MEASURING THE VALUE OF PHARMACOGENOMICS

Kathryn A. Phillips and Stephanie L. Van Bebber

Abstract | Pharmacogenetics and pharmacogenomics offer the potential of developing DNA-based tests to help maximize drug efficacy and enhance drug safety. Major scientific advances in this field have brought us to the point where such tests are poised to enter more widespread clinical use. However, many questions have been raised about whether such tests will be of significant value, and how to assess this. Here, we review the application of economics-based resource-allocation frameworks to assess the value of pharmacogenomics, and the findings so far. We then develop a resource-allocation framework for assessing the potential value of pharmacogenomic testing from a population perspective, and apply this framework to the example of testing for variant alleles of CYP2D6, an important drug-metabolizing enzyme. This review provides a framework for analysing the value of pharmacogenomic interventions, and suggests where further research and development could be most beneficial.

PHARMACOGENOMICS/ PHARMACOGENETICS
We use these terms interchangeably to broadly mean the use of genetic information to guide drug prescribing.

School of Pharmacy and Institute for Health Policy Studies, University of California, San Francisco, 3333 California Street, Box 0613, San Francisco, California 94143, USA. Correspondence to K.A.P. e-mail: kathryn@itsa.ucsf.edu
doi:10.1038/nrd1749
Published online 24 May 2005

After several decades of research into the influence of genetic factors on inter-individual variation in drug response — pharmacogenetics and PHARMACOGENOMICS (PGx) — the widespread clinical application of PGx tests seems inevitable. However, many questions have been raised about whether PGx interventions will be of value and how to measure their value[1–23]. For example, two recent high-profile articles have noted the importance of considering value from a population perspective. One article points out that it is becoming increasingly important to analyse the relative benefits of genomics research for public-health applications because of the large resources that have been devoted to such research and the urgent need to find clinical applications[24], and another comments that it would be helpful to achieve consensus on which drugs merit study[25]. There are also concerns that investment in PGx will be less than optimal from a societal perspective if priorities are set solely according to industry criteria[26].

Such questions about the value of PGx have taken on new importance for three reasons. First, new PGx tests for drug response (toxicity and/or efficacy) in individuals with common diseases and for frequently used drugs are poised to enter the market. This broader availability of PGx testing for commonly used drugs is a major step in the field that has implications for many future tests and drugs. Until recently, most PGx tests were developed for narrowly defined, high-risk populations, such as testing tumours for expression of HER2/*neu* to target trastuzumab (Herceptin; Roche/Genentech) to women with a specific type of breast cancer. Now, Roche Diagnostics has developed a gene chip for broad diagnostic use (see Further information online). The AmpliChip CYP450 test identifies germline variations in two important genes for drug metabolism, *CYP2D6* and *CYP2C19*. The AmpliChip CYP450 test was approved by the FDA in December 2004[27]. Other companies are expected to obtain FDA approval for cytochrome P450 tests in the near future, and there is at least one company, Genelex Corp., that already sells these tests directly to consumers by offering a testing alternative that does not require FDA approval.

Second, the issue is also timely because in recent years the FDA has been pursuing a better foundation of knowledge on PGx and has invested in developing guidance to maximize the translation of PGx from bench to bedside[28]. The FDA issued its final guidance document[29] on PGx data submissions in March 2005, which

addresses two key issues: when and how PGx data can be voluntarily submitted for information purposes versus when data will be required for drug approvals, and approval procedures for drugs when combined with a genetic test[30–32]. Furthermore, the FDA has embarked on a Critical Path Initiative to overcome the drug and diagnostic 'pipeline problem'. This initiative includes the use of PGx at various stages of drug and diagnostic development, approval and surveillance[33]. It is also likely that recent concerns about the safety of drugs (for example, the cyclooxygenase inhibitors rofecoxib (Vioxx; Merck) and celecoxib (Celebrex; Pfizer)) will create additional pressure on the FDA to use tools such as PGx to increase drug safety.

The AmpliChip CYP450 test also illustrates the ongoing controversies about the oversight of genetic tests in the United States[12,34]. Most tests in the United States, including genetic tests, are conducted in-house by laboratories using their own components or ANALYTE-SPECIFIC REAGENTS (ASR). Historically, the FDA has not required extensive regulatory review of these tests and components. This situation changed with the introduction of the AmpliChip CYP450. Roche Diagnostics originally planned to market the test widely as an ASR, but the FDA determined that the test could not be commercially distributed without an appropriate premarket determination from the FDA because it was "intended for a use which is of substantial importance in preventing impairment of human health"[35,36]. This determination signals that some genetic tests could be more closely regulated in the future.

Third, these developments are taking place within the context of ongoing concerns about adverse drug reactions and prescription drug costs. Many commentators have asserted that PGx will reduce health-care costs and improve health outcomes by reducing adverse events, improving drug response and more efficiently targeting drugs[12,14,17,37]. But there has been little empirical evidence so far to evaluate such assertions.

In this article, we discuss the application of economics-based resource-allocation frameworks to assess the value of PGx, and the findings so far. We then develop a resource-allocation framework for assessing the potential value of PGx testing from a population perspective, and apply this framework to the example of tests for variant alleles of the important drug-metabolizing enzyme CYP2D6, as such tests could ultimately be relevant to the majority of the population.

Review of resource-allocation frameworks

Our previous studies have highlighted the factors likely to influence the economic impact of PGx[6,9,10,38], as well as providing general overviews of the methods for quantifying value[7,39]. We discuss here in detail the two frameworks that are currently most relevant to PGx: COST–EFFECTIVENESS ANALYSIS and COST-OF-ILLNESS ANALYSIS. Economics is the study of how to best allocate resources, and several economic frameworks have been developed for resource allocation, including cost-of-illness, COST-MINIMIZATION, COST–CONSEQUENCE, cost-effectiveness, COST–UTILITY and COST–BENEFIT ANALYSIS.

Cost-effectiveness analysis has been the most commonly applied framework for evaluating PGx, as well as other types of health-care intervention. Cost-effectiveness analysis uses comparisons of the costs and effectiveness of alternatives to answer a simple question: is the 'bang' worth the 'buck'?[40] We recently reviewed the literature on cost-effectiveness analyses of PGx interventions and found 11 published studies[39]. The most commonly examined disease was deep vein thrombosis, followed by cancer and viral infections. Most mutations examined were inherited mutations, although several studies examined acquired (tumour or viral) mutations. The majority of studies reported a favourable cost-effectiveness ratio for the PGx-based strategy, although two studies reported that the PGx-based strategy was not cost-effective and two were equivocal. We concluded that there have been only a few cost-effectiveness evaluations of PGx interventions, that they have covered only a limited number of conditions, and that their cost-effectiveness has not been widely documented.

Another resource-allocation framework that is particularly relevant to PGx is the cost-of-illness approach, which takes a broad view in determining value from a population perspective[41–43]. This framework addresses a different question: where could there be a bang? Cost-of-illness studies examine the size of the problem in monetary terms, and thereby provide information on who could be affected by an intervention. For example, these studies have been used by the National Institutes of Health (NIH) to inform the allocation of research dollars across diseases[44].

We were unable to locate any studies that have examined the population impact of PGx testing using a cost-of-illness framework. One article did evaluate the population impact of genomics on complex diseases, and focused on identifying diseases that were more likely to benefit from further genomic research[24]. This article was not a cost-of-illness study and it focused on genomics rather than PGx, but it did indicate that the public-health impact must be considered in setting priorities for genetics research.

Cost-of-illness studies assess the question 'how big is the pie' — that is, what are the relevant populations and their costs. Cost-effectiveness analysis then compares, within the relevant population, one intervention to an alternative (for example, screening for genetic variation or not). Cost-effectiveness analyses are crucial for determining the value of specific PGx strategies, but are less useful for examining the overall population impact of PGx interventions, because they typically examine only one PGx-based intervention within one population and they do not provide a relative comparison across drugs and conditions. To illustrate this point, a PGx-based intervention could be cost-effective but have little impact on population health because the population being tested is small. Cost-of-illness studies, therefore, provide input into the allocation of resources on the basis of the disease burden, whereas cost-effectiveness analyses provide input into the allocation of resources into a specific intervention and

ANALYTE-SPECIFIC REAGENT (ASR)
A commercial reagent for tests sold to laboratories conducting in-house tests.

COST-EFFECTIVENESS ANALYSIS
An analysis in which the costs and effectiveness of alternatives are compared using a ratio of incremental costs to incremental effect.

COST-OF-ILLNESS ANALYSIS
An analysis of the total costs incurred by a society due to a specific disease.

COST-MINIMIZATION ANALYSIS
An analysis in which costs are compared among alternatives assumed to have equivalent effectiveness.

COST–CONSEQUENCE ANALYSIS
An analysis in which costs and effectiveness are computed but not aggregated into ratios.

COST–UTILITY ANALYSIS
An analysis in which costs and effectiveness of alternatives are compared using the ratio of incremental costs to incremental quality-adjusted life years.

COST–BENEFIT ANALYSIS
An analysis in which costs and benefits are expressed in monetary terms and a net gain/loss or cost/benefit ratio is computed.

Table 1 | **Summary of measures in a pharmacogenetics resource-allocation framework**

Relevant measure	Description	CYP2D6 example
Relevant populations		
Mutation prevalence	Measure of the size of the population in which testing could have an impact on outcomes	Prevalence of individuals with slow or rapid metabolism due to *CYP2D6* variant alleles
Drug utilization	Measure of the size of the population that could be tested	Utilization of drugs metabolized by CYP2D6
Prevalence of condition for which drug is used	Another measure of the size of the population that could be tested, but which includes individuals who are untreated or treated with another drug but for whom testing might be relevant	Prevalence for primary indications of drugs metabolized by CYP2D6
Relevant costs		
Drug expenditures	Measure of the potential outcomes of testing because testing could change the utilization of drugs	Expenditures on drugs metabolized by CYP2D6
Condition expenditures	Measure of the potential outcomes of testing because testing could change disease costs	Prevalence for primary indications of drugs metabolized by CYP2D6
Association of genetic variation		
Mutation effect on drug outcomes	Measure of the potential impact of testing because mutations must be associated with drug metabolism, drug response and clinical outcomes in order for testing to have an impact	Relationship of *CYP2D6* variant alleles to variation in metabolism, drug response and clinical outcomes

for a specific disease. As will be discussed below, in the case of CYP2D6 testing it is more important to consider first the broader population perspective in order to provide a context for future cost-effectiveness analyses and to identify what data are available or lacking for such analyses.

An example: CYP2D6 testing

We apply a resource-allocation framework to the example of CYP2D6 testing in order to provide an empirical illustration. In addition to its importance because of the newly approved AmpliChip test, CYP2D6 is one of the most studied drug-metabolizing enzymes, and has been estimated to be responsible for metabolizing 25% of drugs[45,46]. The FDA singled out CYP2D6 as one of only two examples of 'VALID' BIOMARKERS for regulatory purposes[47]. Moreover, because CYP2D6 metabolizes an array of commonly used drugs, such testing for relevant variants is likely to have implications not only for current drug utilization but also for future drug utilization, because test results can be used over a lifetime. CYP2D6 testing therefore provides an example of a PGx test that could ultimately be relevant to the majority of the population and used across drugs and diseases.

Our resource-allocation framework draws from and addresses elements of both the cost-of-illness and the cost-effectiveness approaches. It addresses three key questions as they relate to CYP2D6: what is the size of the relevant populations?; what are the costs associated with those populations?; and what is known about the association of genetic variation with drug metabolism, response and clinical outcomes?

In the case of CYP2D6, there are several relevant and overlapping populations. A population perspective that describes the 'pie' — the relevant populations and costs — is therefore the most relevant initial step in analysing the potential value of CYP2D6 testing. However, we also examined what is known about associations between CYP2D6 genotype and clinical response because it is a first step towards examining the actual impact of PGx and its cost-effectiveness.

TABLE 1 summarizes the key measures in our resource-allocation framework. It also includes specific descriptions of the data that are needed when considering the case of testing for CYP2D6 genotypes to guide drug prescribing.

Data for a resource-allocation framework

Data for a resource-allocation framework must typically be compiled and synthesized from multiple sources, as no one data source provides relevant data across all of the categories. In cases such as the analysis of CYP2D6 that involve many drugs and conditions, it is also necessary to conduct a synthesis of summary data sources rather than an analysis of original articles (there are hundreds of relevant original articles). There are a number of possible data sources. Characteristics of ideal data sources include data from review articles; most recent data available; sources that contain standardized information (for example, package inserts); data that include multiple drugs or conditions in a single source (for comparability); data published or sponsored by federal, federally supported or academic groups; and publicly available (non-proprietary) data. These searches can be supplemented with consultation with experts.

TABLE 2 describes data sources that can be used in resource-allocation studies, including sources specific to P450 drug-metabolizing enzymes and the specific data sources that we used to examine CYP2D6 testing[48–55].

Review and summary of data sources

The example of CYP2D6 testing illustrates how data can be reviewed and summarized in a resource-allocation framework. All data were collected between May and September 2004.

VALID BIOMARKER
A biomarker that is measured in an analytical test system with well-established performance characteristics.

Prevalence of slow or rapid metabolizers of CYP2D6 substrates. The literature estimates that 5–10% of Caucasians are slow metabolizers of CYP2D6 substrates and therefore potentially at higher risk of adverse drug reactions, whereas 1–3% of Hispanics, African-Americans and Asian-Americans are estimated to be slow metabolizers[15,48]. It has been estimated that 5–10% of Caucasians are ultra-rapid metabolizers and are therefore potentially at higher risk of non-response to drug therapy[48].

Relevant drugs. We first identified all relevant drugs using a website that is considered a useful and current source for information on P450 drug metabolism[56] (see Cytochrome P450 Drug Interaction Table in Further information). The table provided on the site lists CYP2D6 drug substrates (that is, the drug on which an enzyme acts) if there is published evidence that it is metabolized, at least in part, by that isoform. This data source provides a conservative estimate of relevant drugs, as compared with industry-sponsored websites (see, for example, Genelex Corp. in Further information).

We then identified those drugs metabolized by CYP2D6 for which there were high expenditures and/or high utilization. We used lists of the 'Top 200 branded and generic drugs by expenditures and unit volume 2003' that were publicly available versions of data collected in Verispan's Source Prescription Audit (see Verispan website in Further information)[50–53]. We excluded drugs for which the best-selling or greatest use was not relevant to CYP2D6 metabolism — for example, ophthalmic and topical formulations.

TABLE 3 shows 22 drugs that are among the top 200 best-selling drugs in the US and which are metabolized by CYP2D6. Several of these drugs account for a large percentage of drug utilization and expenditures. Five drugs account for more than 10 million prescriptions each (including both branded and generic forms). Four of these drugs are for mental conditions, and one is for heart disease. One drug, metoprolol (Toprol; AstraZeneca), is the sixth most commonly used branded drug in the United States. Three of the top-selling drugs (branded and generic combined) had sales of more than US$1 billion each.

Primary indications. We identified 'primary indication' as the main indication for which the drug is typically prescribed on the basis of clinical judgment. We obtained the full lists of indications using prescribing information in Mosby's Drug Consult, which is a database for clinicians[54]. Drug information in the database is based primarily on package inserts supplemented by information obtained from FDA (A. Schriber, personal communication). Multiple indications were identified when relevant.

We searched for data sources using PubMed and Google, and identified multiple sources for prevalence and expenditures data, particularly websites maintained by the NIH and other government agencies or by disease-focused organizations. We used the distribution of the data to summarize the literature because it allows for a better comparison across indications.

Drugs that are metabolized by CYP2D6 are used for a variety of indications, particularly heart disease and mental health disorders[57–72] (TABLE 4). Several of the specific conditions occur frequently in the US population and have high direct health-care expenditures — for example, 17% of the population has hypertension, which is associated with estimated expenditures of US$41.5 billion annually[57], and 7% of the population has depression, which is associated with estimated expenditures of US$12.4 billion annually[58,59]. These conditions are treated by several top-selling drugs that are metabolized by CYP2D6 — for example, hypertension has three associated drugs and depression has six associated drugs. TABLE 4 also suggests that CYP2D6 testing for drugs for relatively inexpensive conditions (such as coughs and pain) could be important because they are common and have high indirect expenditures because of lost productivity. Conversely, conditions such as breast cancer, which receive a lot of public attention, are relatively less frequent and expensive.

Relationship of CYP2D6 variant alleles to variation in metabolism, drug response and clinical outcomes. There is no one source of comprehensive information on the relationship of CYP2D6 variant alleles to variation in metabolism, drug response and clinical outcomes. We therefore reviewed multiple sources and examined their congruence. Because of the evolving nature of the field and limitations of these data sources, our results summarize what had been documented in the selected sources at the time of this study.

The data we reviewed were organized on the basis of categories used by the Pharmacogenetics and Pharmcogenomics Knowledge Base (PharmGKB; see Further information) (described below)[55]: metabolism (genetic variation in processes involved in the metabolism of a drug can result in changes in drug availability); drug response (genetic variation in drug targets can

Table 2 | **Summary of data sources for resource-allocation studies**

Category	Data source(s)	References
Prevalence of slow or rapid metabolizers	Published literature	48
Relevant drugs	Academic website (P450 Drug Interaction Table)	49
	Online Database (Verispan Source Prescription Audit data provided by Drug Topics)	50–53
Primary indications	Online medical database with drug prescribing information (MDConsult)	54
Prevalence of, and expenditures on, primary indications	Multiple sources (see Table 3 for references)	
Relationship of variant alleles to drug metabolism, response and/or clinical outcomes	Academic research group website (PharmGKB)	55
	Academic website (P450 Drug Interaction Table)	49
	Published literature review	15
	Online medical database with drug-prescribing information (MDConsult)	54

cause measurable differences in the response of an organism to a drug); and clinical outcome (genetic variations in the response to drugs can cause measurable differences in clinical endpoints, such as rates of cure, morbidity, side effects and death).

We surveyed a number of data sources, which are summarized in the following sections.

Academic research group database. PharmGKB is a publicly available Internet research tool developed

Table 3 | **Utilization and expenditures for key drugs metabolized by CYP2D6**

Drug	Brand or generic	Number of Rx in US (in millions) (2003)	Rank* of Rx in US (2003)	US expenditure on drug (in US$ millions) (2003)	Rank* in US expenditures on drugs (2003)
Utilization (>10 million)					
Paroxetine	Generic	3.6	75	291.3	28
	Paxil	14.8	25	1,400.9	22
	Paxil CR	8.4	44	775.6	46
	Total	26.8	—	2,467.8	—
Venlafaxine	Effexor XR	16.5	20	2,047.2	9
Fluoxetine	Generic	20.0	15	1,338.8	3
	Prozac	1.4	198	238.6	131
	Total	21.4	—	1,577.4	—
Metoprolol	Generic	18.1	17	292.6	27
	Toprol XL	25.1	6	889.8	38
	Total	43.2	—	1,182.4	—
Amitriptyline	Generic	14.6	23	181.8	54
Utilization (5–10 million)					
Risperidone	Risperidal	7.5	50	1,468.4	20
Amphetamine	Generic	2.7	98	199.6	50
	Adderall XR	6.4	63	621.0	54
	Total	9.1	—	820.6	—
Tramadol	Generic	9.6	35	389.0	17
Propranolol	Generic	4.4	67	71.8	111
	Inderal LA	3.2	114	190.8	153
	Total	7.6	—	262.6	—
Metoclopramide	Generic	5.6	56	83.0	102
Promethazine/ Codeine	Generic	5.4	58	69.5	116
Utilization (<5 million)					
Carvedilol	Coreg	4.6	93	485.4	67
Ondansetron	Zofran	N/A	N/A	463.7	71
Atomoxetine	Strattera	3.5	109	393.3	81
Tamoxifen	Generic	3.0	89	289.9	29
Chlorpheniramine Polistirex; Hydrocodone Polistirex	Tussionex	3.2	116	160.6	175
Fluvoxamine	Generic	1.1	195	126.2	73
Nortriptyline	Generic	3.4	80	85.7	99
Imipramine	Generic	2.1	132	68.1	119
Propafenone	Generic	N/A	N/A	58.9	128
Flecainide acetate	Generic	N/A	N/A	51.3	139
Haloperidol	Generic	1.1	195	35.0	174

*Generic drugs and branded drugs are ranked only compared to their type and not each other. Data on fluvoxamine are from year 2002. N/A indicates that drug was not one of the top 200 drugs for 2003 and no other data were found on this drug.

by Stanford University and is part of the NIH Pharmacogenetics Research Network (PGRN), a nationwide collaborative research consortium. The PharmGKB database is a central repository for genetic and clinical information about people who have participated in research studies at various medical centres in the PGRN. In addition, data are accepted on a voluntary basis from the scientific community at large[55,73].

Academic website. The Cytochrome P450 Drug Interaction Table (described earlier) also includes a 'clinically relevant' Cytochrome P450 Drug Interaction Table (see Further information).

Published literature review. Fishbain *et al.* conducted a structured review of genomic testing for enzymes of drug metabolism as part of a review of whether testing has imminent clinical relevance for the practice of pain medicine[15].

Prescribing information. We used package insert information obtained from MD Consult (described above) to code similar association categories as the PharmGKB database.

We found that there are limited data available on the relationship of CYP2D6 variant alleles with variations in drug metabolism, response and clinical outcomes (TABLE 5). There are relatively extensive and consistent data on drug metabolism, relatively fewer and more inconsistent data on drug response and few data on clinical outcomes. Seven drugs have some data on clinical outcomes; however, data for these drugs are not consistently identified across sources. There is agreement among sources on the evidence of drug metabolism and response for three additional drugs, but no data on clinical outcomes. The package insert for only one drug (atomoxetine (Strattera; Eli Lilly)) notes the availability of CYP2D6 testing.

Conclusions and next steps

This review illustrates how a resource-allocation framework can be used to assess the value of PGx-based interventions. Such analyses suggest where the population impact could be greatest and where further research and development could be most beneficial. However, it is important to recognize that this framework represents only a portion of the issues relevant to the translation of PGx to clinical practice and that other economic, business and social issues are also important.

In the case of CYP2D6 testing, our analyses suggest that such testing is potentially relevant to large populations that incur high costs. The most commonly used drugs metabolized by CYP2D6 account for 189 million prescriptions and US$12.8 billion annually in expenditures in the US, which represent approximately 5–10% of total utilization and expenditures for outpatient prescription drugs. Almost 75% of these drugs are for heart disease or mental health conditions, which are highly prevalent and expensive to treat, with each condition occurring in approximately 25% of the population at an approximate combined cost of US$300 billion including indirect costs[57,74].

These results are consistent with our previous study on the potential role of PGx in reducing adverse drug reactions[8]. Several of the drugs identified in the current study were also identified in the previous study as causing adverse drug reactions, potentially as a result of CYP2D6 mutations (the drugs include fluoxetine, metoprolol, nortriptyline and imipramine).

An equally important conclusion, however, is that crucial data for assessing the value of PGx with regard to its impact on clinical practice and outcomes are currently lacking. In our CYP2D6 example, only one-third of the identified drugs had data on clinical outcomes and there were no drugs that had comprehensive documentation of associations for metabolism, drug response and clinical outcomes. Although these findings are based on data summaries that are by necessity incomplete, they suggest that it is important both to obtain and to disseminate further data if testing is to be implemented in clinical practice.

Next steps. Our review suggests two important areas for future research and policy: obtaining additional data on the association of genetic variation and drug metabolism, response, and clinical outcomes as well as data on adverse drug reactions; and achieving an additional synthesis and dissemination of existing data.

The prevailing consensus that there is a lack of PGx data is confirmed by our review; however, by analysing a specific example, we are now better able to identify which specific data are lacking and what will be needed. One glaring problem is the dearth of relevant data on adverse drug reactions, even though a better understanding of the relationship between genetic variation and adverse drug reactions will be crucial. We found a dearth of data on incidence of adverse drug reactions (particularly for specific drugs) and the economic costs resulting from adverse drug reactions. We could not, therefore, include these estimates in this analysis. We explored a variety of means by which to obtain data on adverse drug reactions for the drugs identified in our analysis; however, all of the available data sources have significant limitations. These limitations include the lack of a national, systematic and comprehensive database of adverse drug reactions, because the FDA's MedWatch database is self-reported and most studies on adverse drug reactions have relied on selected inpatient populations[75]; the lack of relevant and comparable data in drug package inserts; and the lack of data on adverse drug reactions for individual drugs. More fundamentally, the extent to which adverse drug reactions are due to genetic variation is often not examined and so simply obtaining more data on adverse drug reactions will not resolve this problem.

Our review also documents a lack of data on the association between genetic variation and clinical outcomes. The current understanding of genotype–phenotype relationships in this field is still evolving and we are not able to conclude that all poor metabolizers will be identified with a single test or that we

Table 4 | **Characteristics of primary indications for key drugs**

Indications	Prevalence (low<1%, medium 1–10%, high>10%)	Expenditures (<$1 M low, $1 M–$25 B medium, >$25 B high)	Relevant drugs
Heart disease			
Hypertension	High[57]	High[57]	Carvedilol Metoprolol Propranolol
Myocardial infarction	Medium[57]	High[57]	Propranolol
Angina	Medium[57]	Medium[60]	Metoprolol Propranolol
Heart failure	Medium[57]	Medium[57]	Carvedilol Metoprolol
Arrhythmia	Low[61]	Medium[57]	Flecainide Propafenone Propranolol
Mental conditions			
Depressive disorder	Medium[58]	Medium and high indirect expenditures[59]	Amitriptyline Fluvoxamine Fluoxetine Imipramine Paroxetine Venlafaxine
Obsessive–compulsive disorders	Low[58]	Medium and high indirect expenditures[62,63]	Fluvoxamine
ADHD	Low[64]	Medium and high indirect expenditures[65]	Amphetamine Atomoxetine
Schizophrenia	Low[58]	Medium and high indirect expenditures[66]	Haloperidol Risperidone
Other conditions			
Cough and common cold	High[67]	Low direct expenditures but high indirect expenditures[68]	Chlorpheniramine Polistirex; Hydrocodone Polistirex Promethazine/ Codeine
Pain (chronic)	High[69]	NA/High indirects (only indirect $ data available)[70]	Tramadol
Nausea	Medium[71]	High[72]	Metoclopramide Ondansetron
Breast cancer	Low[71]	Medium[72]	Tamoxifen

ADHD, attention-deficit hyperactivity disorder; B, billions; M, millions.

know the complete set of genotypes (or other factors) associated with variations in drug metabolism. For example, a recent case study reports on a patient who nearly died after he was given small doses of codeine because he was found to be an ultra-rapid CYP2D6 metabolizer[76]. However, other factors contributed to this outcome and, furthermore, many individuals have adverse outcomes to codeine who are not ultra-rapid metabolizers.

The association between genetic variation and outcomes is a crucial input for conducting cost-effectiveness analyses because a linkage between genetic variation and outcomes must be estimated in order to estimate the impact of a PGx intervention on costs and effectiveness. Our review illustrates the complexity of cost-effectiveness analyses of PGx tests: such analyses will require estimates of the prevalence of genetic variation among the relevant populations; the impact of testing on non-response as well as adverse drug reactions; the availability of alternative diagnostic and therapeutic approaches; the availability of effective interventions that can be implemented on the basis of genetic information; the cost of testing; and potential downstream costs and benefits, such as the benefits of knowing one's genotype for other drugs and conditions[6,7,9,77].

Finally, many commentators have also noted that large, prospective and well-controlled clinical trials will be required to provide the evidence base necessary to change clinical practice and to better understand the nature of genetic variation[17,78,79]. As Evans and Relling point out, "our enthusiasm for advancing molecular technology and defining the human genome has not yet been matched by a willingness to incorporate this technology and knowledge into well-controlled and monitored clinical trials." [80]

Our review confirms the conclusion of other studies that additional synthesis and dissemination of existing data could move the field forward. For example, Zineh *et al.* reviewed the PGx data in drug package inserts and found that few inserts included PGx data and that the information provided was inadequate to guide therapeutic decisions[81]. Similarly, Kirchheiner *et al.*, after reviewing available data on the pharmacogenetics of antidepressants and antipsychotic drugs, concluded that dose adjustments based on genetic variability in drug-metabolizing enzymes, such as CYP2D6 polymorphisms, are ready for validation in prospective studies, but that it is not yet possible to translate these data into therapeutic recommendations[82].

Our review of data sources was designed to reflect what clinicians and researchers would be able to obtain through publicly available data summaries and therefore cannot be considered comprehensive. Furthermore, information in the field changes rapidly, and we appreciate the challenges involved in developing mechanisms for data sharing, synthesis and dissemination. One noteworthy approach is the Pharmacogenetics Knowledge Base, which is a public database of genotype and phenotype information relevant to pharmacogenetics that is described above[73,83]. A key to the ongoing success of this database and its growing repository of data will be contributions from within and outside the collaborative network, and the PharmGKB group proactively welcomes submissions to its effort.

Moving the field forward. An important next step is to identify strategies to encourage the collection and dissemination of PGx data so that academia, industry and policy makers are better equipped to make decisions about where to focus research and translational efforts. Many groups and organizations have important roles in facilitating the greater availability and utility of PGx data. We focus here on the FDA, which

Table 5 | **Available data on key drugs and CYP2D6 in selected sources**

Drug	Drug metabolism			Drug response			Clinical outcomes		
	Prescribing Information (MD Consult)[54]	PharmGKB (academic research group website)[55]	Liter-ature review[15]	Prescribing information (MD Consult)[54]	PharmGKB (academic research group website)[55]	P450 Drug Interaction Table (academic website)[49]	Prescribing information (MD Consult)[54]	PharmGKB (academic research group website)[55]	Liter-ature review[15]
Drugs with clinical outcome data available in addition to data on drug metabolism and drug response									
Fluoxetine	Y	Y	Y	Y	—	—	—	Y	—
Atomoxetine	Y	—	—	Y	—	—	Y	—	—
Promethazine/ Codeine	—	Y	Y	—	Y	—	—	Y	Y
Venlafaxine	Y	Y	Y	Y	—	Y	—	—	Y
Imipramine	Y	Y	Y	Y	—	Y	—	—	Y
Nortriptyline	Y	—	Y	Y	—	—	—	—	Y
Propranolol	Y	—	Y	Y	—	—	—	—	Y
Drugs with high agreement across sources for data on drug metabolism and drug response but no clinical outcome data									
Metoprolol	Y	Y	Y	Y	Y	Y	—	—	—
Risperidone	Y	Y	Y	Y	Y	Y	—	—	—
Tramadol	Y	Y	Y	Y	Y	Y	—	—	—
Drugs with some available data for drug metabolism and drug response									
Propafenone	Y	Y	—	Y	Y	Y	—	—	—
Amitriptyline	Y	Y	Y	Y	—	Y	—	—	—
Carvedilol	Y	—	—	Y	—	—	—	—	—
Flecainide	Y	Y	—	—	—	Y	—	—	—
Fluvoxamine	Y	Y	Y	Y	—	—	—	—	—
Haloperidol	—	Y	Y	—	Y	Y	—	—	—
Paroxetine	Y	Y	Y	—	—	Y	—	—	—
Ondansetron	Y	—	Y	Y	—	Y	—	—	—
Amphetamine	—	—	Y	—	—	—	—	—	—
Chlorpheniramine Polistirex; Hydrocodone Polistirex	—	—	Y	—	—	—	—	—	—
Tamoxifen	Y	—	—	—	—	Y	—	—	—
Metoclopramide	—	—	—	—	—	—	—	—	—

Y, yes; —, no data given.

has a crucial role. Although the FDA is not actively involved in resource-allocation decisions and does not consider costs in evaluating drugs or devices, the FDA does recognize that they have a responsibility to balance the risks and benefits of regulation so as to promote public health but not impede industry innovation[33].

Regulatory policies implemented by the FDA can directly affect the availability and accessibility of PGx data by creating incentives or disincentives — for example, to share data or to collect certain types of data. As noted previously, the FDA is therefore proactively developing initiatives to improve the use of PGx data. We discuss here three key initiatives. First, the FDA has issued guidance to industry on PGx data submissions[29]. The FDA developed this guidance to encourage the use of PGx in drug development, to encourage industry to voluntarily share PGx data, and to clarify when PGx data might be required and used for approval[30,31]. The guidance is expected to increase the amount of PGx data that are used and to make such data more widely available.

Directly related to the PGx guidance is an FDA initiative to develop guidance for the co-development of PGx-based drugs, biological products and diagnostic tests[84]. Currently, both the FDA and the Centers for Medicare and Medicaid Services have authority over diagnostic tests, although many tests are now being conducted that are not FDA-approved because they are clinical services conducted in laboratories using their own reagents or commercial ASRs[85]. The co-development of drugs and diagnostics could therefore

increase the amount of data available on PGx-based therapies, and also increase the amount of PGx data included in drug labels.

Another FDA initiative is the Critical Path Initiative, which addresses the much-discussed 'pipeline problem'[33]. This initiative is directly relevant to resource allocation because it is based on the belief that large resources are invested in drug development stages but that the public-health benefits of such investment are not being realized as rapidly as they could be. Although this initiative does not focus exclusively on PGx, it does note PGx as an opportunity for stimulating innovation, and it is likely that the initiative will increase the amount and utility of PGx data.

In summary, we conclude that our review provides evidence both for the assertion that there is high potential value in expanding the use of PGx but also that there are major challenges to doing so. Future research will need to continue to address these questions.

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Acknowledgements

We are grateful for comments from D. Veenstra, University of Washington; B. Shen, Institute for the Future; A. Issa, University of California, Los Angeles; T. E. Klein, Stanford University; and C. R. Burrow, CardioDx. We are also grateful for contributions by S. Adams, University of California, Berkeley. This study was partially funded by an R01 grant to K.A.P.

Competing interests statement

The authors declare no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
CYP2C19 | CYP2D6

FURTHER INFORMATION

Cytochrome P450 Drug Interaction Table:
http://medicine.iupui.edu/flockhart/table.htm
Genelex Corp.: http://www.genelex.com
Pharmacogenetics Knowledge Base:
http://www.pharmgkb.org/
Roche AmpliChip CYP450: http://www.roche-diagnostics.com/products_services/amplichip_cyp450.html
Verispan: http://www.verispan.com
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Entrez Gene:
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CYP2C19
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=1557

CYP2D6
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Genelex Corp.:
http://www.genelex.com/

Pharmacogenetics Knowledge Base:
http://www.pharmgkb.org/

Roche AmpliChip CYP450: http://www.roche-diagnostics.com/products_services/amplichip_cyp450.html

Verispan: http://www.verispan.com

Biographies
Kathryn A. Phillips, Ph.D., is a Professor of Health Economics and Health Services Research in the Department of Clinical Pharmacy and the Institute for Health Policy Studies at the University of California, San Francisco. She holds degrees from the University of California-Berkeley, Harvard University and the University of Texas at Austin, and previously worked for the federal government in Texas and Washington DC. Phillips is also on the editorial board of *Medical Care Research and Review*.

Phillips's research focuses on the application of quantitative tools to policy issues. Her activities in the areas of genomic medicine and pharmacogenomics focus particularly on examining their utilization, cost-effectiveness and regulation. She serves as an advisor to the FDA on the regulation of pharmacogenomics, as well as a consultant to biotech companies on the economics of pharmacogenomics. She has been awarded several National Institutes of Health (NIH) R01 grants, including a 5-year NIH career development award. Phillips has published more than 60 peer-reviewed articles in policy and clinical journals and served on several national and international panels, including a 4-year term on the NIH Health Services Organization and Delivery Study Section. She serves on the editorial board of the *American Journal of Preventive Medicine* and is a reviewer for more than 30 journals.

Stephanie Van Bebber, M.Sc., holds a Master of Science in Health Administration from the University of Toronto, Canada. She has been working as an Analyst at the University of California, San Francisco, since 2002 in the Department of Clinical Pharmacy. Van Bebber's recent research emphasis has been on economic and policy evaluation of pharmacogenomics and related uses of genetic information. Additional research interests and areas include the evaluation of preventive health services, preferences evaluation and the application of patient preferences in practice, and economic and policy evaluation of women's reproductive health care.

Summary

- There have been many questions raised about whether pharmacogenomics (PGx) interventions will be of significant value, and how to assess this value.
- These questions have taken on more importance because new PGx tests for common diseases and frequently used drugs are poised to enter the market, the US Food and Drug Administration has issued new guidance documents related to PGx, and there are increasing concerns about drug safety and costs.
- Here, we discuss the application of economics-based resource-allocation frameworks to assess the value of PGx, and the findings so far.
- We develop a resource-allocation framework for assessing the potential value of PGx testing from a population perspective, and apply this framework to the example of tests for variant alleles of the important drug-metabolizing enzyme CYP2D6, as such tests could ultimately be relevant to the majority of the population.
- Our review provides evidence for the assertion that there is high potential value in expanding the use of PGx but also that there are major challenges to doing so.
- Two important areas for future research and policy will be obtaining additional data on the association of genetic variation and drug metabolism, response, and clinical outcomes as well as data on adverse drug reactions, and achieving an additional synthesis and dissemination of existing data.