Pharmacogenetic Testing May Improve Drug Treatments and Shorten Disability Leaves

This article describes how methods of personalized medicine—specifically, pharmacogenetic (PGx) testing—can benefit private health plans, benefits managers, care providers and consumers alike. The authors cover pharmacogenomics as a science and also introduce an innovative way to optimize drug treatments. The article touches on some important clinical outcomes drawn from a recent study in community pharmacy and reviews the application and return on investment of PGx testing in disability and medication management.

by **Antoine Lefaivre** | *GeneYouIn,* **Veronika Litinski** | *GeneYouIn* and **Maria Vandenhurk** | *Banyan World Health Solutions*

About Pharmacogenetic (PGx) Science

Everyone metabolizes medications differently. In fact, 90% of people have a genetic variation affecting drug response. Similar to how genetics can affect an individual's eye color, genetics also can determine an individual's response to medications. Two people can take the same dose of the same drug but respond in very different ways. A drug may cause serious side effects for one person but none for someone else.

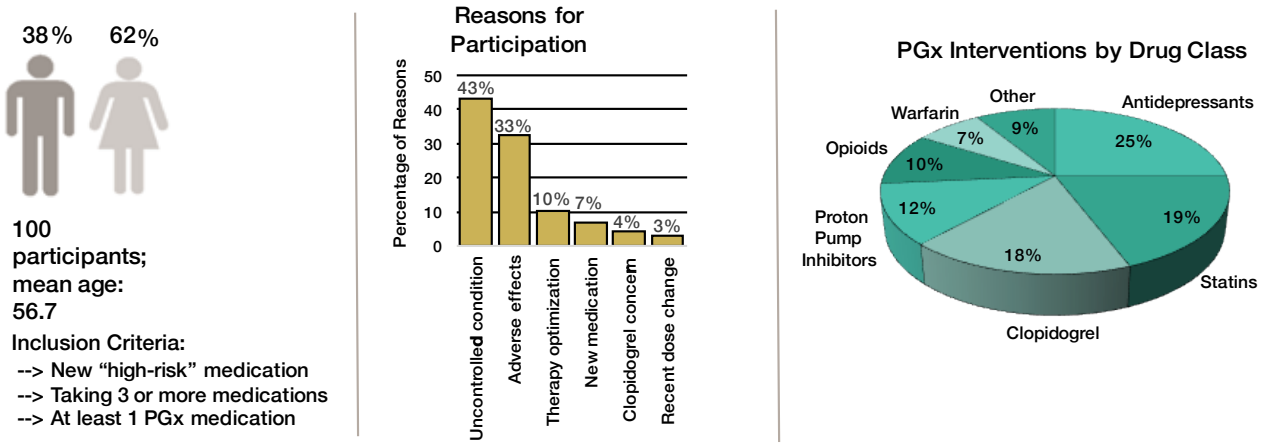
Ample clinical evidence links genetic variations in drug metabolic enzymes and transporters to variability of drug response in the general population. Leading health care providers in the United States are adopting PGx testing to improve quality and reduce cost of care. PGx testing helps reveal how the body is likely to utilize and react to (or *metabolize*) different drugs based on a person's genetic profile. It represents a key component of personalized medicine: individualized drug therapy.

The U.S. Food and Drug Administration (FDA) has been adding recommendations for PGx testing to drug labels[1] for commonly prescribed medications, many of which are now available in generic form, such as metformin, selective serotonin reuptake inhibitors (SSRIs), pro-opioids and cardiology medications. A handful of innovative platforms offer genetic tests and analytics with the aim of accelerating the medication adjustment process. These tests identify predictable genetic factors that influence an individual's medication response and optimize medication therapy by indicating the right drug at the right dose based on an individual's genetic profile.

PGx testing reduces the risk of adverse side effects and

FIGURE 1

Pilot Study: PGx Medication Optimization in Community Pharmacies



Source: J. Papastergiou, P. Tolios, W. Li, and J. Li. (J. Papastergiou is affiliated with The Leslie Dan Faculty of Pharmacy, University of Toronto; School of Pharmacy, University of Waterloo and Shoppers Drug Mart. P. Tolios and J. Li are affiliated with The Leslie Dan Faculty of Pharmacy, University of Toronto. W. Li is affiliated with Shoppers Drug Mart.)

improves efficacy and adherence. It also reduces cost to insurers by reducing adverse reactions and spending on ineffective drugs. A PGx profile also can have a lifetime value by helping a patient in the future when starting a new medication or undergoing minor surgery or hospital procedures.

How Do PGx Testing Applications Work?

Today, most medication services include PGx tests for more than 100 commonly used medications. A few services include an online medication review by a consulting pharmacist trained in PGx. Cost-effective genetic tests assess common variations in drug metabolic and transport genes. Testing can provide a personalized drug response profile and enable pharmacists to recommend changes in patients' prescriptions and treatment in accordance with the patient's drug metabolic profile. Medication optimization services reduce patients' treatment noncompliance, which often is due to their prior experience of, or simply anxiety over, side effects. It helps eliminate the use of inappropriate medications.

Web portals provided by PGx testing services typically are compliant with the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada. They enable effective communication among patients, case managers, pharmacists and physicians.[2] The portals collect patients' consent for testing and PGx medication review and also provide full transparency as to who has access to patients' PGx data.

A robust information technology platform for storing and sharing genetic information is essential for compliance with the data management requirements specific to health information in general and to individuals' genetic data in particular.

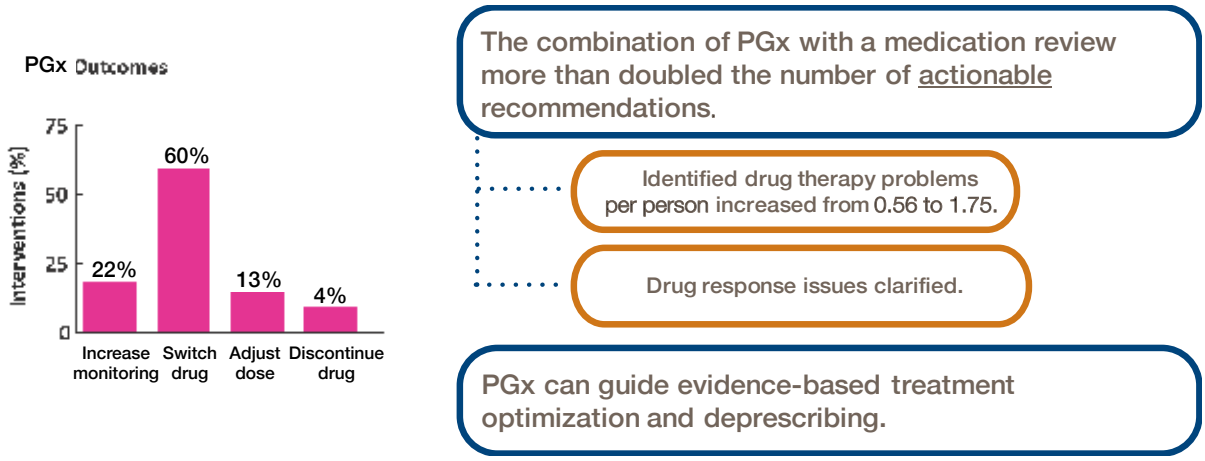
Community Pharmacy Practice Study

Two Toronto, Ontario–based community pharmacies undertook PGx profiling and medication reviews for 100 patients receiving three or more drugs, as well as patients starting treatment with one type of medication highly impacted by genetic variations (e.g., antidepressants, opioids and antiplatelets).

Patients were assessed with the standardized MedsCheck review, a provincial program in Ontario in which patients who are taking three or more medications are eligible for a pharmacist review to reduce risk of drug-drug interactions. The main reasons participants were selected for the study were that treatment was either ineffective or it caused side effects. Study participants provided informed consent and a cheek

FIGURE 2

Conclusion



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swab sample on site. PGx testing was conducted at a contract laboratory certified under the Clinical Laboratory Improvement Act. Upon receiving the PGx report, pharmacists provided a second medication review. When warranted, they also issued pharmaceutical opinion letters for the attending physician to expedite appropriate changes in therapy.

As shown in Figure 1, 100 patients were recruited over a three-month period. Their mean age was 56.7 years. The mean number of chronic medications was 4.9 drugs per person, of which 2.0 had PGx guidelines available. Pharmacist reviews identified 175 drug therapy problems (1.75 per individual), 119 (68%) of which were revealed by PGx testing. Pharmacists' PGx interventions consisted of a drug switch in 60% of cases, a change in dosage in 13%, medication discontinuation in 4% of cases and further monitoring in 22% (Figure 2).

The study indicated that integration of PGx information in clinical practice is a powerful tool physicians and pharmacists can use to individualize treatment. It should be viewed not simply as a cost-containment tool but also as a way to realize more value from effective medication management. Personalizing treatment options and minimizing trial-and-error approaches improve treatment outcomes by reducing adverse drug reactions and making patients more adherent to their drug therapy.

Integration Into Health Benefits—Landscape of Disability

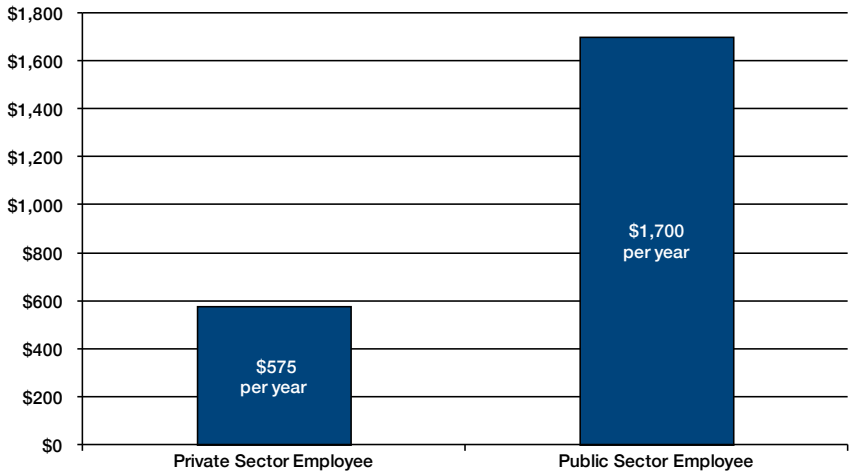
In Canada, disability claims are a significantly higher risk product in the benefit lineup than health and dental benefits. In fact, while disability represents 30% of premiums collected, it represents 56% of the risk capital required by Canada's Minimum Continuing Capital and Surplus Requirements to ensure the payment of those claims.[3] Unless disability claims are well-managed, benefits can become a significant liability. Successfully managing disability cases necessarily involves solid medical management and a complementary focus on functional and vocational requirements.

It is estimated that about half of employers in Canada do not track early-stage absence,[4] and even more fail to track it in a manner that allows for analysis and more effective management. Since 2000, there has been a steady rise in disability claims, with mental health contributing substantially to that rise. In 2012, the Conference Board of Canada estimated the cost of absenteeism to the economy at $16.6 billion, the brunt of it assumed by employers. The cost of early-stage absence, combined with long-term disability/absence, amounts to an annual expense of $1,700 per employee per year. The cost is high and shows no sign of abating.

It is broadly accepted that a smaller percentage of disabil-

FIGURE 3

Cost of Disability—Public vs. Private Sector



Source: Conference Board of Canada, September 2013 and *Benefits Canada,* August 2012.

ity cases represents the majority of the cost. Depending upon the work environment—public sector organizations tend to have much higher absence-related costs than those in the private sector (Figure 3)—the majority of the cost related to disability stems from approximately 20% to 40% of the cases.

These cases require additional investment and sophisticated case management tools and interventions to curtail duration and cost. The cases have a range of requirements, but a thorough medical intervention is first among them, the most crucial step to ensuring proper resolution of the case. PGx testing fits into this introductory stage. Without rapid and accurate medication management, other costly behavioral, cognitive and physical interventions generally have less impact. An effective drug regimen leads to improved symptom management and health outcomes and promotes better return-to-work performance. It also increases the impact of other interventions, all leading to shorter periods of disability. Duration is a somewhat hidden cost of disability. The length of time away from work represents a more substantial cost element than the actual costs typically attributed to management and interventions themselves.

The next section examines a disability case that presented significant challenges in terms of duration and reintegration to the workforce, essentially because the plan member was not receiving the right medication treatment.

Disability Case Study

Jane, a 27-year old woman diagnosed with anxiety disorder and depression, left work on January 13, 2015. She had a history of anxiety and depression dating back to her teens but had never been formally treated. During the onset of her claim, Jane's family physician tried several medications (from January through July 2015), including citalopram (Celexa®) and sertraline (Zoloft®), both of which were ineffective and caused side effects such as dizziness and drowsiness. Jane also had a history of nonadherence due to the limited benefits.

Jane's doctor referred her to a psychiatrist for a medication review in July 2015 and, in the interim, Jane continued to see her psychologist biweekly for cognitive behavioral therapy (CBT), with the goal of developing coping strategies to assist her with managing anxiety.

While awaiting the appointment with the psychiatrist, Jane began weaning herself off her medications and started working with a rehabilitation professional to whom Jane was referred by her long-term disability (LTD) insurer. The consultant recommended a PGx test.

The Process

Jane's case was reviewed against the eligibility and exclusion criteria, and she received a full description of the test and its potential benefits. Jane was receptive to the suggestion, and her insurer agreed to fund the test. Jane provided her formal consent and agreed to share the results of her test with her treatment team. She received her cheek swab kit in the mail 24 hours later and completed the test on the same day (November 5, 2015). The results were made available to Jane and her treatment team on November 17, 2015.

The results included a pharmaceutical review in which a pharmacist trained in PGx assessed Jane's medication profile and issued a pharmaceutical opinion letter to her treatment team. The opin-

ion highlighted that Jane was an intermediate metabolizer of antidepressants/antianxiety medications and sensitive to their inherent side effects. The opinion also indicated that "her previous symptoms of dizziness and nausea may have been linked to a higher dosage of medication accumulating in the body." The pharmacist recommended specific medications and dosages that would align with Jane's genetic capability to metabolize antidepressants/antianxiety medications.

The Results

In the subsequent appointment with her psychiatrist (November 23, 2015), he approved adjusting Jane's medications according to the recommendations outlined in the pharmaceutical opinion letter. More specifically, Jane started taking Celexa® again but at a much lower dose (of 5 mg) and was to increase very slowly every three to four weeks (to a maximum dose of 20 mg).

Impact

Jane began her new treatment on November 23, 2015 and, during a phone call with her rehabilitation consultant in late December, she reported that her mood had improved and her side effects had decreased. Jane's treating psychologist confirmed the improvement in Jane's mood.

Furthermore, when the rehabilitation professional called Jane's psychiatrist to discuss and review a return-to-work plan, the psychiatrist confirmed that Jane was making considerable improvements in regard to her anxiety and depression.

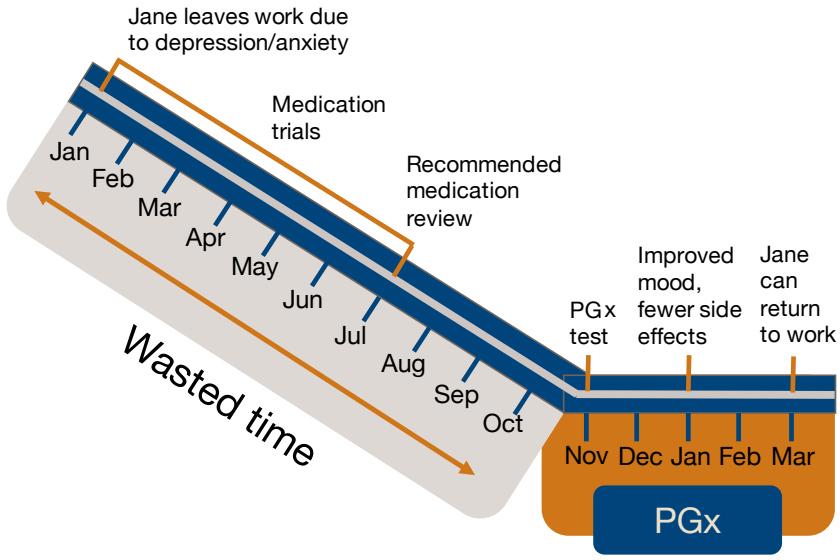
Return on Investment

Jane experienced an improvement in her symptoms within one month of receiving the results of her report (Figure 4). With continued counseling, and by adhering to her new medication regime (gradually increasing her dosage over three months), Jane returned to work in March 2016 (3.5 months from receiving the results of her report).

If Jane had been referred for PGx testing at the onset of her LTD claim, she likely would have returned to work much sooner. Based on the wage-replacement benefits paid to Jane in her occupation, the insurer could have saved more than $11,950 in total monthly benefits alone. Ideally, the test could have been performed even prior to the claim.

FIGURE 4

Jane's Course of Treatment Before and After PGx Intervention



Source: Banyan Work Health Solutions.

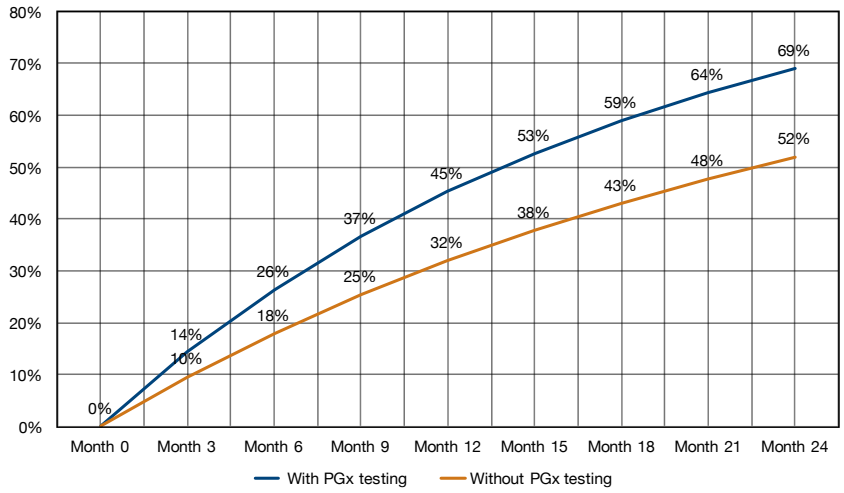
Return on Investment (ROI) Analysis Framework

Improved accuracy in drug selection and dosing, made possible using PGx in managing mental health, can lead to improved treatment compliance and earlier remission. This could represent an important economic benefit for both employer and the health care system. It has been documented that PGx testing increases the rate of remission and reduces the number of health care visits, absenteeism and length of disability. Modeling these outcomes for antidepressant users suggests that PGx testing will increase earlier remissions.

One economic model predicts that, on average, two years after treatment initiation, 69% of PGx users will have achieved full remission versus 52% for those not using PGx (Figure 5). Productivity losses are averted by getting plan members back to work earlier. With PGx testing, plan members suffering from a mental disorder require, on average, 78 days of absenteeism per individual over two years—35 fewer days than the 113 days for those who did not receive PGx testing.

FIGURE 5

Depression/Anxiety Remission Rate Over Two Years



Source: Economic model developed by GeneYouIn.

These averted productivity losses can be translated into monetary benefits. A day of lost work can be evaluated in wages an employer is willing to pay to replace that employee. Using an average Canadian wage of $200 per day, the 35 days of absenteeism averted by using PGx testing equates to $7,000 in averted productivity loss. In this respect, the systematic administration of a PGx test to plan members initiating antidepressant therapy carries a solid economic rationale. The productivity gain of bringing employees back to work faster and having them fully productive again is at least ten times greater than the cost of the PGx testing itself. Moreover, PGx testing in depression/anxiety can generate significant health care cost savings, including a reduction in drug spending ($200 per capita), reduced inpatient/outpatient/doctor visits ($800 per capita) and lower consumption of social services ($700 per capita).

Statistics show that one in four primary care patients in North America is prescribed at least one medication that will cause an adverse drug reaction because of genetic variability in drug metabolism.

A health-economic model using real drug claims data from private plans in Canada shows 5% to 14% potential savings for a health benefits plan when PGx is implemented for a multitude of conditions, including gastrointestinal disorders, cardiovascular health, pain and mental health management.

Broader Health Benefit Applications— PGx as a Drug Benefit

PGx testing has the potential to affect more than mental health treatment and recovery. The testing has been known to have a positive impact, for example, on individuals dealing with cardiovascular diseases as well as those suffering from chronic pain.

To illustrate the benefits of PGx in this setting, meet Jim, another real-life story. Jim suffered a heart attack while driving home from work. After a brief stay in the hospital, where doctors inserted a stent to open a blocked blood vessel, Jim was released with prescriptions for four different medications: aspirin and ticagrelor (Brilinta®) to reduce blood clotting, a statin and an antihypertensive drug. The cardiologist explained that these medications would reduce his risk for stroke or another heart attack.

While at the pharmacy, Jim learned that Brilinta® was an expensive therapy. Since he is self-employed, he would have to pay $800 per month out of pocket for his medication. During a followup appointment, the cardiologist explained that an older (and less expensive) drug called clopidogrel (Plavix®) is ineffective in more than 19% of patients, so he had prescribed Brilinta®. Soon after, Jim began experiencing side effects that are quite commonly associated with his drug regimen—Muscle aches and dizziness prevented him from returning to work.

Jim's wife decided to research the side effects of medications online and stumbled on a genetic test that revealed how patients respond to medications. The test showed that Jim could safely switch to clopidogrel and save $600 per month. Furthermore, based on the genetic test results, Jim's family physician decided to change his cholesterol treatment and prescribed rosuvastatin, which helped to reduce the muscle aches.

What would have happened if Jim had access to a health benefits plan through his employer? When a pa-

tient uses a medication that costs more but offers no clinical advantage, waste ripples throughout the system. He likely would not have been as concerned about the cost of his prescription drugs, and his employer would have likely absorbed that cost.

Conclusion

Rapid advancement in technology has made it possible to quickly and cheaply identify genetic variations that influence the effectiveness of commonly prescribed medications. The potential exists for payers to adopt initiatives to contain costs and increase the value of health care benefits. The integration of PGx into clinical practice provides physicians and pharmacists a powerful tool to individualize treatment, better manage costs and realize more value from effective medication management. BQ

Authors' note: The authors gratefully acknowledge consultations with Dr. Ruslan Dorfman.

Endnotes

1. U.S. Food and Drug Administration, "Table of Pharmacogenomic Biomarkers in Drug Labeling." Available at www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.
2. See www.osfi-bsif.gc.ca/eng/fi-if/rg-ro/gdn-ort/gl-ld/pages/mccsr2015.aspx.
3. Marla Dabboussy and Sharanjit Uppal, "Work absences in 2011." *Perspectives on Labour and Income.* Summer 2012, Vol. 24, No.2. Statistics Canada Catalogue No. 75-001-XIE.
4. Ibid.

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