PHARMACOGENETICS IMPROVES HEALTH SYSTEM PERFORMANCE

Economic Benefits and Key Decisions

Abstract
Successful integrated health systems see value in bringing precision medicine to their patient populations. Progress starts in the laboratory. Discover the latest pharmacogenetics facts and trends.
Executive Summary

Health systems compete to deliver value to their stakeholders by providing better and more efficient care for their patients, offering up-to-date services for their team of health professionals, and meeting the needs of their major payers. In this white paper, we show that one of the best opportunities for health systems to be competitive and reduce costs is through offering widespread use of pharmacogenetic testing. Pharmacogenetics can reduce patient readmissions and adverse drug events as well as provide patients and physicians with better drug choices, often at lower costs. Frequently, pharmacogenetics is key to better drug management and reducing polypharmacy for patients.

Numerous leading health systems—like Geisinger, Northshore Hospital, Duke University, Vanderbilt University, University of Chicago, University of Vermont, and University of Florida—pioneered the implementation of successful and impactful pharmacogenetics programs. These centers have proven that pharmacogenetics is a powerful way to enhance precision medicine; and by doing so, they have proven their institutional ability to provide cutting-edge, modern health care. Very few new technologies are able to improve care while also lowering health care costs, but pharmacogenetics has that capability. With the rapidly falling costs of both lab equipment and supplies, services like in-house pharmacogenetic testing are among the most promising areas for attention and investment. In this white paper, we discuss the recent history and progress in precision medicine, powered by easy and low-cost genetic testing, and lay out some of the key considerations for health system leaders.
Overview

Genetic tests are increasingly used in health care as it becomes more practical for both large and small health systems to implement genetic profiling in their own laboratories. This requires close collaboration between the laboratory and the clinicians it serves. Currently, the most widely applicable genetic test is pharmacogenetics since a large proportion of patients in every health system are treated with drugs that benefit from precise selection and dosing. To date, there are over 20,000 articles in PubMed that discuss pharmacogenetics and over 130 medications whose selection, use, and dosing are improved by knowing a patient’s genetic makeup (Weinshilboum and Wang 2017). In this white paper, we highlight some key findings from recent clinical literature.

Pharmacogenetics is able to improve clinical outcomes as well as provide financial value to the health system. There are many compelling studies that found significant cost-savings value from introducing pharmacogenetics to physicians and patients. The cost savings are especially clear for those complex or chronic patients who require excessive resources from health systems and payers.

The favorable cost/benefit impact of pharmacogenetics will continue to grow as the direct cost of testing falls. While pharmacogenetics programs can be developed with next-generation sequencing (NGS) techniques, less intensive and costly methods based on fabricated chips and readily available thermal cyclers can effectively support most real-world pharmacogenetics programs. Pharmacogenetics is the future of health care.

Why Is Pharmacogenetic Care Arriving in More Health Systems Now?

During the past decade, pharmacogenetics was thought of as the technology of the future, and today it is finally a reality. By 2015, embedded pharmacogenetics programs were already established at roughly 1 in 10 US medical centers (Pedersen et al. 2017). The number of programs is predicted to grow rapidly as the positive impact of pharmacogenetics becomes clearer and is applied to a wider group of patients. In our complex US health care system, far too many patients are forced to try multiple drugs before they are effectively treated, and patients suffer from negative side effects that erode compliance (Lazaridis 2017). Physicians can now easily help patients avoid medications that interact poorly with their drug response profile by determining their genetic makeup. Leading health centers are therefore turning to
preventive or “preemptive” genetic testing. This new approach can identify problems before they start, help physicians choose the proper treatment and dose, and facilitate patient compliance. Together, the benefits of pharmacogenetics help health systems avoid adverse drug events.

The High Costs of Adverse Drug Events for Health Systems

Adverse drug events are well understood as a high burden for hospitals. Compiling a range of studies, the FDA estimated that 6.7% of hospitalized patients will have a major adverse drug event, likely accounting for >100,000 deaths per year. They also estimated that additional hundreds of thousands of adverse drug events occur in nonhospital settings (e.g., nursing homes). Further, the FDA noted that adverse events can double the mean length of stay, raise the hospital’s costs, and increase the hospital’s mortality rates (FDA 2018). Adverse drug events are also a major cause of readmissions, a measure that is watched closely by Medicare and other payers, and is publicly available for most hospitals. Finally, adverse drug events drive emergency room visits. Increasingly, major payers like Anthem are tightly monitoring emergency department visits and have stopped paying for those deemed non-emergent (Livingston 2017).

Not every adverse drug event is preventable by pharmacogenetics. However, some of the biggest causes—ineffective drug prescriptions, improper dosing, and negative drug–drug interactions—can be avoided through genetic testing. A retrospective report studied individuals who received a 3-gene pharmacogenetic panel and found that 34% of all potential major adverse drug interactions were caused by the patient’s genetics rather than drug–drug interactions (Verbeurgt et al. 2014). This type of data argues for wider use of preemptive testing, at least in older, high-risk, and polypharmacy patients. Furthermore, a systematic review found that pharmacogenetic testing is rapidly becoming more cost-effective, and more often cost-saving, as the direct cost of testing falls below $100 per patient (Verbelen et al. 2017).

New Studies Demonstrate Impressive Savings from Pharmacogenetics

In the past, most genetic studies only identified benefits using a narrow perspective—studying one gene and one drug in isolation. Today, health economists are assessing the greater impact that occurs when panels of pharmacogenetic genes and potential drugs are studied together. As reviewed in this section,
these studies find that the use of pharmacogenetics results in dramatic cost savings. This is an important discovery for patients, physicians, and health systems as a whole. Physicians and health systems are penalized for high costs associated with adverse patient drug reactions, which can easily be prevented by pharmacogenetic profiling. Additionally, high-performing institutions attract more patients, turning the treatment benefits of pharmacogenetic testing into financial benefits.

**Savings in home health care.** When primary care providers make drug choices guided by pharmacogenetics in a home health setting, substantial improvements in economics are observed in as little as two months (Elliott et al. 2017). A study comparing patients that either received treatment based on a 6-gene pharmacogenetic panel or on the usual recommendation based on a standard drug information resource found that pharmacogenetics greatly reduced the rate of rehospitalization and emergency department visits. Specifically, at 60 days after hospital discharge, the rate of rehospitalization was halved and the rate of emergency department visits was nearly halved for pharmacogenetics patients. The reduction in additional treatment needed after hospital release resulted in an estimated cost savings of $4,382 per patient during the course of the study. These are huge savings compared to the $914 it cost to perform the 6-gene panel used (Elliott et al. 2017). Furthermore, if hospitals performed a 6-gene panel on-site, the in-house cost would be only a fraction of that reported by these authors.

**Savings in long-term care settings.** In long-term care settings, use of gene panel–based prescriptions significantly reduced real-world costs (Saldivar et al. 2016). This study looked at patients who were taking five or more medications in long-term care focused on the cost savings generated by three real-world impacts of pharmacogenetics: replacing poorly suited medication, taking patients off medications likely to be incompatible or ineffective, and consolidating two medications into one prescription. Using two different models, it was estimated that replacing or eliminating poorly performing drugs resulted in a cost savings of $621 per patient within a year period. Extrapolating these results, ~$1,900 per patient is saved over a three-year period. Pharmacogenetics therefore demonstrated significant cost savings when compared to the ~$800 cost of the test used (Saldivar et al. 2016). This is another example where in-house testing would further reduce the test costs cited by the researchers, resulting in even higher savings.
**Cost savings in psychiatric patients.** Multiple studies looking at the treatment of psychiatric patients determined that pharmacogenetics resulted in significant cost savings. A meta-analysis examining three prospective clinical studies found that pharmacogenetic testing saved ~$3,700 per patient over a patient’s life in direct medical costs (Hornberger et al. 2015). A more recent meta-analysis study looking at the treatment of psychiatric patients forecasted savings of ~$4,000 per patient per year when pharmacogenetics was used (Brown et al. 2017). Finally, a retrospective study found savings of $562 per patient over just a four-month period with pharmacogenetic testing after taking into account the drug costs represented by increased patient adherence to their prescriptions (Fagerness et al. 2014).

Studies looking at pharmacogenetics use for psychiatric patients found significant benefits for patients beyond just the dollar savings. These benefits include increased drug adherence (Fagerness et al. 2014), response to treatment, and quality of life (Hornberger et al. 2015). While not every study included direct economic modeling, it is clear that the marked improvement of symptoms and the higher rate of recovery found in clinical studies would result in lower costs of psychiatric care and admissions. The world’s largest randomized, controlled study of the impact of pharmacogenetics on psychiatric patient treatment to date found that clinical response rose from 36% to 73% and remission rose from 13% to 35% for severely depressed patients when pharmacogenetics was implemented (Bradley et al. 2018). Clearly, health outcomes at this scale would result in net cost savings. This robust study enrolled more than 500 patients.

**Cost savings in cardiology patients.** Many studies have looked at the cost-effectiveness of pharmacogenetics in a range of cardiac conditions. In one modeling study, Reese et al. either blindly prescribed prasugrel or clopidogrel or selected the best drug based on a patient’s genetics. When a patient’s genetic profile was taken into account, cost savings of ~$6,700 per cardiovascular event avoided (when compared to uninformed clopidogrel treatment) or ~$11,700 per cardiovascular event avoided (when compared to uninformed prasugrel treatment) were achieved (Reese et al. 2012). In another study modeling the use of the cardiovascular drugs clopidogrel, ticagrelor, and prasugrel, pharmacogenetics was found to lead to cost savings of $445 per patient annually (Johnson et al. 2015).

**Results are achievable in real-world settings.** The studies above were not performed in abstract research settings, but represent studies of real-world patients in practicing clinics. A broader study looking at health care utilization in elderly patients found that the rate of hospitalization was reduced
from 16% to 10% when pharmacogenetics was employed. Furthermore, the rate of emergency department utilization dropped from 15% to 4% when pharmacogenetics was used. Cost savings from pharmacogenetic profiling were estimated at $1,132, which amounted to $218 per patient when the cost of the test was taken into account (Brixner et al. 2016).

**Pharmacogenetics can contribute to cost savings in accountable care organization (ACO) settings.** Increasingly, health systems are held accountable for patient outcomes and receive financial penalties for excessive costs, including the rate and cost of readmissions caused by adverse drug events. For example, emergency room use is scrutinized closely by payers, affecting hospitals’ bottom lines. These pressures now apply directly to physicians as well. In ACO settings, physician bonuses and penalties are tied to overall resource use. Recent changes to Medicare will directly penalize physicians, even in fee-for-service practices, when their patients have higher costs, such as readmissions, compared to their peers.

**External economics: high-profile programs can attract patients to health systems.** While not a focus of this white paper, some health systems advertise precision medicine and genetically driven medicine as a way to attract trend- and health-conscious patients. Cancer care centers have used genetic screening as a marketing tool for several years, advertising that they will rigorously profile a patient’s tumor to find the best therapy. Recently, Stanford Medicine is using pharmacogenetics as a marketing tool, stating that “Stanford is one of the only places in the world where this vision of Precision Health can be attained”. Stanford adds that “the future of medicine will rely on prediction and prevention rather than exclusively on diagnosis and treatment. From cancer care to cardiac diseases, from neurological diseases to food allergies and heart transplantation—our advances in diagnostic methodologies and therapies will lead to the most precise molecular diagnoses and to the treatments that are individually tailored based upon these diagnoses”. Clearly, leading health centers are beginning to view pharmacogenetics programs as a key factor in the competition for patients.
The Center of a Pharmacogenetics Program Is the Laboratory

The center of a pharmacogenetics program is the molecular testing laboratory; however, the laboratory needs to be able to collaborate with other critical components, including the pharmacy and pharmacists, a range of clinicians across departments and divisions, and electronic health records professionals (Caraballo et al. 2017). We will talk more about this system-wide rollout in the next section. But first we will look at the lab itself since a precision medicine program cannot be launched without accurate genetic results.

There are three major techniques available for pharmacogenetic panel testing: real-time PCR (RT-PCR), microarray, and NGS platforms. While there is a lot of enthusiasm for NGS in complex applications, most institutions find that RT-PCR and microarrays are highly cost-effective, accurate, and efficient when used for personalized medicine. The key benefit of these technologies is that they all serve multiple purposes; they can be used within a health system laboratory to study pharmacogenetics, other germline genetics, and tumor oncology.

Key factors for lab directors to consider (reviewed in Johnson et al. 2012) include:

1) Turnaround time for genotyping
2) Net labor costs
3) Number of samples per array expected
4) Cost of the array
5) Content of the array
6) Flexibility to adjust array content

Experienced suppliers can help labs understand the economics of different choices, the relevant economies of scale, and the best fit to their particular institutions. Upfront capital equipment costs will vary based on the technology chosen and the required throughput; however, pharmacogenetic testing by RT-PCR or microarrays can cost as little as $20 per case in reagent and disposables costs. Additionally, the turnaround time for RT-PCR is only 5 hours. Note that any capital equipment investments are for general-purpose molecular platforms that can be used for many types of assays in the laboratory.
How Institutions Are Approaching the Rollout of Pharmacogenetic Testing

We spoke to Scott Megill, the CEO of Coriell Life Sciences—a consulting group with special expertise in bringing precision medicine programs on board at both small and large health systems and in working directly with health plans, such as employer- or union-sponsored insurance—about implementing pharmacogenetics programs. Megill noted that different health centers can use a specialty as a key advantage in developing a local pharmacogenetic program. For example, surgery and anesthesia departments benefit from pharmacogenetic testing by identifying better drug choices and reducing adverse events. In turn, this speeds patient throughput for both inpatient and outpatient surgical centers while improving patient care. Megill added that another target specialty area is cardiology because of the broad range of medications used that require a precise dose to be effective without incurring adverse cardiologic events. All major classes of cardiac drugs, including antiarrhythmic, blood pressure, and statin drugs, depend on dosing that is sensitive to the genetic profile of the patient.

Other health systems may rollout pharmacogenetics to treat patients with specific features rather than particular diseases. One of the most important target populations is complex patients that have multiple disorders or are treated with multiple medications. Consultancies (e.g., Coriell Institute) can help health systems learn how to screen their existing medical and pharmacy records to identify patients who are at high risk for drug-based problems. This allows pharmacogenetics to be applied where it will give patients and the health system the highest return on investment (Haga et al. 2015).

Pharmacogenetics Brings Together Stakeholders from Across the Entire Health System

Institutional pride. The roster of leading US health centers who have implemented clinical pharmacogenetics programs is impressive—including Geisinger, Northshore University, Duke University, Vanderbilt University, University of Chicago, University of Vermont, and University of Florida, St. Jude Children’s Research Hospital, University of Indiana, University of Pittsburgh, and others. These institutions used pharmacogenetics and national initiatives like the Precision Medicine Initiative to garner visibility and grant support and to develop a steady stream of publications.
**Patients.** Precision medicine has an outstanding reputation with patients since its value can be readily grasped by patients and their families. Patients have a better chance of receiving the right drug and achieving improvement or remission early while avoiding the possibility of major adverse events.

**Clinicians.** Clinicians appreciate precision medicine when it can be delivered in a user-friendly format. Multiple vendors supply integrated, physician-friendly reports which often list drugs using a straightforward green-, yellow-, and red-light system, where red-light drugs for a particular patient should be avoided in favor of better-targeted alternatives (Dunnenberger et al. 2015). In a study of 2,279 patient encounters in Chicago, O’Donnell and colleagues found that the rate of patients who were prescribed or were taking high-risk drugs was drastically lowered by providing pharmacogenetic results to the clinicians (odds ratio, 26.2) (O’Donnell et al. 2017). By providing local labs with software that grants clinicians access to well-designed, actionable reports, outside suppliers and consultants, such as Coriell and Translational Software, make precision medicine significantly easier to implement.

**Pharmacists.** The route to implementation may actually be the easiest for pharmacists since genetic information can be linked to patient records through drug interaction software (medication management systems) already in use.

**Information technology (IT) support.** Information technology support is another important aspect of pharmacogenetic programs. For benefits to be realized, clinicians need easy access to pharmacogenetic information on their patients or learn if a patient is at high-risk for an adverse drug reaction (e.g., polypharmacy) but lacks a pharmacogenetic profile. Ideally, pharmacogenetic profiles will be distributed through health IT systems to multiple service points, including primary care electronic health records and the health system’s pharmacies.

In pharmacies, automated software can help identify drug–drug interactions, whether they are intrinsic to the drugs themselves or are driven by the patient’s genetic profile. These approaches are likely to become the standard of care within the next few years. Major electronic record providers have begun incorporating genetic data into clinical decision support systems through application programming interfaces (APIs) (Brixner et al. 2016, Sugarman et al. 2016).
Everyone benefits when health care stakeholders work together. Pharmacogenetics programs work best when there is management-level institutional support (Spellberg et al. 2016) and collaborative work between institutional stakeholders, such as the laboratory, pharmacy, information technology services, and primary care providers or selected specialties (cardiology, anesthesiology, psychiatry, etc.).

**Conclusions**

In the past few years, the range of applications and the enormous impact of pharmacogenetic panel testing was documented across an impressive number of institutions, both in the US and in Europe. Per-test costs for gene panels have decreased markedly, making preemptive testing—especially of selective chronic or multi-drug populations—a very real possibility. Most professionals in the field, supported by the extensive literature on pharmacokinetics translation and implementation, agree that pharmacogenetics will soon be used much more extensively in the US. While reference laboratories provide one route to pharmacogenetic testing, faster and more affordable lab platforms in combination with widely available software for reporting make it more practical to implement pharmacogenetics locally.

The full benefits of pharmacogenetics cannot be realized if testing capabilities exist only in reference laboratories. Some institutions start implementing pharmacogenetics programs with a targeted rollout to high-risk patients, (e.g., older patients with long medication lists and multiple chronic diseases). Other institutions have been successful using a different approach, rolling out pharmacogenetics to patients in targeted clinical areas like cardiology. Either approach can work. Best practices suggest that institutional support and participation make these programs successful. Therefore, clinicians must be aware of the value of pharmacogenetics, institutions must support the rollout, and pharmacy and electronic health system professionals should be available to cooperate.


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