

# An Economic Evaluation of Pharmacogenomic Testing

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# Content

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|              |   |
|--------------|---|
| Purpose      | 3 |
| Introduction | 4 |
| Key Findings | 6 |

# Purpose

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Genetic testing promises to improve quality of care and lower healthcare costs through the development of predictive one-time assays that will help practitioners personalize the diagnosis and treatment of health conditions. One of the frontrunners in this burgeoning field is pharmacogenomic (PGx) testing, which uses genetic markers to anticipate a patient's response to medications, improving their efficacy and safety. Historically, genetic testing has suffered from an insufficient number of studies that demonstrate economic utility. However, in the past few years, the gap in our understanding of the cost-effectiveness of PGx testing has narrowed. This whitepaper aims to provide a review of current knowledge surrounding PGx testing with regard to cost-effectiveness and to highlight where evidence clearly supports its use.

## Key Takeaways

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1. While many precision medicine tests are narrowly focused on disease risk in small subsets of the population, pharmacogenomic testing is relevant to a large portion of the population.
2. The evidence surrounding the economics of pharmacogenomics is growing and has consistently supported the cost-effectiveness and even cost savings of genotype-guided strategies.
3. Pharmacogenomics testing is quickly becoming a new standard of care when prescribing medications with established and actionable drug-gene interactions.

# Introduction

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The advent of cost-effective genomic testing has brought with it the hope of utilizing genetic information to better tailor medical interventions. While deciphering the impact of genetic variation is challenging given the potential involvement of multiple loci and environmental interactions, breakthroughs in the past few years have made genomic characterization an important part of healthcare across many medical specialties.

## Terminology Used in Economic Evaluations

The preponderance of new advances in medicine amid the backdrop of rising healthcare costs highlights the importance of evaluating new interventions in light of their cost-benefit ratio. In order to understand how new technologies undergo economic evaluation, it is important to first define several terms.

The term “cost-effectiveness” refers to technologies that improve the quality of care at a cost that is commensurate

with the clinical value they provide. For example, this is typically the case with new medications, which often improve patient quality of life, albeit at a premium to previous drug-based therapies. The Institute for Clinical and Economic Review (ICER) proposed that for medical interventions to be cost-effective, they must cost less than \$50k-\$100k to achieve an additional Quality Adjusted Life Year (QALY) for an individual.<sup>1</sup>

A related concept is that of “cost-saving” or “dominant” technologies, which refers to technologies that both improve the quality of care and reduce costs to the system. For example, some novel minimally invasive surgical techniques can reduce recovery times and infection risks, leading to improved quality and reduced healthcare costs.

Precision medicine technologies generate individualized knowledge that can provide insight into clinical care. These tests have the potential to produce outsized value and may even result in cost savings as that knowledge is applied prospectively without the need for ongoing expenditures.

# Pharmacogenomic Testing

Pharmacogenomics is the study of how genetic variability affects a patient's response to medications. It has been one of the fastest-growing subspecialties of clinical genomics due to the relatively well known underlying physiology surrounding how the body processes medications (pharmacokinetics). The most prominent class of proteins involved in this process are the cytochrome *P450* enzymes (*CYPs*). Unlike genetic disease, where variants are classified on a scale from benign to pathogenic, pharmacokinetic variants are classified based on their effects on the protein function into normal, reduced, increased, and no-function variants. Once these variants are identified by a PGx test, the subsequently associated phenotype known as the metabolizer status can usually identify four subcategories of patients: ultrarapid (UM), extensive (or normal, EM), intermediate (IM), and poor (PM) metabolizers. A wide variation in *CYP* gene family and other pharmacokinetic-related genes and immunological biomarkers exists in the general population, highlighting PGx analysis as a broadly applicable clinical decision support tool.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has supported a broad effort to characterize drug-gene interactions that has resulted in a curated list of clinically significant drug-gene interactions.<sup>2</sup> This effort continues to lend credibility to the growing consensus surrounding the clinical utility of PGx testing.

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**A WIDE VARIATION IN *CYP* GENE FAMILY AND OTHER PHARMACOKINETIC-RELATED GENES AND IMMUNOLOGICAL BIOMARKERS EXISTS IN THE GENERAL POPULATION, HIGHLIGHTING PGX ANALYSIS AS A BROADLY APPLICABLE CLINICAL DECISION SUPPORT TOOL.**

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# Key Findings

## Methods

We performed a thorough literature search for a list of known PGx genes and terms used in relation to cost-effectiveness. The analysis included studies written in English and performed on medicated patients. Additional inclusion criteria focused on original research or meta-analysis, actual data on genotyped individuals, and direct costs of healthcare utilization data. Studies that did not contain pharmacogenomic testing, utilized simulated data, and only focused on efficacy or adverse events were excluded as were reviews. Due to the variability in the cost of PGx testing, the cost of individual PGx testing was not included in any aggregate calculations.

## Findings

### CLOPIDOGREL AND PERCUTANEOUS CORONARY INTERVENTION

Clopidogrel is an orally administered, antiplatelet medication used to prevent heart disease and stroke in at-risk individuals. It is a prodrug that requires a conversion into its active form in order to be effective. This conversion is primarily performed by the enzyme *CYP2C19*, which is encoded by a highly polymorphic gene. Individuals who have increased *CYP2C19* activity (*CYP2C19* ultrarapid metabolizers) will convert the drug more rapidly, making them potentially more susceptible to bleeding, while those with slower or no activity (*CYP2C19* intermediate metabolizers or *CYP2C19* poor metabolizers) will convert the drug more slowly or not at all, increasing their risk of treatment failure and future cardiac events or strokes.

Mitropoulou *et al.* performed a retrospective analysis of 121 patients who received a percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction and received clopidogrel. Patients were divided into groups that experienced in-hospital bleeding (55) and those that did not (66). Genotyping of *CYP2C19* revealed that intermediate metabolizers and poor metabolizers were generally less prone to bleeding (42.8 percent vs. 59.3 percent) but had an increased risk of reinfarction (11.2 percent vs. 2.3 percent). They also averaged a higher cost compared to normal metabolizers (€2,799 vs. €2,547). A model taking into account health resource utilization and the cost of alternative medication demonstrated a cost savings of €80, not including the cost of testing (€63).<sup>3</sup>

Another PCI study by Deiman *et al.* took an observational genotyping approach to antiplatelet therapy and analyzed 3,260 PCI patients who were genotyped for *CYP2C19*. Poor metabolizer (PM) patients were given either clopidogrel or prasugrel and followed for 1.5 years. PMs prescribed clopidogrel were more likely to have a major adverse cardiovascular event versus those who received prasugrel (31 percent vs. 5 percent;  $p = 0.003$ ). The study concluded that unguided treatment aimed at avoiding potential *CYP2C19* genetic implications using prasugrel in all patients would have resulted in a QALY cost of €38,611. This number was brought down to €5,972–€9,792 when various genotype-guided strategies were employed.<sup>4</sup>

Based on these analyses, the use of PGx testing prior to PCI represents a cost-effectiveness well below the \$50,000 (€43,246) per QALY threshold and perhaps can even represent a cost savings.

## PSYCHIATRIC PHARMACOGENOMICS

The highly variable response rate to pharmacological intervention in mental health is a major challenge for the specialty. The fact that most psychiatric medications interact with multiple PGx genes suggests that at least some of the patient variability in adverse drug reactions (ADRs) and symptom remission can be identified through proper PGx-guided drug selection and dosing.

Multiple retrospective analyses have been performed looking at cost savings of psychiatric PGx. Chou *et al.* demonstrated that the cost of care was increased by \$4,000–\$6,000 per year for *CYP2D6* ultrarapid

metabolizers and poor metabolizers compared to normal or intermediate metabolizers in a psychiatric hospital cohort. They also noted that *CYP2D6* poor metabolizers averaged seven more in-hospital days per year than normal metabolizers (24 vs. 17). A trend toward greater ADRs in poor metabolizers was also reported.<sup>5</sup> Another study looked at health resource utilization by 96 psychiatric patients tested with a multi-gene panel that included *CYP2D6*, *CYP2C19*, *CYP1A2*, *SLC6A4*, and *HTR2A*. It found that patients on genetically suboptimal medications had twice as many healthcare visits, three times as many medical absence days, and four times as many disability claims, amounting to an estimated \$5,188 in additional healthcare utilization.<sup>6</sup> A further study, by Fagerness *et al.*, showed that a group of 111 PGx-guided patients saved \$562 and experienced improved medication adherence compared to 222 controls receiving treatment as usual (TAU).<sup>7</sup>

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**THE FACT THAT MOST PSYCHIATRIC MEDICATIONS INTERACT WITH MULTIPLE PGX GENES SUGGESTS THAT AT LEAST SOME OF THE PATIENT VARIABILITY IN ADVERSE DRUG REACTIONS (ADRS) AND SYMPTOM REMISSION CAN BE IDENTIFIED THROUGH PROPER PGX-GUIDED DRUG SELECTION AND DOSING.**

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Most recently, Benitez, Cool, and Scotti retrospectively analyzed a group of 205 PGx-guided and 478 TAU psychiatric patients in light of the actual cost to the payer. This study took a comprehensive approach by including pharmacy, inpatient, outpatient, and professional care costs. They recorded an average cost savings of \$866 across all psychiatric disorders and a difference of \$5,505 in the post-treatment expenditures in the trailing 12 months post index.<sup>8</sup>

Prospective, randomized control trials have largely backed up the retrospective findings. Herbild *et al.* found that *CYP2D6* and *CYP2C19* genotyping reduced treatment costs among poor metabolizers and ultrarapid metabolizers from a group of 104 schizotypal patients by 28 percent when compared to 103 TAU patients ( $p = 0.054$ ). They also discovered that these patients' treatment costs typically rose to 239 percent of the mean, but that this expense could be reduced by 68 percent (\$67,064 → \$20,532) when PGx testing was used.<sup>9</sup> Another recent study comparing 178 genotype-guided patients with 59 TAU controls linked PGx testing with a 50 percent reduction ( $p = 0.001$ ) in ADRs that led to an 84 percent reduction ( $p = 0.02$ ) in healthcare costs, leading to a cost savings of \$1,100 per patient.<sup>10</sup>

The largest prospective psychiatric PGx study to date utilized prescription data from 2,168 PGx panel-tested individuals along with 10,880 propensity-matched controls. Winner *et al.* found that over the course of 12 months post index, the genotyped group accrued \$1,035 less medication expenditures compared to the TAU group. Surprisingly, 70 percent of the cost savings were related to non-psychiatric medications.<sup>11</sup>

Perlis *et al.* recently published the results of a large trial in mood and anxiety disorder patients that demonstrated decreased healthcare utilization and costs in a cohort of 817 PGx-guided versus 2,745 TAU participants. Over the six-month observation, PGx-guided patients experienced 40 percent fewer ER visits ( $p < 0.0001$ ) and 58 percent fewer hospitalizations ( $p < 0.0001$ ) resulting in an annualized reduction of \$2,456.<sup>12</sup>

Taken as a whole, these studies demonstrated an average savings of \$1,800 in healthcare and \$500 in medication savings, representing total cost savings of \$2,300 per year. In summary, the evidence overwhelmingly supports the use of PGx testing when prescribing psychiatric medications as a cost-saving measure.



## POLYPHARMACY

Multiple prospective studies have looked at the impact of PGx testing on polypharmacy, a major culprit of high healthcare costs. One open-label, randomized control trial looked at 250 PGx-guided compared to 802 TAU patients that were over 65 and on at least three medications with one or more having a PGx indication. It demonstrated a total healthcare cost savings of \$1,132 in the PGx-guided group.<sup>13</sup> Another prospective study followed a group of age 50+ PGx-tested patients (57) and propensity-matched controls (53) for 60 days and generated a model that revealed a \$4,342 reduction in costs associated with PGx testing.<sup>14</sup> Both of these studies demonstrated that PGx testing in polypharmacy is effective at reducing hospitalization and emergency room visits. However, the first study suggests that it increased outpatient visit rates, though this did not outweigh the cost benefits of reduced inpatient visits.

While the amount of data surrounding polypharmacy is limited, it nevertheless suggests that PGx has cost-saving potential and improves quality of care in this high-risk population. A potential cost savings of \$1,132–\$4,400 represents significant added value to PGx testing in this population.

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## DPYD AND FLUOROPYRIMIDINES

Fluoropyrimidines are a class of anti-cancer drugs that are used to treat a broad range of malignancies. Mutations in the *DPYD* gene can result in an inability to break down fluoropyrimidines by the metabolizing enzyme dihydropyrimidine dehydrogenase (DPD) leading to severe or even fatal toxicity.

A prospective evaluation by Deenen *et al.* compared fluoropyrimidine chemotherapy in 2,038 PGx-guided patients to a historical cohort of 3,974. They found that the highest grades of toxicity were reduced by 45 percent ( $p < 0.001$ ) and that PGx guidance led intermediate or poor metabolizers to experience similar toxicity to normal metabolizers.<sup>15</sup> An economic analysis estimated a cost savings of \$136 per patient, demonstrating that PGx testing alongside fluoropyrimidine treatment is cost-effective, and possibly cost-saving, depending on the cost of the test.

## ABACAVIR

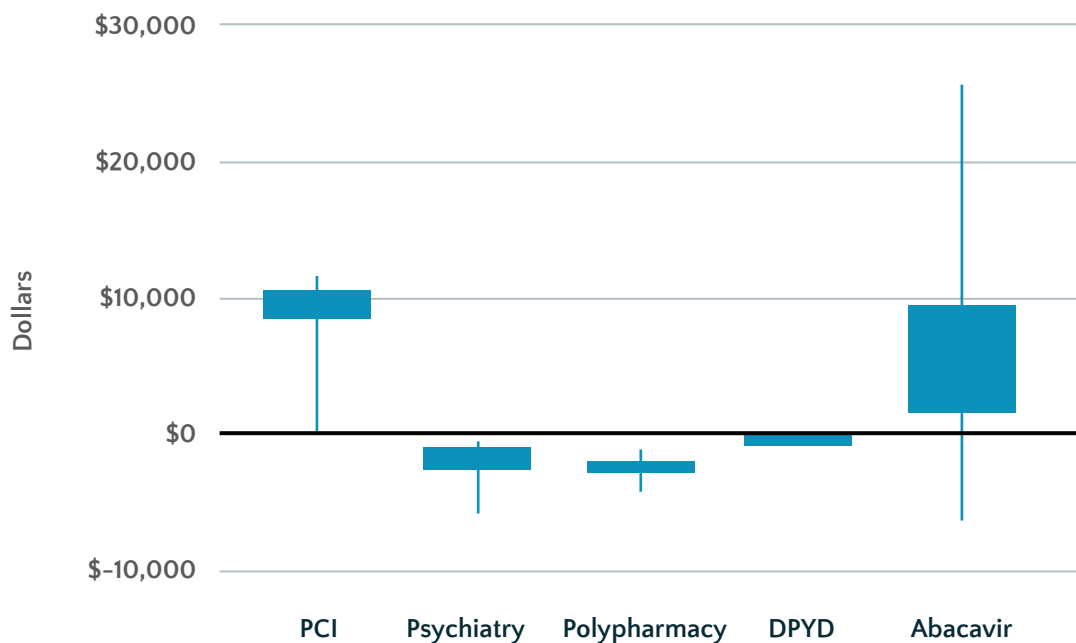
A member of a class of drugs known as nucleoside analog reverse transcriptase inhibitors, abacavir is commonly used in conjunction with other medications to treat HIV/AIDS. In some ethnic populations, such as Caucasians, Indo-Americans, and certain African subgroups, a severe hypersensitivity reaction to abacavir has been linked to the presence of the *HLA-B\*5701* allele.

Hughes *et al.* sought to determine if genotyping for *HLA-B\*5701* was cost-effective. They identified 13 patients who experienced a hypersensitivity reaction and 51 who did not. Forty-six percent of hypersensitive patients were

*HLA-B\*5701* positive, while only 10 percent of the non-sensitives carried the allele (OR: 7.9, 95 percent CI: 1.5–41.4,  $p = 0.006$ ). When this data was pooled with other published data, the odds ratio rose to 29 (95 percent CI: 6.4–132.3,  $p < 0.0001$ ). Depending on the treatment strategy derived from PGx guidance, cost-effectiveness was estimated to range from cost-saving (i.e. negative cost) to €22,811 (\$26,404) per hypersensitivity reaction avoided.<sup>16</sup>

Based on these findings, *HLA-B\*5701* genotyping appears to be cost-effective in Caucasians and other high-penetrance ethnic populations being considered for abacavir treatment.

### Cost of treatment with pharmacogenetic testing compared to TAU (below \$0 = cost-saving)



| Therapeutic area | Study                     | Type of study/intervention  | Time frame  | Cost difference<br>PGx vs. TAU cost |
|------------------|---------------------------|---|---|-------------------------------------|
| PCI              | Mitropoulou <i>et al.</i> | Retrospective   | 1 year  | -91                                 |
|                  | Deiman <i>et al.</i>      | Genotype-guided prasugrel   | Patients followed for 1.5 years, cost reported per year | 10,376                              |
|                  | Deiman <i>et al.</i>      | Genotype-guided ticagrelor  | Patients followed for 1.5 years, cost reported per year | 6,801                               |
|                  | Deiman <i>et al.</i>      | Prasugrel for <i>CYP2C19</i> poor metabolizers                      | Patients followed for 1.5 years, cost reported per year | 11,152                              |
| Psychiatry       | Winner <i>et al.</i>      | Retrospective   | 1 year  | -5,188                              |
|                  | Fagerness <i>et al.</i>   | Retrospective   | 4 months  | -562                                |
|                  | Benitez <i>et al.</i>     | Retrospective/Depression  | 1 year  | -2,203                              |
|                  | Benitez <i>et al.</i>     | Retrospective/Anxiety   | 1 year  | -2,729                              |
|                  | Benitez <i>et al.</i>     | Retrospective/Bipolar Disorders                                     | 1 year  | -3,257                              |
|                  | Benitez <i>et al.</i>     | Retrospective/All CNS   | 1 year  | -5,505                              |
|                  | Maciel <i>et al.</i>      | Genotype-guided depression ADR related medical costs                | 1 year  | -1,100                              |
|                  | Winner <i>et al.</i>      | Genotype-guided depression and anxiety medications                  | 1 year  | -1,036                              |
|                  | Perlis <i>et al.</i>      | Genotype-guided mood and anxiety disorder healthcare costs          | 6 months  | -2,456                              |
| Polypharmacy     | Brixner <i>et al.</i>     | Open label RCT in 65+ population                                    | 8 months  | -1,132                              |
|                  | Elliott <i>et al.</i>     | Genotype-guided prescribing in 50+ population                       | 60 days   | -4,342                              |
| DPYD             | Deenen <i>et al.</i>      | Genotype-guided fluoropyrimidine                                    | Up to 52 treatment cycles, median of 4-5                | -136                                |
| Abacavir         | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Nevirapine + Combivir             | 6 weeks   | -3,102                              |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Efavirenz + Combivir              | 6 weeks   | -1,861                              |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Nelfinavir + Combivir             | 6 weeks   | 3,220                               |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Kaletra + Combivir                | 6 weeks   | 6,567                               |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Ritonavir + saquinavir + Combivir | 6 weeks   | 18,176                              |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Ritonavir + indinavir + Combivir  | 6 weeks   | 26,053                              |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Didanosine                        | 6 weeks   | 560                                 |
|                  | Hughes <i>et al.</i>      | <i>HLA-B*5701</i> Genotype-guided Tenofovir                         | 6 weeks   | -6,204                              |

## Implications

A preponderance of evidence suggests that PGx testing is cost-effective and often cost-saving when considering treatment with medications that have known genetic interactions. The economic benefit is often largest in clinically high-risk populations or when testing can help determine when patients are likely to need more expensive treatments, thereby reducing even more expensive trial-and-error strategies. Furthermore, as is apparent in psychiatry, PGx testing is especially invaluable when multiple medications with well-documented pharmacogenetic associations are being considered.

The widespread use of PGx testing poses a significant potential benefit to the health system. For example, the mean cost savings associated with the use of PGx testing in depression in this analysis was approximately \$3,000 per patient per year. With approximately 16.7 million individuals having at least one major depressive episode in 2015<sup>17</sup> and 13 percent of Americans taking at least one antidepressant in 2017,<sup>18</sup> the overall benefit to the system could be well into the billions of dollars. Research into structured models of the economic benefit of PGx testing to the health system is needed.

For many genetic tests, the standard of success is not solely in decreasing overall costs but also in improving patient quality of life. The fact that PGx testing informs medication selection can cause cost savings to easily overcome the cost of testing and reduce healthcare expenditures. As demonstrated by our findings, some of the primary areas of savings include reduction of ADRs, polypharmacy, risk exposure, and the unnecessary prescribing of expensive medications.

Since PGx testing is a relatively recent innovation in care, some medical providers are surprised to see how well its clinical utility has been demonstrated. Because studies of economic utility necessarily follow those of clinical utility, our understanding of the cost-effectiveness of PGx testing is still maturing. Despite this, for PCI, psychiatry, and polypharmacy, multiple studies have consistently demonstrated cost savings. These savings, combined with the evidence of clinical studies, lead many experts to believe that routine testing should be considered standard of care in many cases. Even in use cases with limited data, such as fluoropyrimidines and abacavir treatment, PGx testing is still likely to provide an economic benefit, given the cost risk associated with the selection of genetically incompatible medications.

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