Cost Effectiveness of Pharmacogenetic Testing for Drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines: A Systematic Review

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The objective of this study was to evaluate the evidence on cost-effectiveness of pharmacogenetic (PGx)–guided treatment for drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. A systematic review was conducted using multiple biomedical literature databases from inception to June 2021. Full articles comparing PGx-guided with nonguided treatment were included for data extraction. Quality of Health Economic Studies (QHES) was used to assess robustness of each study (0–100). Data are reported using descriptive statistics. Of 108 studies evaluating 39 drugs, 77 (71%) showed PGx testing was cost-effective (CE) ($N = 48$) or cost-saving (CS) ($N = 29$); 21 (20%) were not CE; 10 (9%) were uncertain. Clopidogrel had the most articles ($N = 23$), of which 22 demonstrated CE or CS, followed by warfarin ($N = 16$), of which 7 demonstrated CE or CS. Of 26 studies evaluating human leukocyte antigen (HLA) testing for abacavir ($N = 8$), allopurinol ($N = 10$), or carbamazepine/phenytoin ($N = 8$), 15 demonstrated CE or CS. Nine of 11 antidepressant articles demonstrated CE or CS. The median QHES score reflected high-quality studies (91; range 48–100). Most studies evaluating cost-effectiveness favored PGx testing. Limited data exist on cost-effectiveness of preemptive and multigene testing across disease states.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ There is varying information on the cost-effectiveness of pharmacogenetic testing for drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines and no systematic review has collated these data on all drugs with CPIC guidelines to date.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the evidence on cost-effectiveness of pharmacogenetic testing for drugs with CPIC guidelines?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ For the first time, we demonstrate that 71% of studies evaluating the cost of pharmacogenetic testing for drugs with CPIC guidelines determined testing was cost-effective or cost-saving. The analysis provides details of key study characteristics and differences in cost outcomes.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These data provide valuable information on the impact of pharmacogenetic testing on cost and may support further coverage determinations by payors to increase accessibility to evidence-based pharmacogenetic testing.

Pharmacogenomics (PGx) has been studied and applied across many therapeutic areas to evaluate and predict an individual's response to specific drugs based on his or her genetic makeup.[1] PGx-guided dosing and treatment can be used to normalize systemic drug exposure, reduce side effects, and/or improve clinical response for drugs with established evidence. There are several robust examples where PGx testing can improve drug safety (e.g., abacavir/*HLA-B*5701*),[2] and/or enhance clinical effectiveness (e.g., clopidogrel/*CYP2C19*,[3] psychiatric medications, and *CYP2D6/CYP2C19*).[4]

As of April 2022, the US Food and Drug Administration (FDA) has over 400 biomarkers for roughly 300 distinct medications mentioned in drug labeling, with most related to somatic mutations for cancer targeted therapies.[5] In February 2020, the FDA published a Table of Pharmacogenetic Associations with a focus on germline variations, which was most recently updated in May 2022.[6] These tables outline drug–gene associations for which data support therapeutic management (56 drugs) and have a potential impact on safety or response (19 drugs) or a potential pharmacokinetic impact only (39 drugs). As of July 2022, there are eight drugs with black box warnings related to germline PGx: abacavir/*HLA-B*5701*, carbamazepine/*HLA-B*1502*, clopidogrel/*CYP2C19*, codeine and tramadol/*CYP2D6*, pegloticase and rasburicase/*G6PD*, and valproic acid/*POLG*.[5] Greater awareness, improved testing accessibility, and expanding evidence base has increased the adoption of PGx testing at some hospitals.

A key process in implementing PGx testing is the ability to standardize the translation of PGx data into actionable prescribing decisions that are driven by evidence-based medicine. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international group focused on creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed drug–gene clinical practice guidelines focused on actionability (26 guidelines across roughly 70 drugs, as of April 2022).[7] A key assumption underlying these guidelines is that clinical high-throughput and preemptive genotyping will become more widespread and that clinicians will be faced with interpreting PGx information even if they have not explicitly ordered a test. Factors considered in guideline development include available evidence supporting PGx intervention, risk of an adverse drug reaction, and available test for a gene or set of genes. The guidelines purposefully do not address cost of testing nor provide guidance on who should be tested, albeit many institutions who have adopted PGx testing utilize CPIC guidelines as a reference for drug–gene inclusion.

Cost is an important consideration to healthcare systems and patients when applying PGx in clinical practice and is often ranked as a major barrier to implementation.[8] Third party payors especially want to understand if PGx test coverage will save or increase healthcare costs downstream. Cost-effectiveness of PGx testing is changing rapidly as molecular testing platforms are becoming more sophisticated, cheaper, accessible, and are transitioning from single-gene to multigene tests.[9] While it is understandable that cost is excluded from clinical practice guidelines, it is still critical that cost evaluations are conducted in PGx studies and systematic reviews.

Verbelen *et al.* conducted an economic evaluation for PGx associations listed in the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, which included 10 drugs and determined that over half of the 44 evaluations drew conclusions in favor of PGx testing.[10] The evaluation was limited to drugs listed in the FDA website up to September 2015. Given CPIC guidelines have become a universally accepted tool for PGx interpretation among implementers and these guidelines do not include information regarding cost, we proposed an updated systematic review of economic evaluations of drugs with CPIC guidelines. The goal was to evaluate whether the evidence suggested PGx-guided treatment for CPIC drugs was cost-effective, cost-saving, uncertain, or not cost-effective for all drugs with CPIC level A or B evidence and published guidelines.

MATERIAL AND METHODS

Search strategy

CPIC assigns levels of evidence to gene-drug pairs based on prescribing actionability ranging from "A" to "D" with "A" meaning genetic information should be used to change prescribing (preponderance of evidence is high or moderate in favor of changing prescribing), "B" meaning genetic information could be used to change prescribing because alternative therapies/dosing are extremely likely to be as effective and as safe as nongenetically based dosing (preponderance of evidence is weak with little conflicting data) and "C" and "D" meaning clinical actionability is unclear. CPIC actionability levels may evolve as more data emerges. As of June 2021, 66 drugs with a published CPIC guideline had an evidence level of "A" or "B," indicating a prescribing action is recommended for that gene-drug pair. We conducted a comprehensive literature search from database inception to June 2021 for the 66 drugs with a published CPIC guideline and level "A" or "B" evidence. Pharmacogenomics, genes, and cost terms were searched for in PubMed, Embase, Ovid MEDLINE, and Scopus. Pharmacogenomics and gene terms were also searched in the Tufts CEA registry. Specific search criteria are included in the **Supplemental Information**. This systematic review was exempt from Institutional Review Board review and was not registered.

Study selection

Primary literature assessing any component of cost within a PGx study for any drug with a published CPIC guideline and evidence level of "A" or "B" was evaluated for inclusion. We excluded studies that were non-English, review articles without original data, drugs for which there were no CPIC guidelines available, in abstract format only (or full text not available), and if no economic evaluation was presented in the analysis. Only studies comparing a PGx-guided approach with a non-PGx-guided approach were included. Duplicated studies were excluded from the final selection. A.T.A. performed the initial literature search; S.A.M. and C.M. conducted an independent search for additional articles and reviewed the initial list; S.A.M. and J.N.P. reviewed the final list of studies for eligibility.

Data extraction and presentation of results

Data extraction of each study focused on three domains. (i) The gene(s) and drug(s) under review. (ii) Cohort (hypothetical, observational prospective/retrospective, randomized controlled trial) and type of population. (iii) Cost outcomes (cost-effective, cost-saving, not cost-effective, or uncertain), including incremental cost-effectiveness ratio (ICER) and willingness-to-pay thresholds. Studies which demonstrated the PGx intervention resulted in sufficient benefit or value compared with the costs (i.e., below the willingness-to-pay threshold) were categorized as cost-effective. Studies which found the PGx intervention resulted in savings (overall reduction in healthcare costs, as determined by the study investigators) were categorized as cost-saving. PGx interventions which did not create adequate benefit or value compared with cost (e.g., ICER greater than the willingness-to-pay threshold) were categorized as not cost-effective. Studies which had conflicting results or indicated that cost-effectiveness was dependent upon one or more parameters in the model (e.g., event rate, sample size, allele frequency, cost of the drug and/or event of interest) were categorized as uncertain.

Other information collected included the publication year, continent and country where the study was performed, perspective of the potential decision maker, time horizon, and funding source. This information was collected or identified as missing for every study and reported in **Supplemental Table S1**. No assumptions regarding the data were made.

Two reviewers were assigned to extract data independently from each article that passed inclusion criteria. Data, including study characteristics and cost outcomes, are synthesized and reported using descriptive statistics, summary tables, and a narrative method.

Quality of Health Economic Studies (QHES)

The Quality of Health Economic Studies (QHES) tool was used to assess the robustness of each study,[11] emphasizing appropriate methods, valid and transparent results, and comprehensive reporting. The instrument includes 16 criteria selected by a panel of eight health economics experts. The QHES tool is scored from a scale of 0–100 indicating lowest to highest quality studies. Studies with a QHES score of 75–100 were considered high quality and a score <75 considered not high quality.[12]

To standardize the QHES scoring process, a multiple-step method for inter-rater reliability was developed: (i) Six raters reviewed and familiarized themselves with the instrument.[13] (ii) All raters individually reviewed and scored five selected papers as a "training set" from the antidepressant studies, which were then discussed among all raters and consensus was formed for each question and the total score. Based on this discussion, a document was created to standardize interpretation of each QHES question.[14] (iii) Raters were arranged into three groups of two. Each pair was assigned articles to score independently then discuss as a pair until consensus was reached to create a single score for each paper. (iv) The original "training set" was re-scored by two raters so that they would be assessed in the same methodological fashion as the remaining papers. (v) Differences in interpretation or discrepancies in scores between paired raters was brought to the larger group for further discussion and consensus.

RESULTS

Study selection

As shown in **Figure 1**, the search strategy identified 2,819 unique articles. We excluded 2,680 articles resulting in 139 full-text articles assessed for eligibility. Of these, 108 articles were included for data extraction. The most common reasons for exclusion were article(s) did not compare PGx-guided to non-PGx-guided treatment or costs were not evaluated.

Summary of study designs and characteristics

All studies evaluated CPIC level A drug–gene pairs with nine multigene antidepressant studies and one multigene multidrug study also including drug–gene pairs with lower levels of evidence. Of the 108 studies included, 75 (69%) used hypothetical populations with model parameter estimates derived from previously published randomized controlled trials or observational studies (**Table 1**). Most studies were conducted using data from North America (*n* = 51,
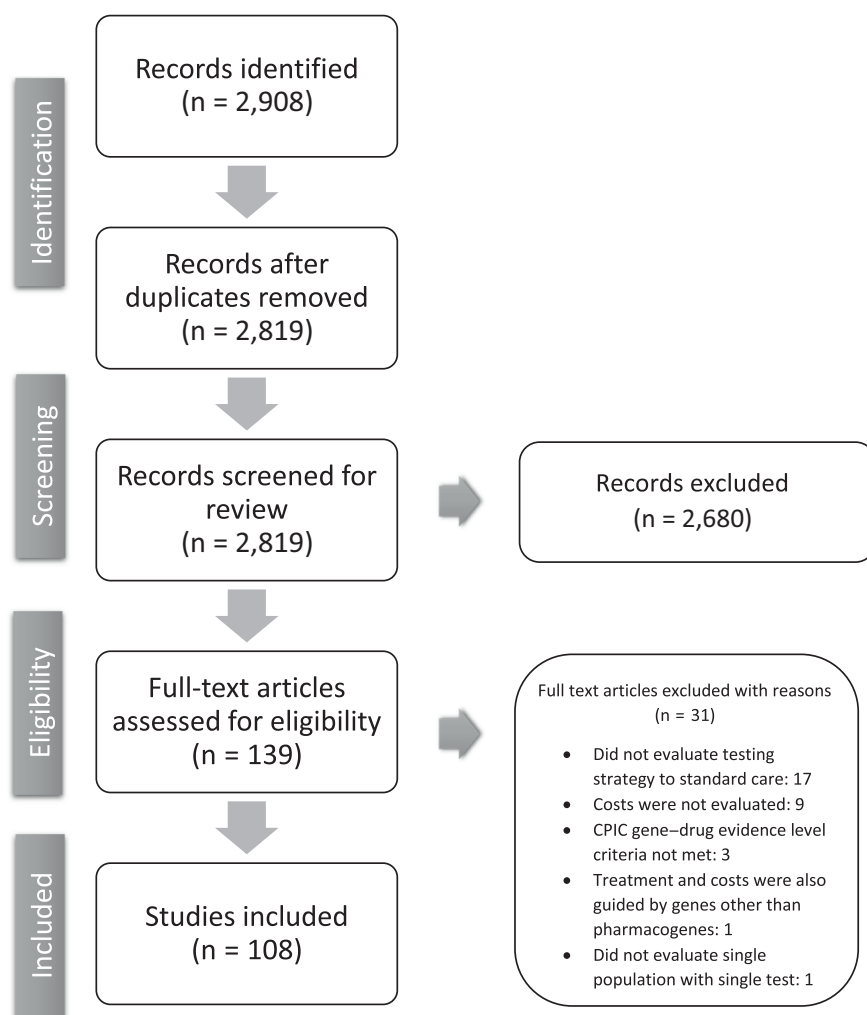

Figure 1 Flowchart of the literature screening. Of the 2,819 unique articles identified, 139 full-text articles were assessed for eligibility and 108 were included in the final analysis. CPIC, Clinical Pharmacogenetics Implementation Consortium.

Table 1 Summary of study characteristics

Study characteristics	N = 108 n (%)
Year	
2002–2005	7 (6%)
2006–2010	11 (10%)
2011–2015	39 (36%)
2016–2021	51 (47%)
Continent	
North America	51 (47%)
Europe	26 (24%)
Asia	28 (26%)
Australia	3 (3%)
Gene	
CYP2B6	2 (2%)
CYP2C19	25 (23%)
CYP2C9	1 (1%)
CYP2D6	6 (6%)
DPYD	5 (5%)
HLA-A*31:01	1 (1%)
HLA-B*15:02	7 (6%)
HLA-B*57:01	8 (7%)
HLA-B*58:01	10 (9%)
IFNL3 (IL-28B)	2 (2%)
mt-RNR1	1 (1%)
TPMT	11 (10%)
UGT1A1	1 (1%)
Multiple genes	28 (26%)
Antidepressants	9 (8%)
Clopidogrel/tramadol	1 (1%)
Cardiovascular medications	2 (2%)
Multiple drug classes	1 (1%)
Warfarin	15 (14%)
Cohort Type	
Hypothetical	75 (69%)
Observational	19 (18%)
Randomized controlled trial	7 (6%)
Multiple	7 (6%)
Perspective	
Patient	1 (1%)
Payer	32 (30%)
Societal	20 (19%)
US healthcare system	13 (12%)
Universal healthcare system	24 (22%)
Multiple	4 (4%)
Not stated	14 (13%)
Funding source	
Government	6 (6%)
Grant/foundation	46 (43%)

(Continued)

Table 1 (Continued)

Study characteristics	N = 108 n (%)
Pharma	14 (13%)
University/institute	9 (8%)
No funding	16 (15%)
Not stated	17 (16%)
QHES scores	
High quality (≥75)	94 (87%)
Not high quality (<75)	14 (13%)

CYP, cytochrome P450; DPYD, dihydropyrimidine dehydrogenase; HLA, human leukocyte antigen; IFNL3, interferon lambda 3; mt-RNR1, mitochondrially encoded 12S ribosomal RNA; Pharma, pharmaceutical industry; SLCO1B1, solute carrier organic anion transporter family member 1B1; TPMT, thiopurine-S-methyltransferase; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

47%), followed by Europe ($n = 26$, 24%), Asia ($n = 28$, 26%), and Australia ($n = 3$, 3%). *CYP2C19* had the most single gene studies performed ($n = 25$, 23%), followed by *TPMT* ($n = 11$, 10%). Multigene testing was evaluated in 28 articles (26%), including genotype-guided trials for depression (e.g., *CYP2D6*, *CYP2C19*, *HTR2A*, and *SLC6A4*) and warfarin (*CYP2C9*, *VKORC1*). Only two studies evaluated cost-effectiveness of multigene testing across multiple therapeutic areas.[15,16] Most studies were published after 2010 ($n = 90$, 83%). About one-third of the studies were from the payor perspective ($n = 32$, 30%) or universal healthcare system perspective ($n = 24$, 22%). The source of funding primarily came from a grant and/or foundation ($n = 46$, 43%), whereas 31% ($n = 33$) did not indicate any funding source or stated that there was no funding used. The entire list of articles reviewed, including drug / drug class, gene, year published, study title, study design, population, continent/country, cost outcome, PubMed ID, QHES score, sample size, perspective, time horizon, funding, willingness-to-pay threshold, and ICER are summarized in **Supplemental Table S1**.

Quality of studies
The overall median QHES score reflected robust studies (91; range 48–100). Most studies were of high quality with a score >75 ($n = 94$, 87%). There were 63 studies (58%) in the highest decile (scores between 90 and 100), including 7 studies with a score of 100.

Cost outcomes
Of the 108 articles reviewed, 77 (71%) found PGx-guided treatment to be cost-effective ($N = 48$) or cost-saving ($N = 29$), whereas 21 (20%) were found to be not cost-effective, and 10 (9%) were uncertain (**Figure 2**).

The drug classes, types of drugs within each class, gene(s) related to each drug or class, number of articles reviewed, and cost outcomes are summarized in **Table 2**. The number of studies ranged between 1 and 23 per drug or drug class, with an average of 7. Clopidogrel had the most publications analyzing cost associated with PGx testing, including 23 articles with 96% concluding *CYP2C19* genotyping was cost-effective or cost-saving. Warfarin had the second most publications with 16 articles, but
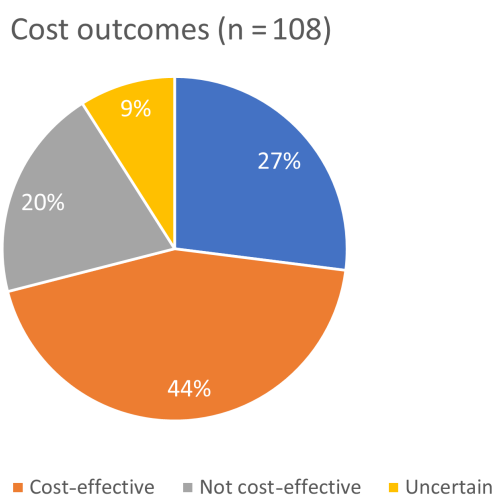
Cost outcomes (n = 108)

Figure 2 Cost outcomes (*N* = 108). Of 108 articles included in the systematic review, 44% demonstrated pharmacogenetic testing was cost-effective, 27% cost-saving, 20% not cost-effective, and 9% uncertain.

only 44% suggested cost-effectiveness and no article found it to be cost-saving. Twenty-six articles evaluated HLA testing for either abacavir, allopurinol, carbamazepine, or phenytoin, 15 of which were found to be cost-effective or cost-saving. Nine out of 11 articles evaluating antidepressants were found to be cost-effective or cost-saving. Eight articles evaluated fluoropyrimidines (*N* = 5) or tamoxifen (*N* = 3), all of which were found to be cost-effective or cost-saving except one for tamoxifen, which was uncertain.

Thirty-four studies did not calculate an ICER and 36 did not indicate a willingness-to-pay threshold. All studies evaluating *DPYD* and fluoropyrimidines, 10 of 11 thiopurine studies, both voriconazole studies, 2 of 8 abacavir studies, 7 of 11 antidepressant studies, 4 of 23 clopidogrel studies, 1 proton pump inhibitor study, and 2 of 16 warfarin studies did not report an ICER. Of studies classified as either cost-effective or cost-saving and reporting both an ICER and willingness-to-pay threshold, the ICER was consistently less than the willingness-to-pay threshold (**Supplemental Table S1**). Of the studies that did report a willingness-to-pay threshold, the currency and value varied drastically (~ US $5,000 to over US $100,000).

Cost outcomes by study characteristics

Figures for cost outcomes stratified by study characteristics, including drug / drug class, gene, publication year, cohort type, perspective, continent, QHES score, and funding are illustrated in **Supplemental Figure S1**. Several notable trends existed; however, statistical comparisons were not applied due to small numbers. For example, 13 out of 14 (93%) studies funded by pharmaceutical companies demonstrated PGx testing was cost-effective or cost-saving, whereas 64 out of the remaining 94 (68%) studies funded by the government, grants/foundations, universities/institutes, or no funding was used, demonstrated PGx testing was cost-effective or cost-saving. Regarding continent, studies performed in Asia (*n* = 28) had a higher rate of demonstrating PGx testing was not cost-effective (*n* = 10; 36%) compared with North America, Europe, and Australia where 11 out of 80 (14%) studies

demonstrated PGx testing was not cost-effective. Nineteen out of 75 studies (25%) based on a hypothetical cohort demonstrated PGx testing was not cost-effective, whereas 2 out of 33 studies (6%) based on a cohort from observational, retrospective, prospective, or randomized controlled trials demonstrated PGx testing was not cost-effective. Studies with high QHES scores (75–100) appeared more likely to demonstrate PGx testing was not cost-effective or uncertain (29 out of 94; 31%) compared with those with QHES scores <75 (2 out of 14; 14%).

DISCUSSION

To aid in the adoption and interpretation of PGx results in clinical practice, CPIC has published many peer-reviewed guidelines on how to translate PGx results into actionable prescribing decisions, while the FDA has published their standards for which drug–gene pairs have sufficient scientific evidence to suggest PGx impacts drug safety/response and/or metabolism.[6,7] Importantly, these resources do not evaluate or reflect on whether PGx testing is cost-effective, which is a common cited barrier to adoption.[8] In one of the largest systematic reviews evaluating the evidence on cost-effectiveness of PGx-guided therapy for drugs with CPIC guidelines, we identified that about three-quarters of articles determined PGx testing was either cost-effective or cost-saving, most of which were based on single-gene tests.

Although the cost of PGx testing has declined dramatically over the last decade, it continues to be one of the major barriers to widescale adoption in clinical practice. Verbelen *et al.* provided important insight into which drug–gene pairs with FDA labeling had undergone cost evaluations prior to 2015.[10] The results showed more than half of the 44 articles reviewed found PGx testing was either cost-effective (30%) or cost-saving (27%). Warfarin accounted for more than one-fourth of the studies included. The authors concluded that as genetic testing becomes cheaper, more widely available, and more accessible, further economic evaluations would likely find PGx-guided treatment to be more cost-effective compared with standard treatment. Importantly, the focus was on drug–gene pairs with PGx mentioned in the FDA label, whereas our analysis focused on those with CPIC guidelines since these are widely used among implementers in the United States for translating PGx results in clinical practice. Since the Verbelen *et al.* publication in 2015, 64 articles evaluating cost of a PGx-guided to non-PGx-guided approach for drugs with CPIC guidelines have been published. Of these, 47 (73%) found PGx-guided treatment to be cost-effective or cost-saving.

It is important to consider the clinical utility and cost impact of multigene testing vs. single gene. It is recognized that there are minimal cost differences between single-gene testing and multi-gene testing platforms for targeted candidate genes. Thus, the cost of one panel test may inform drug/dose selection for many drugs. Hart *et al.* evaluated the cost-effectiveness associated with a preemptive multigene test focused on *CYP2C19* genotype-guided antiplatelet therapy and *CYP2D6* genotype-guided pain management, compared with single-gene test for *CYP2C19* with random assignment for pain treatment, and with no testing.[15] As expected, the multigene testing strategy showed a favorable ICER compared with other treatment strategies.

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Table 2 Summary of drug–gene pairs and cost outcomes

Class	Gene	Total articles reviewed	Cost-saving	Cost-effective	Not cost-effective	Uncertain	Drugs
Aminoglycosides[23]	mt-RNR1	1	—	—	1	—	Tobramycin
Analgesics[24]	CYP2D6	1	—	—	1	—	Codeine
Anticoagulant[25–40]	CYP2C9 & VKORC1	15	—	6	5	4	Warfarin
	CYP2C9	1	—	1	—	—	
Antidepressants[41–51]	CYP2D6	2	—	—	1	1	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine, desipramine
	Multigene panel[a]	9	8	1	—	—	
Antiepileptic[52–59]	HLA-A*31:01	7	1	2	4	—	Carbamazepine, phenytoin
	HLA-B*15:02	1	—	1	—	—	
Antifungal[60–61]	CYP2C19	2	2	—	—	—	Voriconazole
Antigout[62–71]	HLA-B*58:01	10	1	4	5	—	Allopurinol
Antiplatelet[15,72–93]	CYP2C19	22	4	17	1	—	Clopidogrel
	CYPC19 & CYP2D6	1	1	—	—	—	Clopidogrel, tramadol
Antiretroviral[94–104]	HLA-B*57:01	8	2	4	1	1	Abacavir
	CYP2B6	2	2	—	—	—	Efavirenz
	UGT1A1	1	—	—	—	1	Atazanavir
Cardiovascular medications[18,105]	CYP2C9, CYP2C19, SLCO1B1, & VKORC1	2	—	2	—	—	Clopidogrel, simvastatin, warfarin
Fluoropyrimidines[106–110]	DPYD	5	4	1	—	—	Fluorouracil, capecitabine
Multidrug[16]	CYP2D6, CYP2C19, CYP2C9, CYP3A4, & VKORC1	1	—	—	—	1	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine, desipramine celecoxib, hydrocodone, flurbiprofen, ibuprofen, meloxicam, tramadol, piroxicam, phenytoin, clopidogrel, codeine, voriconazole
Pegylated interferon[111–112]	IFNL3 (IL-28B)	2	—	2	—	—	Pegylated interferon alpha
Proton Pump Inhibitors[113]	CYP2C19	1	1	—	—	—	Omeprazole, lansoprazole
Selective Estrogen Receptor Modulator[114–116]	CYP2D6	3	—	2	—	1	Tamoxifen
Thiopurines[117–127]	TPMT	11	3	5	2	1	Azathioprine, mercaptopurine
Total	All	108	29	48	21	10	All

[a]Antidepressant studies contain variable multigene panels ranging from 6 to 13 genes. —, none.

Most articles evaluated in this review addressed PGx testing for one or specific set of genes and one associated drug or drug class in a single therapeutic area, all of which were deemed to be appropriate populations for the drug–gene pair tested. There is likely downstream cost savings if using one multigene panel to estimate the combined cost impact on cancer, cardiology, depression, and other therapeutic areas throughout one's lifetime; however, this has not been quantified. There are many instances when one or two genes can impact dozens of drugs across different drug classes. For example, *CYP2C19* genotyping could be informative for antidepressants, clopidogrel, proton pump inhibitors, and voriconazole. The cost of PGx testing is a potentially one-time fixed cost, while the downstream benefits are multiple and beyond what these studies addressed. Further, in clinical practice patients are often taking more than one drug or are at risk of requiring multiple drugs later in life. Thus, the generalizability of these studies is rather limited by their study design, which is focused on limited gene(s) and drug(s). For example, 9 out of 16 articles did not find genotyping before warfarin to be cost-effective or cost-saving, which could potentially change if one considers the lifelong benefit of a one-time multigene PGx test (i.e., if *CYP2C9* and *VKORC1* results were readily available). Inevitably, the more drugs the patient is on or may require in the future that are affected by a given gene or set of genes, the more likely a PGx test will yield cost-effectiveness or cost-savings.

Preemptive vs. reactive PGx testing is likely to impact cost outcomes. Single-gene testing is most often performed reactively (e.g., after the patient initiates a specific drug), but as multigene testing becomes more widespread, the results may be used both reactively and preemptively for future medications in various therapeutic areas. Zhu *et al.* performed a systematic review on cost-effectiveness of PGx-guided treatment for cardiovascular disease and identified that two-thirds of studies were cost-effective, but only 2 of the 46 articles evaluated panel testing and only one examined preemptive testing.[17] Subsequently, the investigators compared the cost-effectiveness between preemptive PGx panel testing, reactive testing, and usual care (no testing) in cardiovascular disease management, including *CYP2C19*-clopidogrel, *CYP2C9/VKORC1*-warfarin, and *SLCO1B1*-statins.[18] Using a decision analytic model, the authors demonstrated that preemptive testing was cost-effective compared with usual care, while reactive testing was not. Those with longer follow up and aged 45 to 64 benefited the most. The PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment) study from Vanderbilt demonstrated that preemptive genotyping of nearly 10,000 patients allowed for almost 15,000 reactive genetic tests to be avoided when data on multiple genes was available beforehand, thereby saving genotyping test costs by reducing the number of single-gene tests required.[19] The Mayo Clinic RIGHT (Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment) program reported that among 1,013 patients tested, 99% carried an actionable variant in *SLCO1B1, CYP2C19, CYP2C9*, or *VKORC1*.[20] Analysis of the first 5,000 patients tested in the eMERGE-PGx (partnership of the Electronic Medical Records and Genomics Network and the Pharmacogenomics Research Network) project found that >96% of samples had CPIC-designated high-priority

actionable variants.[21] It is consistently shown that most patients undergoing multigene panel testing harbor actionable variants. Based on these data and findings from the present systematic review, it is evident preemptive panel testing may yield significant cost savings over the course of a patient's medical care.

Some notable trends emerged when evaluating cost outcomes by study characteristics, such as source of funding, continent where the analysis occurred, and cohort type. While statistical comparisons between these groups was not possible due to small numbers, it is important to note that certain characteristics may influence study findings. Studies funded by pharmaceutical companies overwhelmingly demonstrated that PGx testing was cost-effective or cost-saving. Slight differences in methodology, including established willingness-to-pay thresholds, may also influence cost outcomes. Country or continent of origin may also impact findings. Studies conducted in Asia or based on hypothetical cohorts were more likely to demonstrate PGx testing was not cost-effective. Genetic ancestry is also likely to influence allele frequency and number-needed-to-test to avoid an adverse drug reaction.

There are limitations of this analysis, including a limited number of studies for some drug–gene pairs. Of the 108 articles included in this review, 39 focused on warfarin or clopidogrel, accounting for 36% of all articles. The finding that most studies were cost-effective or cost-saving cannot be generalized to all drugs with CPIC guidelines given the limited representation of drugs in the literature (e.g., analgesics and proton pump inhibitors only had one study each that evaluated cost). Further, almost half of the drugs with CPIC guidelines have no published studies evaluating cost, which are needed to inform the clinical, research, and economic communities. Publication bias may also impact which studies were available from the systematic literature search. The analysis was meant to be inclusive of any study evaluating cost and PGx testing of a drug with a CPIC guideline with full article available. These comprehensive criteria resulted in the inclusion of some studies which assessed additional drug–gene pairs which are not CPIC level A or B with a guideline (e.g., multigene panels for antidepressant selection). We did not exclude articles based on country of publication, type of journal, study design/cohort, or year. Most articles were based on a hypothetical cohort, which may not translate to real-world practice. The cost impact could potentially vary between countries due to differences in cost of testing and the frequency of genomic variants based on ancestry. In addition to the range of willingness-to-pay thresholds between studies, the currency of the threshold and ICER also varied as most studies reported in the currency of the country of the population evaluated. Thus, it is difficult to generalize cost-effectiveness or cost-savings without accounting for potential differences between the populations studied and population of interest. Although cost outcomes were dependent on the respective study investigators' conclusions/findings, the average QHES was overall high, suggesting these studies were mostly robust. Studies with lower QHES scores were more likely to find an intervention cost-effective, suggesting a more robust evaluation may lend itself to identifying lack of cost-effectiveness; however, the number of studies with low QHES scores was very low. Lastly, we included drugs with CPIC guidelines as of June 2021. Inevitably, more guidelines have and will be produced as the data evolve and several

drugs are considered provisional, which if included, may change the findings of this systematic review.

In conclusion, we identified that most published studies evaluating cost and PGx testing for genes with CPIC guidelines determined that PGx-guided treatment was cost-effective or cost-saving. This is similar to prior publications and systematic reviews, such as the evaluation by Verbelen et al. of drugs with PGx in the FDA label.[10] The novelty in this systematic review is that it is all inclusive of drugs with CPIC guidelines published up to June 2021, which are considered the most widely utilized guidelines to facilitate adoption and interpretation of PGx-guided therapy in clinical practice in the United States. CPIC guidelines and evidence levels are also now cited in various local coverage determinations such as those from the Centers for Medicare and Medicaid Services.[22] Empey et al. highlights how expanding evidence has led to new PGx payor coverage and proposes mechanisms to overcome implementation obstacles to fully comprehend the value of PGx testing, including harmonization of coverage between states and jurisdictions, greater standardization of testing and interpretation, greater clarity on the regulatory landscape, practitioner education, and point-of-care clinical decision support.[22]

While some drugs, like clopidogrel, have an abundance of cost data showing there is enough evidence to support the use of PGx testing, others, like anesthesia and NSAIDs, still lack robust cost evaluations. Future studies and cost evaluations should focus on the impact of reactive and preemptive multigene panel testing on downstream clinical outcomes across drugs and drug classes and reduction in healthcare utilization. In addition to data on clinical utility, the data presented herein may support further coverage determinations by payors, thus increasing accessibility to evidence-based PGx testing.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
All authors wrote the manuscript, performed the research, and analyzed the data. S.A.M. and J.N.P. designed the research.

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