Realizing the **Value** of Pharmacogenomic Testing: For Patients and Health Systems

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Abstract

In this white paper, we discuss the clinical and economic value of pharmacogenomic (PGx) testing and how the implementation of PGx testing by health systems may help improve patient outcomes while reducing healthcare cost. PGx testing is a powerful tool that can identify the genotypes of major metabolic enzymes and determine whether a patient is at risk for under- or over-metabolizing a drug. Suboptimal or elevated drug metabolism can result in poor patient outcomes, adverse drug events, and unnecessary cost to patients and health systems. Given the broad applicability of PGx to a variety of therapeutic areas and healthcare settings, ongoing efforts from health systems, physicians, and the United States government are devoted to integrating PGx testing into mainstream patient care.

Introduction

Variability in drug responses among individual patients is a widespread problem in healthcare and can lead to diminished patient outcomes and inefficient healthcare expenditure. Due to genetic variations among individuals, many drugs are optimally effective only in a subset of patients. For instance, available estimates suggest relatively low rates of response to major drugs among patients with Alzheimer's disease (30% response rate), diabetes (57%), or asthma (60%).[1] Suboptimal drug selection and dosing pose a significant potential burden to both patients and health systems. Numerous studies have found that genetic variations can lead to therapeutic failures (e.g., codeine) and adverse drug reactions (ADRs), such as those associated with diazepam, warfarin, and the thiopurine class.[2] Ineffective prescriptions may unnecessarily lengthen the treatment process and lead to poor medication adherence.

ADRs are also associated with considerably higher incidences of morbidity and mortality. In hospitalized patients in the United States, the incidence of serious ADRs was estimated to be 6.7% and fatal ADRs was 0.32%.[3] ADRs were ranked the fourth leading cause of death.[3] Despite the magnitude of the problem, data have shown that about half of all ADRs are preventable.[4] In addition, results from a 2018 study showed that hospital readmissions due to drug-related events could have been prevented in 69% of cases (median percentage across hospitals).[5]

Beyond the clinical burden of ADRs, the economic costs are considerable. The management of ADRs may account for as much as $30.1 billion annually in the United States.[6] The management of ADRs is associated with several cost drivers, including increased and prolonged hospitalizations, as well as additional medications and other medical interventions.[7] A strategy that could reduce this figure in any amount is likely to have a significant impact on healthcare expenses in the United States.

Reducing ADRs and drug-related hospital readmissions represents a significant opportunity to help improve patient care, clinical outcomes, and the efficiency and performance of health systems. The importance of preventing and managing readmissions is also reflected in many patient-care quality measures, with all-cause readmission included in metrics from the Healthcare Effectiveness Data and Information Set (HEDIS), the Centers for Medicare and Medicaid Services (CMS), and the National Quality Forum.

What is PGx testing?

PGx testing identifies genetic variations that may influence the effectiveness and safety of different medications in a given patient. Variations in drug-

metabolizing enzymes, drug-target proteins, and drug transporters can influence a patient's drug response. These variations may cause a patient to metabolize a drug too quickly, too slowly, or not at all, potentially leading to treatment failure or ADRs.

PGx testing is in use in both clinical research and real-world practice. To date, researchers of several clinical trials, such as (but not limited to) TAILOR-PCI and GENETIC-AF, have incorporated PGx testing into their study designs.[8] Health systems have also implemented PGx testing in their patient care plans.[9,10] In both instances, use of PGx has enabled clinicians to more effectively identify the target treatment population, improving safety and efficacy/effectiveness outcomes.

While PGx testing can be targeted to single-gene assessment, multi-gene tests are also available. In fact, an analysis of 5 genes among patients (N=1013) who had an increased chance of initiating a statin drug within the next 3 years showed that 99% carried at least one actionable variant as determined by preemptive PGx testing.[11] Multi-gene tests can also facilitate combinatorial analysis, in which an algorithm is applied to synthesize data on multiple genes simultaneously. This is of benefit as, in some cases, combinatorial testing can predict drug response and healthcare utilization better than single-gene analysis.[12,13]

In addition, unlike gene-based diagnostics used to assess viral or tumor DNA, PGx testing is performed to analyze the patient's germline DNA. Unlike the mutations in viral or tumor DNA, mutations in the germline DNA are static. Therefore, PGx testing is associated with the advantage that the test needs to be performed only once in each patient because the genetic results remain valid for a patient's lifetime.[14]

Discovering the value of PGx testing

PGx testing can provide the data that clinicians and health systems need for improving patient outcomes and reducing healthcare costs. Over the past decade, studies in diverse therapeutic areas, including psychiatry, HIV, cardiology, and oncology, have presented compelling evidence indicating that PGx testing has made an appreciable improvement in both effectiveness and cost.[15-17]

Improved patient outcomes

Because PGx testing provides information about an individual's unique drug metabolism profile, it can facilitate a personalized approach to pharmacotherapy. Such a method can improve drug effectiveness, help optimize dosing, and reduce the risk for adverse events. The application of PGx testing in efficacy improvement has been explored in several clinical trials of psychiatric drug therapies. In one prospective clinical trial, patients with depression and/or anxiety underwent PGx testing with a panel of 10 genes. PGx-guided treatment significantly improved response and remission rates and reduced anxiety symptoms.[18] In another clinical trial involving patients with major depression, those receiving genotype-guided prescribing had a 2.52-fold greater chance of remission.[19]

Examples of reduced adverse events based on PGx testing have been reported in HIV medicine, cardiology, and oncology:

HIV – Abacavir is indicated for the treatment of HIV infection and used as part of some highly active antiretroviral therapy regimens. However, patients with the *HLA-B*57:01* allele are at risk for severe, potentially life-threatening hypersensitivity reactions.[15]

To reduce the risk of a life-threatening hypersensitivity reaction, drug labeling for abacavir recommends that all patients should be screened for the *HLA-B*57:01* allele before initiating or reinitiating abacavir, unless the patient has been previously tested.[15]

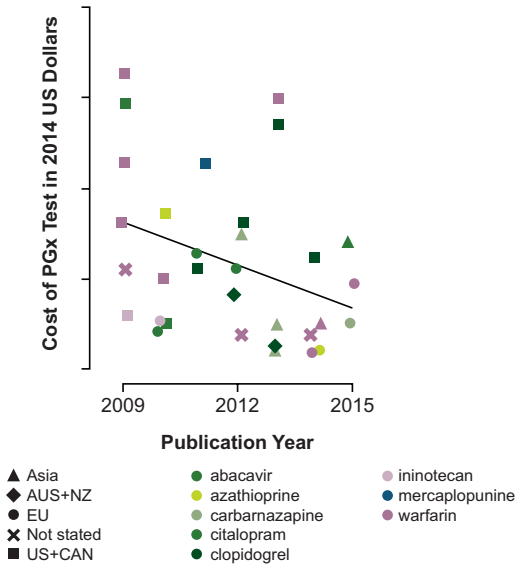
Cardiology – In a large-scale, national, prospective clinical study with a 6-month follow-up period, genotype-guided dosing of warfarin reduced the rate of hospitalizations by 31% in outpatients initiating warfarin.[16]

Oncology – Fluoropyrimidine-based chemotherapy is a frequently prescribed class of anticancer drugs. In a prospective study by Deenen et al, the authors reported that genotype-guided dosing of the fluoropyrimidine therapy was associated with significantly reduced toxicity, risk of drug-induced death, and treatment costs.[17]

Cost effectiveness

As summarized in 2 recent review articles, numerous economic evaluations have concluded that most PGx tests indicate favorable cost effectiveness.[14,20] The cost of the test is an important factor to consider in the economic assessment of PGx-guided treatment. With technological advancement, the costs of PGx tests have decreased, especially since 2009 (**Figure 1**).[14] As PGx information has been increasingly included in the labeling of drugs, Verbelen et al conducted a review of economic analyses specifically focusing on PGx testing listed in the US Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labeling.[14] A total of 137 distinct drugs were listed in the table, and 68 drugs with germline PGx associations were included in the analysis. The authors reviewed 44 economic evaluations relating to 10 drugs from the National Health Services Economic Evaluations Database and concluded that overall, 57% of evaluations favored PGx testing (27% showed PGx to be both more effective and less costly [dominant], and 30% found PGx to be cost effective, meaning that the improved effectiveness outweighed the additional cost (**Figure 2A**).[14] Furthermore, with the model assumption that genetic information would be freely available in the future, the analysis showed that 50% of PGx testing would provide cost savings and 25% would be cost effective (**Figure 2B**).[14] Together, these findings demonstrate that PGx testing could be a cost effective or even a cost-saving clinical service.

Figure 1. Cost of PGx tests as reported in the reviewed economic studies in Verbelen et al, 2017. The regression line of the cost was fitted since 2009 and shows a steady decline.

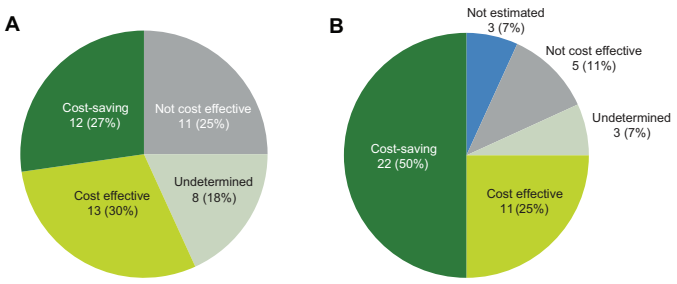


PGx, pharmacogenomic.
Adapted from Verbelen et al, 2017.[14]

Similarly, in another report, Berm et al analyzed 80 economic studies from 2000 to 2014 and found that most treatment strategies using PGx tests (>80%) were cost effective, provided cost-savings, or were both less costly and more effective when compared to therapy implemented without PGx tests.[20] In a systematic review, Plumpton et al identified 47 economic analyses of PGx testing aimed at the prevention of ADRs.[21] Among these analyses, robust evidence was found supporting the

cost effectiveness of testing prior to the treatment with abacavir, allopurinol, carbamazepine, clopidogrel, and irinotecan.[21]

Figure 2. Cost effectiveness of PGx testing strategies of reviewed economic evaluations (A) and same analysis with the assumption that there was no extra cost for genetic information (B).



Adapted from Verbelen et al, 2017.[14]

Cost savings from reduced pharmacy cost and healthcare utilization

In addition to cost effectiveness analyses, several studies have identified cost savings that can be achieved by implementing PGx testing. These studies were conducted in various healthcare settings and presented results from clinical trials, observational studies, and economic models. The achieved cost savings are mainly driven by reduced pharmacy costs and reduced hospitalization rates and emergency-department visits. A summary of these studies is shown in **Table 1**.

As demonstrated by Winner et al, combinatorial PGx-guided treatment, when compared to the standard of care, significantly improved psychiatric medication adherence and reduced the risk for drug discontinuation, while lowering pharmacy costs.[22]

Table 1. Cost savings of PGx testing from reduced pharmacy cost and healthcare utilization

Healthcare setting/ patient population	Study design	Outcomes associated with PGx testing
Home health management/ polypharmacy patients[23]	Randomized controlled trial	• Reduced rehospitalizations and emergency-department visits at 60 days following enrollment
Long-term care/polypharmacy patients[24]	Randomized controlled trial	• Elimination or replacement of 1–3 drugs per patient • Annual savings of $621 per patient
Elderly polypharmacy patients[25]	Observational study	• A significantly lower hospitalization rate and a lower emergency-department visit rate • A cost savings of $218 per patient during the 4-month follow-up period
Psychiatric patients[26]	Observational study	• A cost savings of $3988 per member per year
Psychiatric patients[22]	Observational study	• Improved medication adherence and drug discontinuation • Average cost savings of $2774.53 per patient in 1 year
Patients with depression[27]	Economic model	• A cost savings of $3711 in direct medical costs • $2553 in work-productivity costs per patient in a lifetime
Patients with cardiovascular diseases[28]	Economic model	• A cost savings of $445 per patient annually

Because medication adherence and persistence are important quality metrics captured by HEDIS scores, implementation of PGx testing may not only help improve patient outcomes but may also assist with the health system's measurable performance and effectiveness.

Cost avoidance and savings from high-price drugs

Prescription drug expenditure is significant and has been growing in the United States. Many high-priced medications are specialty drugs, including those indicated for oncology, hepatitis C, and orphan/rare diseases. Even with generics entering the market, the competition may not be sufficient to achieve an appreciable reduction in price and a commensurate increase in patient access to prescription medications. In the case of the chemotherapy drug capecitabine, for example, its generic version has a list price of ~$2300 per month, which is only 36% lower than the brand version's price.[29] For a subset of drugs (many with higher prices and/or toxicity issues), clinical guidelines on PGx testing have been established to help improve treatment effectiveness and minimize ADRs. For example, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that an alternative drug should be prescribed for patients who are poor metabolizers of capecitabine due to deficiency in the DPYD gene and a 50% reduced dose for patients who are intermediate metabolizers.[30] In this case and others, utilization of PGx testing, in adherence with the CPIC recommendations, has the potential for not only improving patient safety and effectiveness outcomes, but also for avoiding the cost of unnecessary treatment.

Orphan drugs represent another category associated with higher prices. For instance, eliglustat is an orphan drug approved as a first-line therapy for type 1 Gaucher disease and priced at $23,800 per month in the United States.[31] The FDA-approved drug label states that eliglustat is contraindicated for patients who are CYP2D6 ultra-rapid metabolizers, and that patients who are poor CYP2D6 metabolizers should reduce their daily dose in accordance with label specifications to avoid the risk of overdose-related adverse reactions.[31]

These examples demonstrate that PGx testing may have great potential to prevent therapeutic failure and ADRs, and can help avoid unnecessary drug costs, as well as the costs associated with the management of drug-related complications.

Developing and implementing PGx testing in health systems

As ongoing research continues to broaden our understanding of the application of PGx testing in clinical practice, health systems are recognizing its importance and have begun using it in the patient-care pathway. A study conducted by the Translational Pharmacogenetics Program (TPP) of the National Institutes of Health Pharmacogenomics Research Network showed that PGx testing could be implemented across a wide variety of healthcare settings.[32] The TPP collected several major metrics of the PGx implementations from 7 participating institutions. Scientific, educational, financial, and informatics outcomes suggested that barriers to implementation could be overcome with diverse solutions.

In addition, top-tier health systems have successfully incorporated PGx testing into routine prescribing, providing a roadmap to support similar efforts for other institutions. For instance, St. Jude Children's Research Hospital has developed, implemented, and assessed the clinical decision support tools for multiple PGx test results reported preemptively.[9] Using a comprehensive and systematic implementation

approach, Mayo Clinic has implemented PGx testing at the point-of- care, offering 18 gene–drug pairs in the electronic medical record.[10] Based on the percentage of patients with appropriately PGx-guided prescriptions and the number of drug–gene interactions that had been reviewed, approved, and implemented in the electronic health record, analysis of these programs showed that the implementation of PGx testing has proven to be successful.[9,10] In addition to the measures of implementation itself, data on outcome indicators are being collected. Examples of outcome indicators include: number of hospitalizations and/or emergency-department visits due to potential ADRs caused by PGx drugs (ie, drugs prescribed with a PGx testing component), average therapeutic PGx drug level, and time-to-stable PGx drug dose.[33] These outcome indicators may be used for economic evaluations, which provide valuable information on the benefit or financial burden of the PGx services and the justification to continue or expand the services for health systems.

Conclusions

Variations in drug responses among individuals influence the efficacy and safety of many drugs. The "one-size-fits-all" prescribing strategy may lead to diminished efficacy and safety, and a significant economic burden to patients and health systems. Personalized treatment through the use of PGx testing has demonstrated enormous applicability and economic value in various healthcare settings.

PGx-informed treatment decisions help identify the right drug and dosage before the patient initiates the treatment, and therefore, may significantly diminish the trial-and-error prescribing process. In addition, PGx testing can help improve aspects of patient care captured in quality metrics, such as HEDIS and others. With the declining costs of genetic tests and the increasing number of established PGx programs, PGx is becoming a critical component of the clinical decision-making process for providers and patients in real-world practice. The wide adoption of PGx testing as a core clinical service has the potential to improve patient outcomes and reduce healthcare costs.

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