Although the utility of PGx testing has been proven in various clinical settings such as oncology [25], cardiology [26], and infectious diseases [27, 28], only recently researchers have become interested in applying PGx in psychiatry. Several studies have also focused on summarizing recommendations and guidelines for antidepressants and antipsychotics, either by regulatory bodies (Food and Drug Administration (FDA) and the European Medicine Agency (EMA)) or by research consortia (namely the Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Dutch Pharmacogenomics Working Group (DPWG)), which are albeit slowly, being implemented and reimbursed in the clinical practice [29–31]. Genetic testing for such variations can help identify which patients are more likely to respond to psychotropic and which are likely to experience side effects. The incorporation of such information in psychiatry can be the first step in driving appropriate and effective treatment choices.

The majority of antidepressant and antipsychotic compounds are being metabolized by CYP2D6, CYP2C19, and CYP3A4 enzymes that are mostly expressed in the liver [32]. Since there is a strong association reported between genomic variants and enzymatic activity of CYP2D6 and CYP2C19, analysis of genomic variation for these two enzymes has been an early focus for the clinical implementations of psychiatric PGx. Although many previously published studies have assessed the importance of psychiatric PGx, only five genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-B*15:02*, and *HLA-A*31:01*) have been characterized as clinically actionable, as reported by CPIC (www.cpicpgx.org), the Dutch Pharmacogenomics Working Group (https://upgx.eu/guidelines/) and by an expert group derived from the International Society of Psychiatric Genetics (ISPG; https://ispg.net), respectively [33].

Undoubtedly, there are often some issues in most economic evaluation studies, regarding the cost collection in some PGx studies in the field of economic evaluation in personalized medicine. First, there are no national tariffs of the genetic tests used to genotype for variants affecting drug metabolism and transport, which directly impacts on the risk of developing adverse drug reactions for psychiatric and other drugs. In addition, there is often a lack of cost and/or utility data to generate the results of the economic evaluation. In the majority of economic evaluation studies in PGx, only some direct costs are taken into account and not any other indirect cost that will represent the societal perspective. To this end, it is important to clarify that cost-effectiveness studies assess the extra life year(s) gained or assess intermediate factors, like the progression-free survival. Cost-utility studies though, assess also the quality of life of the patient apart from the life year(s) gained (i.e., QALYs).

One aspect of successful implementation of PGx in psychiatry lies in the assessment of cost-effectiveness or cost-utility of PGx testing for certain antidepressant or antipsychotic treatment, as well as analyzing the costs of such approaches. Up to submission of this study, there was insufficient and inconsistent information concerning the potential cost-effectiveness of routine genotyping for antidepressant or antipsychotic treatment modalities. Here, we performed a systematic review—by following a standardized methodology—to demonstrate whether pharmacogenetic testing, as an alternative therapeutic strategy in psychiatry, can be a cost-effective approach compared to standard therapy guidelines.

METHODS

Questions and strategy

The present systematic review aimed to address the following items: (1) whether reports suggest cost-effectiveness and if the available data is of such quality that it supports the use of PGx; (2) whether the application of PGx in psychiatry is cost-effective.

A schematic diagram of the systematic review's approach is shown in Fig. 1. An extensive literature search in PubMed, Scopus, and Google Scholar was performed in August 2020. PubMed and Scopus searches were conducted using the following querying terms (((pharmacogenomics) AND (cost-effectiveness)) OR (cost-utility)) AND (psychiatry). As for Google scholar search, the terms were the following: (pharmacogenomics cost-effectiveness cost-utility psychiatry). These search terms were in concordance with the terms used by previous systematic reviews [34, 35]. Additional citations were retrieved from manual searching, reference-lists, and consultation with experts on the economic evaluation field. To retrieve more unpublished or ongoing articles on PGx for psychiatric disorders, we searched multiple database sources including relevant psychiatric professional organizations, government reports, conference proceedings, reference tracking, and Google. In total, our literature querying yielded 1159 articles (PubMed: 258, Scopus: 345, Google Scholar: 553, and other sources: 3).

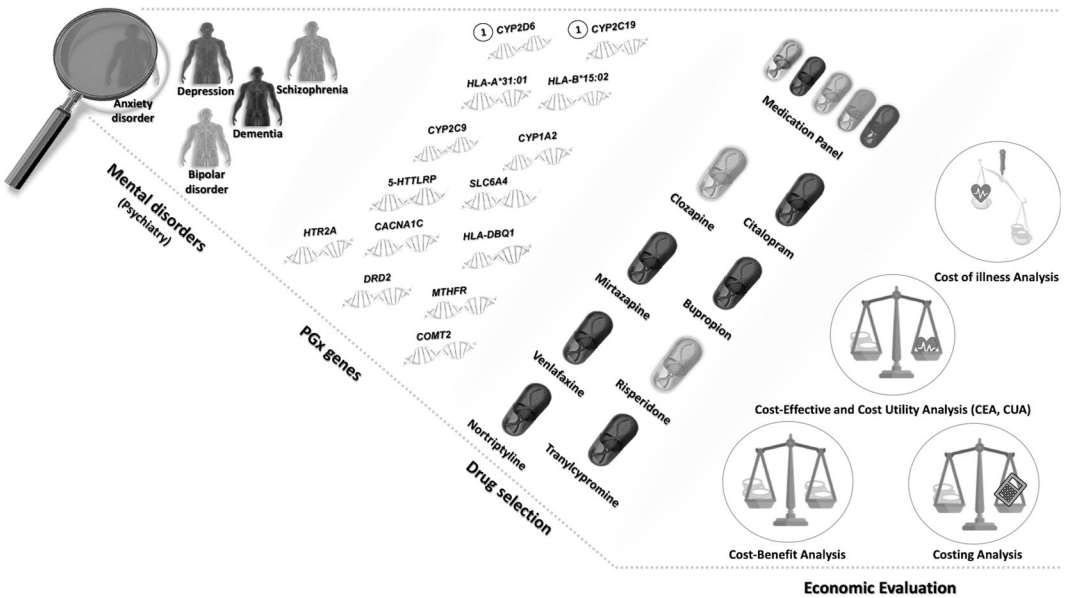

Fig. 1 Main pillars of the systematic review. A representative overview of pharmacogenomics-guided treatment of psychiatric disorders and economic evaluation methods. It should be noted that categories 'Mental disorders' and 'Drug selection' complement each other in terms of psychiatric treatment related to each assessed disease. All depicted data are summarized based on the context, the findings, and the type of the economic evaluation studies (see also Fig. 2). We also denote the clinically actionable PGx genes in psychiatry, namely *CYP2C19*, *CYP2D6* based on the Dutch Pharmacogenomics Working Group (DPWG).

Study selection

The main criteria for selecting articles were (a) adults (18–65 years) with psychiatric illnesses, (b) articles written, peer-reviewed published in English, (c) including PGx testing in the study, (d) genes associated with the metabolism of psychiatric drugs, (e) assessing the clinical utility of psychiatric PGx such as remission, response, quality of life, functional capacity, adverse drug events, general tolerability, (f) including cost data and evaluating economic outcomes. If 5 out of 6 criteria were fulfilled, then the articles were kept for further assessment.

We performed our systematic review by using standardized criteria according to PRISMA (http://www.prisma-statement.org/). We first screened papers based on their title, and if the title was not informative enough, abstracts were carefully analyzed. Through this process, researchers assessed which studies met the prespecified criteria and should be included in the analysis and which articles had to be excluded. Subsequently, researchers conducted a detailed full-text analysis in studies that met the prespecified criteria and assessed which papers should be included for further analysis. All disagreements were thoroughly discussed and resolved by consensus.

We began with an initial number of 1159 articles which was then reduced to 959 after removal of any duplicates (Fig. 2). Records were then screened by title ($N = 134$) and then by abstract screening leading to a total number of 32 articles which were assessed for eligibility. The full-text analysis performed by all authors led to 16 papers, in which 2 more studies were also included from previous systematic reviews. The total number of studies included in this review was 18 articles (Fig. 2). Common exclusion criteria included: the type of genetic test was not related to PGx; the investigated condition was not related to psychiatry or inclusion of other medications than antidepressants and antipsychotics; there was no economic evaluation; and reports were not peer-reviewed.

Data extraction

Continuing from the previous step, the following data were then extracted from the articles: type of article, year of publication, study design, sample characteristics, gene(s) explored by the PGx test, relevant costs associated with the PGx test, pharmaceutical compound influenced by the genetic variation, type of economic evaluation, type of sensitivity analysis (one-way, multi-way, probabilistic), time horizon and discounting factor, main outcome measurements, analytical validity of the PGx test, cost-effectiveness threshold, country where the study was conducted. To interpret the implications of each article's main findings adequately, we analyzed the conclusion, discussion, and limitations sections thus aiming to carefully delineate the key findings of each assessed study.

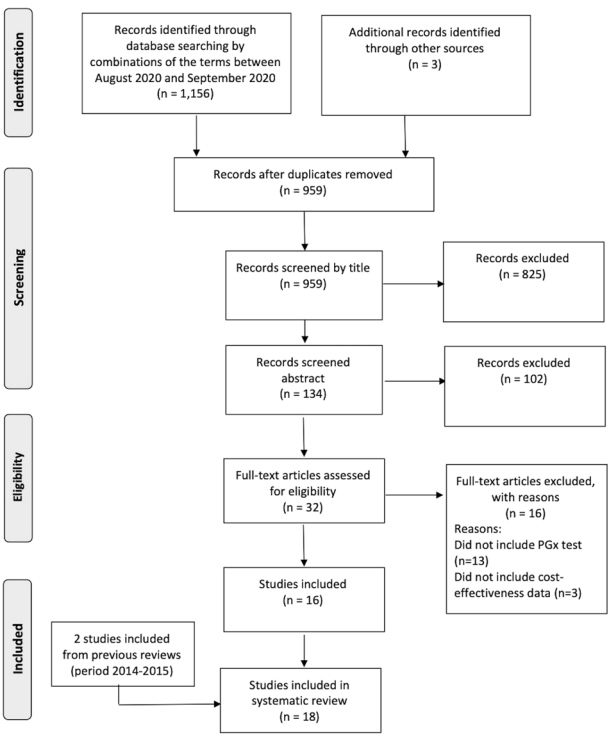

Fig. 2 Schematic pipeline/flowchart of the literature screening. *Exclusion criteria: (1) non-English study, (2) full text not available, (3) not relevant with pharmacogenomics, e.g., genetic diagnostic testing, (4) no economic evaluation, (5) not psychiatric diseases.

Quality of reporting assessment

To assess the quality of all the included studies, we used the Quality of Health Economic Studies (QHES) instrument, which represents a weighted grading system that evaluates the quality of each study based on whether the content of the study meets specific requirements [36]. QHES was used to make the comparison of the present results feasible and relate these to other systematic reviews conducted in the same scientific area [34, 37–39]. According to the QHES checklist, studies are evaluated against sixteen elements, including study characteristics (funding information, patient subgroups, time horizon), study design (variable estimation, perspective), findings, conclusions, and discussion (sensitivity analysis, reliability of costs and outcomes, economic model, bias assessment, limitations, and future recommendations). The QHES checklist can generate a score between 0 and 100, while a score of 75 and more is of the highest quality [40] (Supplemental Table 1). Three reviewers assessed the quality of all included studies [41–58] independently, when results differed ($N = 3$) though, the consensus was reached through discussion by all authors.

Descriptive statistics for each assessed study element were computed by using the SPSS software version 26. The summary statistics illustrate the demographic characteristics of the included studies (e.g., year, country/region, condition studied, etc.), as well as an overview of the effectiveness and costing outcomes of each study regarding implementation of PGx testing.

RESULTS

Summary of the overall study characteristics

Most of our studies (16 out of 18) were published during the last decade (2010–2020), while only two studies were published prior to this period (one in 2009 and one in 2005, respectively). US patients were the most targeted population ($N = 11$, 61.11%), but there was European representation in our sample, including studies from the Netherlands, Italy, the United Kingdom, and Denmark (Table 1, Supplemental Table 3). The most common psychiatric conditions studied were major depressive disorder (MDD) and schizophrenia (SCZ), accounting for 38.89% ($N = 7$) and 22.2% ($N = 4$) of the studies, respectively. The remaining studies covered a variety of psychiatric disorders (as described in DSM-IV) and depression often as comorbid condition with anxiety (Tables 1 and 2, Supplemental Table 2).

Information regarding the prescribed antipsychotic or antidepressant treatment was not clearly stated in most of the studies ($N = 10$, 55.55%) (Supplemental Table 3). The remaining number of assessed studies evaluated the PGx effect with the following treatment schemes: clozapine ($N = 2$), risperidone ($N = 1$), citalopram with bupropion ($N = 2$), nortriptyline with tranylcypromine ($N = 1$), and a 'cocktail' of different antidepressant compounds ($N = 2$).

The majority of the studies ($N = 12$, 66.67%) examined either a panel of genetic testing commercially available or a panel of multiple genes, with the report of the PGx results being used to guide medication choice in patients with psychiatric disorders (Supplemental Table 2, Table 2). Notably, GeneSight panel and NeurolDgenetix panel provided information about the tested genes, although this information could not be retrieved for IDgenetix test (Table 2). The rest of the studies assessed genetic variation within one clinically actionable pharmacogene (in most cases either *CYP2D6* or *CYP2C19*). 66.66% of the studies ($N = 12$) focused on pre-emptive PGx implementation, while only 11.1% of the studies focused on PGx implementation after treatment plan made. The remaining number of studies had no clear statement of which test timing approach was used throughout the study duration. The source of funding was reported for nine studies (50%) and which varied between public, private, and nonprofit

Table 1. Basic demographic details describing each included study in the present review, such as the disease, the cohort type, the age range, the country of origin, the testing time, and the study design.

Study	Study design	Diseases	Patient age range (years)	Country	Type of medication	Test timing (after treatment plan made, after treatment started, pre-emptive, no statement)
Perlis et al. [52]	CEA	SCZ	<60	United States	Clozapine	No statement
Rejon-Parrilla et al. [54]	CEA	SCZ	<60	United Kingdom	Risperidone	Prior to treatment
Hornberger et al. [48]	CEA	MDD	<60	Not given	n/a	No statement
Olgiati et al. [51]	CUA	MDD	18–65	European countries	Bupropion, citalopram	Prior to treatment
Sluiter et al. [56]	CUA	MDD	≥18	Not given	Fluoxetine, citalopram, venlafaxine, mirtazapine, amitriptyline, nortriptyline	Prior to treatment
Groessl et al. [46]	CEA	MDD	<60	United States	n/a	Prior to treatment
Girardin et al. [45]	CEA	SCZ	Not specified	United States	Clozapine	Prior to treatment
Perlis et al. [53]	CEA	MDD	<60	United States	Bupropion, nortriptyline, venlafaxine, citalopram, mirtazapine	Prior to treatment
Berm et al. [42]	CEA	MDD	>60	Netherlands	Nortriptyline, tranylcypromine	Prior to treatment
Serretti et al. [55]	CUA	MDD	<60	Italy	Bupropion, citalopram	Prior to treatment
Najafzadeh et al. [50]	CEA	Dep and Anx.	<60	United States	n/a	Prior to treatment
Herbild et al. [47]	CA	SCZ	>18	Denmark	n/a	Prior to treatment
Winner et al. [57]	CA	Psy diseases	<60	United States	n/a	After treatment plan made
Brown et al. [43]	CA	Psy diseases	<60	United States	n/a	After treatment plan made
Maciel et al. [49]	CA	Dep and Anx.	<60	United States	n/a	Prior to treatment
Fagerness et al. [44]	CA	Psy diseases	Not specified	United States	n/a	Prior to treatment
Benitez et al. [41]	CA	Psy diseases	>18	United States	n/a	No statement
Winner et al. [58]	CA	Dep and Anx.	Not given	United States	n/a	No statement

n/a, no specific information is available (regarding the treatment scheme).

Table 2. Summary of the main findings of each economic evaluation study in the field of psychiatric pharmacogenomics.

Study	Disease	PGx testing	Clinical outcome	Quantitative outcome or ICER	Conclusion
Perlis et al. [52]	SCZ	Putative genetic test for optimum clozapine response	Relapse and/or response probability after treatment with clozapine	Undiscounted life-expectancy: 31 years. ICER: 47,705$/QALY	Likely to be cost-effective based on WTP
Rejon-Parrilla et al. [54]	SCZ	*CYP2D6*	ADE probabilities owing to risperidone treatment	ICER: 19,252$/QALY	Likely to be cost-effective based on WTP
Hornberger et al. [48]	MDD	*CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4,* and *HTR2A*	Treatment response and mortality rates	3764$ total cost savings ICER: −11,911$/QALY	PGx dominates the treatment as usual, Cost-saving
Olgiati et al. [51]	MDD	*5-HTTLPR*	Probabilities of remission, lack of remission and dropout	Euro A: 1147$/QALW Euro B: 1185$/QALW Euro C: 1178$/QALW	Cost-effective in high-income countries
Sluiter et al. [56]	MDD	*CYP2D6*	ADE occurrence	ICER: 77,406$/QALY	Likely to be cost-effective based on WTP
Groessl et al. [46]	MDD	IDgenetix (IDGx) PGx test	Response and mortality rates	ICER: −25,980$/QALY (MDD) ICER: −34,176$/QALY (Severely Depressed)	Cost-saving, Cost-effective and dominant
Girardin et al. [45]	SCZ	*HLA-DBQ1/HLA-B*	Clozapine response	ICER: 3.93 million/QALY	Cost-effective
Perlis et al. [53]	MDD	(SNP) in the serotonin 2A receptor *(HTR2A)* gene	Mortality, relapse, and remission rate	ICER: 93,520$/QALY	Likely to be cost-effective based on WTP
Berm et al. [42]	MDD	*CYP2D6*	ADR occurrence and efficacy of treatment with nortriptyline or trancylpromine	ICER: 1.33 million/QALY	Not cost-effective
Serretti et al. [55]	MDD	*5-HTTLPR*	Remission rates and delay in antidepressant response	ICER: 2890$/QALY	Cost-effective
Najafzadeh et al. [50]	Dep. & Anx.	IDgenetix (IDGx) PGx test	Remission and response rates	ICER: 1394$/QALY (based on direct costs)	Cost-effective and cost-saving
Herbild et al. [47]	SCZ	*CYP2D6, CYP2C19*	–	Actual excess costs for the extreme metabolizers group: 67,064$, Decrease of excess costs after PGx testing: 46,532$	Cost-saving
Winner et al. [57]	Psy diseases	GeneSight panel: *CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	Adherence compared to standard of care	Medication savings after PGx: 1035.60$. Improved adherence after PGX testing: 0.11; Pharmacy cost savings averaged: 2774.53$	Cost-saving
Brown et al. [43]	Psy diseases	GeneSight panel: *CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	–	Medication cost savings for payers and patients of 3988$ per member per year ($p < 0.001$)	Cost-saving
Maciel et al. [49]	Dep & Anx.	NeuroIDgenetix genetic testing: *COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, HTR2A, MTHFR, SLC6A4*	Response or remission rates	Remission rate in the experimental group: 35%; response rate in the experimental group: 73%; Total annual saving after PGx testing per patient: 3962$	Cost-saving
Fagerness et al. [44]	Psy diseases	*CYP2D6, CYP2C19, SLC6A4, CACNA1C, DRD2, COMT, MTHFR*	Adherence to medication	Better medication adherence by using PGx. Cost-saving in outpatient costs over 4-month follow-up period 9.5% or 562$ in total savings	Improved adherence and cost-saving
Benitez et al. [41]	Psy diseases	*GeneSight panel: CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	–	Post-index cost savings (US 5505$) drove a per-member-per-month savings of US 0.07$.	Cost-saving
Winner et al. [58]	Dep & Anx.	*GeneSight panel: CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4* and *CYP1A2; SLC6A4* and *HTR2A.*	Health care visits	Poor metabolizers had 69% more total health care visits and more disability claims per person during the study period (0.56) compared to ultrarapid and intermediate metabolizers.	Increased health care utilization and Potentially cost saving

Details about the author(s) of the study, the disease, the pharmacogenetic test, the quantitative outcome, and its conclusion are provided. Abbreviations are defined in the respective section.

organizations. Two studies reported that the authors received no funding, while seven studies provided no details about their source of funding.

Summary of the study strategies

Regarding the study strategy, six out of 18 studies were classified as economic evaluation studies drawing data from randomized control trials ($N = 1$) or observational ($N = 5$) studies. The rest ($N = 12$) studies used hypothetical cohorts with model parameter estimated being derived from the literature, databases, and registries or previously published clinical studies (Supplemental Table 2). It's worth noting though that even for randomized control trials or observational studies (i.e., clinical studies), a certain type of data could be also drawn from literature or registries/databases. Moreover, eight (44.4%) studies were conducted from a societal perspective, four (22.2%) from the health care system perspective, and five (27.7%) from the third-party payer perspective (Supplemental Table 3). The time horizons used in the included economic evaluation studies were considerably diverse: about 11.1% ($N = 2$) used lifetime models, 27.7% ($N = 5$) used a 1-year horizon, 33.33% ($N = 6$) used 2–10 years horizon, while <1-year horizon comprised each a 27.77% ($N = 5$) of the overall studies' time horizons. 44.4% of the studies were characterized as cost-effectiveness studies (CEA) ($N = 8$), 16.6% were considered cost-utility (CUA) ($N = 3$), while seven studies were reported as cost-analysis studies ($N = 7$, 38.9%) (Table 1).

The cost categories included in the economic model varied across studies (Supplemental Table 2). Most studies included costs characterized as direct medical costs ($N = 13$, 72.22%) whereas five studies measured direct and indirect medical costs ($N = 5$, 27.7%). Regarding the effectiveness outcome measures, eleven studies (61.1%) reported quality-adjusted life years (QALYs) or quality-adjusted life weeks (QALWs), one study reported the adherence rate of the patients (5.55%), while five studies reported no effectiveness outcome measurements (33.33%). To this end, 11 studies presented a quantitative outcome of their cost-effectiveness analysis by estimating the incremental cost-effectiveness ratio (ICER) and in one instance the life expectancy as well (overall, 61.1%), while five studies (27.8%) provided precise estimate of the cost-savings after PGx implementation in psychiatric diseases (Table 2). Moreover, 2 studies evaluated the remission, response, adherence rate, and any potential cost-savings at the same time (11.1%) (Table 2).

One observation of the present systematic review lies also within the fact that eight studies (44.4%) implemented a cost-effectiveness threshold in their analysis, while ten studies gave no estimate of the willingness-to-pay threshold (55.6%) (Supplemental Table 2). This could be explained by the fact that these studies were characterized as cost-analysis studies and thus reported the cost-savings as an outcome of the PGx clinical implementation. Regarding the assessment of uncertainty in the parameters of the respective economic evaluation models, three studies (16.67%) used probabilistic sensitivity analyses to explore different willingness-to-pay thresholds, while four studies (22.22%) performed one-way deterministic sensitivity analyses to account for uncertainties in the model parameter estimates.

As an additional aspect, the number of studies, which were in favor of PGx testing either in terms of cost-effectiveness or in terms of cost-savings, was also assessed (Supplemental Table 2, Table 2). Fifty percent of the studies reached a conclusion that PGx testing is cost-effective ($N = 6$) or could be cost-effective ($N = 4$). 38.9% of the studies ($N = 7$) reported that PGx testing is cost-saving, while only one study reported that PGx is not cost-effective.

Quality of reporting

Quality scores were evaluated using the QHES tool and ranged from 73 to 98, with the mean score for all studies being 87.2. Four studies (36.4%) achieved a perfect score of more than 90, with an additional 5 studies (45.4%%) having scores between 80 and 89. Two studies (18.1%) had a score <80. All 11 studies, which were subjected to quality assessment, clearly articulated their objective (criterion 1), their perspective of analysis (criterion 2), as well as how they handled uncertainty using sensitivity analysis (criterion 5). Moreover, the estimates for 10 out of 11 (90.9%) studies did not come from a subgroup analysis, thus making criterion four not applicable and relevant (Supplemental Table 1). Other highly reported QHES criteria were the outcome measures (criterion 10), the valid and reliable health outcomes (criterion 11), the display of economic models clearly and transparently (criterion 12) and the inclusion of future recommendations (criterion 15). Modest variability was witnessed in the level of reporting regarding three QHES elements. Specifically, the analytic horizon of five studies (45.4%), did not allow adequate time for all relevant and important outcomes to be measured. Moreover, 4 studies (36.3%) did not clearly and explicitly discuss the magnitude of potential biases, whereas 4 studies (36.3%) did not report whether any source of funding was applied to support their projects. In addition, three studies (27.2%) did not offer details of the genes included by the PGx test, four studies (36.3%) did not explicitly articulate whether the derived data from the literature referred to the reported age range of the study, whereas the score of three studies (27.2%) was crucially decreased as they produced an ICER of more than a million without adequately discussing the implications of this finding, while their conclusion (i.e., might be cost-effective) did not reflect the reality given the WTP levels across countries. A description of the QHES framework and the number of articles missing each criterion is presented in a supplemental table at the end of our systematic review (Supplemental Table 1).

DISCUSSION

PGx is constantly gaining momentum as a supportive strategy treatment in different fields of Medicine, given the evidence, the available recommendations, and relatively low costs for genetic testing. For more than a decade, psychiatric PGx has attracted particular attention in terms of drug response and avoidance of adverse drug events. However, apart from the clinical benefits, only a few economic evaluation studies, which focused in demonstrating whether psychiatric PGx, is also cost-effective have been performed to date thus helping payers in their decision-making process.

PGx can contribute toward reducing health care costs in different ways. First of all, PGx reduces adverse drug reactions and reciprocally the relevant costs for treating or managing these adverse drug events [59]. Second, PGx can contribute toward reducing drug switches and recurrent drug dose adjustments, used until optimal clinical effect is achieved, and thereby reducing drug costs. Furthermore, PGx can also reduce the time until disease remission, therefore contracting hospitalization length, which positively impacts on the hospital treatment costs [60]. Last, PGx reduces disease burden and related costs, which includes loss of productivity, both in terms of absenteeism (absence from work) and presenteeism (be present at work but less productive) [61, 62].

In psychiatry, and to be transparent, PGx testing can be used for *CYP2C9*-phenytoin pair, for certain antidepressants and/or antipsychotics metabolized either by *CYP2C19* and/or *CYP2D6*, as well as for HLA-A/B for carbamazepine, oxcarbazepine and—to some extent—for lamotrigine. Moreover, it is important to note that benefits come as negative prediction, such as higher risk for non-response for aberrant metabolizer status of all the CYPs, which has a prevalence of up to 10% for *CYP2D6* in Europeans, and which aberrant metabolizer status is also a minority of (predominantly Asians) for HLA-A/B [33, 63]. Given the relatively low frequency of *CYP2D6* aberrant metabolizer status, the primary question lies in the potential cost-effectiveness of genotyping before any

medication is taken, or whether the genotyping should be performed after the first medication has failed.

Moreover, in several economic studies in PGx, there are some methodological flaws when comparing the outcomes of the various types of economic evaluations [64]. Several studies only include cost comparisons without taking into consideration utility data to measure effectiveness. As such, these studies quality more for economic analysis rather than cost-effectiveness or cost-utility studies. For example, Brown and coworkers assessed with accuracy the medication costs of patients with mental illness [43], while Olgiati and coworkers depicted from the cost-effectiveness acceptability curve the probability of having an ICER value below the recommended willingness-to-pay threshold [51] and hence included utility outcomes in addition to cost data.

For example, in our systematic review, a few studies characterized as 'could be or may be cost-effective' can be characterized as indicating a debatable cost-effectiveness conclusion debating on the cost-effectiveness threshold selected. This could be explained either owing to the inclusion of only direct medical costs [50, 52, 53] or owing to uncertainty in the data as described in Sluiter and colleagues [56]. Therefore, careful assessment and consideration of factors and parameters, which could influence the characterization of PGx-guided treatment as cost-effective, is essential in most economic evaluation studies.

Another issue with these studies lies within the inclusion of different time horizons. In other words, the selected time horizon may reflect on the clinical outcomes observed but not on the economic aspects of disease treatment, hence the economic evaluation cannot be performed. An additional limitation lies in the fact that recommendations were not followed for specific gene–drug pairs for a variety of studies, but different medication modalities were added together in some assessed studies, thus making the importance of PGx and its clinical relevance often hard to interpret. Moreover, there was a certain number of drugs as derived from the present study, for which PGx relevance may be dubious. For example, little PGx information is available for clozapine, while bupropion is mainly metabolized by the CYP2B6 enzyme and there is little data available for the usefulness of genetic testing. Moreover, tranylcypromine and mirtazapine are amongst the drug compounds with little PGx information available for further use.

PGx can contribute to the increase of adherence to treatment, since patients often are reluctant to adhere to the treatment when the latter is not effective, or worse present with side effects, called as the 'nocebo' effect. From the present studies, we can conclude that the PGx testing can reduce costs by increasing adherence to the treatment, which can further contribute to reducing the disease burden, relapses, and hospitalizations days. In a case-control observational retrospective study by Fagerness and coworkers [44], the authors compared adherence to treatment with the possibility of cost-savings, thus indicating that patients, who have undergone genome-guided treatment, can show a statistically significant increase in adherence to treatment, that is 6% more than controls (6.3% vs 0.3%, respectively) in the post index period [43].

In addition, the willingness-to-pay threshold is defined on a national level and varies depending on the country, the GDP as well as on a few additional factors. The desired value for the willingness to pay is approximately three times the average per capita income of the country [65]. For the UK, an ICER value below £20,000 will lead to recommendation unless there is strong evidence suggesting otherwise, while an ICER value between £20,000 and £30,000 will lead to recommendation given that the responsible committee is satisfied with the uncertainty levels in the evidence [66, 67]. A value between US$50,000–70,000 is considered cost-effective in USA, a value below $20,000 is considered particularly attractive, whereas values above $100,000 are considered particularly costly and may be rejected [68]. Still though, the willingness-to-pay threshold of $100,000 may be accepted under certain circumstances as in the case of orphan drugs for rare diseases [69]. In economic theory another process to determine the value of willingness-to-pay threshold (λ) is as follows: to rank all the available health care technologies from the lowest to the highest ICER and select in descending order until the resources are exhausted (the league table approach; [70]). As such, a genome-guided intervention, which is characterized as cost-effective in a certain country, may not be cost-effective in another country, since the willingness-to-pay thresholds may vary in these countries.

Herein, we also observed huge discrepancies between certain ICER values reported in our assessed studies and other ICER reported as cost-effective by other studies. A characteristic example lies in the case of the study by Girardin and coworkers, who reported an ICER of 3.93 million/QALY but which is far from the aforementioned willingness-to-pay thresholds. Similar observations were applied for the studies of Perlis and coworkers [53] and Sluiter and coworkers [56]. Concluding, such studies are potentially relevant in the respective national health care system.

An additional challenge for psychiatric PGx lies in the proper selection of PGx testing, where it will essentially determine to a large extent the broad use of PGx as an alternative therapeutic strategy from a financial standpoint. It is well-known that cytochrome P450 (CYPs) as drug-metabolizing enzymes are involved in a plethora of clinically used drugs (around 70–80%), with CYP2C19 and CYP2D6 enzymes being involved in the metabolism of ~30% of all medications including antidepressants and antipsychotics [71, 72]. To date, the most prevalent PGx panels for psychiatric PGx include both individual gene testing and combinatorial gene testing. In the latter case, recent studies have shown that due to the high complexity of neuropsychiatric medications in terms of drug-metabolism and mechanism of action, combinatorial gene testing can be cost-effective [57, 58]. However, there is still some controversy as far as the use of such combinatorial panels is concerned, as they usually include genes with questionable/minor effects, while the algorithms used for data reporting are often not disclosed.

Given the fact that we are in the dawn of the 'big data' era, an attempt to explore more drug-metabolism enzymes is essential to design a multi-gene PGx panel that will be assist in the prediction of the effectiveness of a wide spectrum of neuropsychiatric medications. For example, a few studies have already highlighted the role of other genes encoding drug-metabolizing enzymes and which could consequently affect the metabolism and the biological availability of psychiatric medications and especially of haloperidol [73, 74]. Finally, raw data should be collected in future studies to measure utility rather than data collected from databases or the literature. In addition to this, patient preferences are not systematically considered. In this case, structured questionnaires should be used to assess patients' perspectives, such as those used in the time-trade off or rating scale, that are directly addressed to the patient.

To our knowledge, this is the first study aiming to review the existing literature for studies related to the economic evaluation of PGx in psychiatry. Not only our literature review summarized the existing knowledge in the field, but also, most importantly, revealed several discrepancies in the existing studies, which can be rectified in the future. It is equally important to note that through our thorough article screening process, we ensured that only articles that met these high-quality criteria remained for further analysis. Overall, we concluded by stating that further assessments of the cost-effectiveness of genetic panel testing and pre-emptive PGx testing will be essential, in order to inform health care systems that aim to implement PGx to improve psychiatric disease care. This could be achieved by employing similar types of economic evaluation, such as cost-utility analysis and decrease the uncertainty concerning the effectiveness of psychiatric drug

treatment modalities. Ultimately, this approach can contribute toward reimbursement of PGx-guided therapeutic interventions in psychiatry [75].

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COMPETING INTERESTS

The authors declare no competing interests. GPP is Full Member and national Representative of the European Medicines Agency, Committee for Human medicinal Product (CHMP) – Pharmacogenomics Working Party (Amsterdam, the Netherlands) and member of the Clinical Pharmacogenetics Implementation Consortium (CPIC). DJM is a member of CPIC and co-investigator in two pharmacogenetic studies where genetic test kits were provided as in-kind contribution by Myriad Neuroscience. No payment or any equity, stocks, or options from any pharmacogenetic testing company was obtained.

ADDITIONAL INFORMATION

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