Innovation in Personalized Medicine: The Role of Business Strategy and Public Policy in Providing Better and More Cost-Effective Healthcare through PGx

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Abstract: Innovative use of personalized medicine in routine clinical practice can both improve healthcare outcomes and reduce costs. Numerous trials demonstrate the clinical benefits of pharmacogenetic patient stratification. Despite the recommendations of several organizations, pharmacogenomics and pharmacogenetics (PGx) have not yet achieved routine implementation in the healthcare systems of Canada, the U.S., and other countries. Barriers to PGx implementation include cost, technical, and strategic issues. This article highlights viable ways for corporate and public players to move past the stumbling blocks in order to reap the full benefits of PGx.

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Introduction to personalized medicine: Improving care and reducing costs

Traditionally, medical treatment relies on applying standard protocols to patients with a given diagnosis. In contrast, personalized medicine tailors treatment to the individual, for example, based on personal history and relevant risk factors (e.g., smoking, diet, exercise and prescribed medications). Pharmacogenetics and pharmacogenomics (here abbreviated together as PGx) refer to using a patient's genetic marker profile and gene expression profile, respectively, which can help guide their care. PGx considers whether a patient is likely to respond to a specific treatment based on their genetic profile and therefore informs whether they should be prescribed treatment such as a certain drug. Drug prescription based on a PGx approach is likely to result in better clinical outcomes for patients, by potentially reducing the occurrence of adverse side effects and treatment failure. In the U.S., for instance, adverse drug events affect one in five outpatients and one in eleven inpatients, and cost at least $80B per year [1, 2]. PGx may therefore lead to more cost-efficient use of medical resources as well as improved care, because better patient outcomes may reduce costs that can arise from treatment failure and adverse drug events.

Despite the recommendations of several organizations, including the FDA, personalized medicine so far has achieved only limited use in clinical settings, with some application in oncology but little in common complex care. The lack of uptake stems from several interdependent issues, including cost, technical, and strategic issues. In this article, we will discuss these barriers to PGx implementation. We will address strategic innovations to overcome key issues at the level of public and corporate involvement.

A. Cost issues

While there is an initial cost to genetic testing that may impede PGx implementation, PGx has the potential to reduce medical expenses, considering the relatively low cost of testing vs. the high costs of unnecessary treatment and treatment failure. The cost of genetic testing has decreased, with further savings gained when a single test can assay for responses to several drugs. To further analyze the costs of PGx, research is being done on how to best evaluate the medical and economic viability of PGx implementation, as well as how to model the time and financial investment needed to achieve improved health outcomes with PGx. Evaluations of PGx require a long-term view involving multiple streams of health care, because there may be initial financial investments involved before long-term benefits are seen.

PGx in chronic disease: cost savings and health benefits. Healthcare providers in countries throughout the world face pressure to control drug expenditure. In 2010, Canadian spending on prescription medications alone exceeded $26.1B, $12.1B of which was financed by the public sector.[1] In the U.S., as we noted above, adverse drug events cost over $80B each year [1, 2]. Personalized medicine and PGx provide the opportunity for more cost-efficient use of medical resources (see Appendix: Case Studies), as is the case with PGx-driven cancer treatments. The cost for targeted cancer therapy is high (e.g., treatments with trastuzumab [Herceptin] and cetuximab [Erbitrux] typically cost $30,

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[1] http://secure.cihi.ca/cihiweb/products/drug_expenditure_2010_en.pdf

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000-$100, 000 per patient), whereas genetic testing typically costs only $300-$1,500. These drugs also have limited impact on duration of patient lives, resulting in very high costs per quality-adjusted life year (QALY) ($5,020 to $134,610 per QALY). The use of PGx improves therapeutic and economic outcomes by focusing expensive drug treatment on patients who are most likely to respond to the drug. This focus also spares patients from treatment side effects, which can be debilitating, unless the patients are likely to benefit from the treatment.

While drug costs for complex chronic diseases (CCDs) such as diabetes, cardiovascular problems, and arthritis are comparable to those for cancer, the medical expenses that arise from treatment failure due to suboptimal or incorrect drug treatment can be even greater. For example, inadequate anticoagulation and antiplatelet treatment of stroke patients leads to a high risk of stroke recurrence, which may cause severe long-term disability or sometimes result in death. The average cumulative direct costs of long-term care for a stroke patient if treatment fails are estimated to exceed CDN$50,000. Indirect costs to society, such as loss of worker productivity and family income, are estimated to be even higher. Considering that stroke patients account for over 20% of patients in long-term care in regions such as Ontario (Table 1), for instance, the health burden of stroke treatment failure is high. Similarly, the economic burden of cardiovascular diseases, which affect a large number of patients (Table 1), is higher than that for cancers in Canada (CDN$24.8B for cardiovascular diseases vs. CDN$17.1B for cancers in 1998). [2]

CCDs often result in the prescription of multiple symptom-specific drugs for a given patient. Polypharmacy leads to a substantial increase in risk of complications and adverse side effects due to drug interactions [3]. Moreover, the drugs prescribed may not address patients' symptoms, because many patients do not respond to one or more forms of medication due to genetic variations in drug metabolism, transport, and drug target genes [4, 5] (Table 2). By minimizing the risk of adverse side effects, PGx reduces or eliminates the need for additional medications to treat side effects, potentially reducing unnecessary polypharmacy. Considering the potential impact of personalized medicine on both health outcomes and cost savings, it is timely to investigate PGx use in these and other chronic complex diseases.

Beyond one drug - one gene testing. Genetic testing is becoming more accessible as costs of genome sequencing decrease, with exome sequencing available for less than $1,000 and genome sequencing likely available within the next two to three years. While single nucleotide polymorphisms (SNP) array technology typically tests for specific gene variants for only one drug at a time, exome sequencing improves on the current "one drug - one gene" testing approach. Exome sequencing analysis can evaluate an established subset of markers proven useful for clinical recommendations, and importantly, the sequence information can be stored and accessed at a later date to obtain information on other genes or drugs. For instance, patients' information can be accessed when they require new prescriptions or when new information on genetic markers becomes available.

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[2] http://secure.cihi.ca/cihiweb/products/drug_expenditure_2010_en.pdf

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Sequence information can also be used to speed up the validation of new genetic tests, by re-analyzing patient data in light of new variant-drug response associations. Since there are low marginal costs of evaluating additional gene variants in the same test, this saves on the set-up costs of re-testing with updated PGx panels. A substantial proportion of genetic testing expenses involve the costs of collecting samples, genotyping, processing genetic data, and maintaining health records, in addition to the direct costs of sequencing. Therefore, comprehensive genetic testing through genome or exome sequencing, amortized over even part of a patient's lifetime, can provide substantial savings compared to repeat testing for additional drugs as needed.

The approach of testing for multiple genes within one test is currently being used for *CYP* genes. Genetic variations in *CYP* genes, which encode the cytochrome P450 enzymes, account for up to 75% of all drug metabolism. Extensive genotyping panels for variations of *CYP* genes have been developed and are being used to predict the potential efficacy of several medications [4, 5], with the possibility of using the same genetic information for additional medications in the future.

Evaluating cost-effectiveness. While the lower costs of genetic testing are promising, evaluation frameworks are needed to further assess whether PGx approaches are cost-effective. Pharmacogenetic testing is medically and economically viable when the genetic test is less expensive than the cumulative cost of treatment, can predict substantial disease risks that could be addressed by earlier intervention, and/or can predict severe adverse side effects that could be avoided. Such assessments require broad patient populations and substantial time to observe the impact of trials and clinical experiences [6]. For instance, the ACCE model assesses analytical validity, clinical validity, and utility, as well legal, ethical, and social implications [7-9]. In Canada, Healthcare Technology Assessment is used as an evaluation model, but currently evaluations are typically limited to a single indication (gene, disease, or drug) with a one drug - one gene testing approach, which risks under-estimating the benefits of genetic testing. To provide a more realistic estimate of the costs involved in using exome or genome sequencing, health economic evaluations would benefit by analyzing scenarios where PGx stratification incorporates testing for multiple drugs within one test.

Modeling the costs and benefits of PGx. Models of the costs and benefits of PGx are useful for helping predict the course of PGx implementation. Arnaout et al. recently used quantitative modeling to predict the time and financial investment needed for PGx variant discovery, validation, and incorporation into clinical guidelines for a reduction in overall drug-related adverse events [10]. Their model predicted that a reduction in drug-related adverse outcomes by 25%-50% would require an investment in the single-digit billions of dollars over twenty years. Interestingly, their analysis predicts that the first five to seven years would represent a priming phase with only a few validated guidelines created then, resulting in little apparent return on investment initially. It is therefore important to consider the long-term benefits of PGx and address initial barriers to investment.

B. Technical issues

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Genetics is a rapidly advancing field of science, but at least two key technical issues concerning variation in markers and standardization need to be addressed for successful implementation of PGx in the clinic.

Variation in markers. The predictive value of genetic testing is directly linked to the number of genetic variants being tested in a gene, with a higher number of variants linked to greater predictive value. In our evaluation of pharmacogenomic stratification of stroke treatments [14], we found significant variation in the number of markers used for PGx tests. Using genotyping panels with few markers often substantially reduces the predictive power of PGx tests. Moreover, PGx approaches may perform poorly in some ethnic groups because some ethnicity-specific variants have not yet been identified. For example, using only two or three SNPs that are common in Caucasians for genetic stratification of a large patient population abolished the predictive value of the test because it did not capture ethnicity-specific variations [15]. Further research is needed to identify additional markers to be included in panels, particularly markers specific to different ethnic groups. Better test performance can be achieved with expanded genotyping panels that include more markers and/or targeted gene sequencing approaches that capture a greater number of relevant variations [16].

Standardization. There is a lack of clinical data on PGx effectiveness and, importantly, available data is not always presented in the same format. Standardization of trial design, including number of markers to analyze, data analysis techniques, and reporting formats would greatly improve assessment of PGx clinical utility across studies. In turn, better assessment of PGx utility would encourage healthcare providers to use new genetic tests.

To be of practical use to healthcare providers, electronic medical records (EMR) technology needs to be standardized. Current electronic medical records (EMRs) have limited data sharing capabilities between healthcare providers, inhibiting the clinical integration of pharmacogenomic data with patient medical records [18]. Standardized EMRs would allow data to be easily transferred between different healthcare providers, institutions, and jurisdictions. In part, this requires regulatory action. In Canada, for instance, Health Canada and provincial regulatory agencies could work to create unified policies for PGx test evaluation and reimbursement.

C. Strategic issues: Limited public resources and misaligned corporate incentives

To date, there has been only limited investment in PGx by the pharmaceutical industry, academic scholars, and public agencies. Barriers to PGx development and implementation arise from limited resources for PGx investment in the public and academic sectors, together with the appearance of misaligned incentives from pharmaceutical companies.

In Canada, regulatory bodies in some provinces, including Ontario, are now encouraging hospitals to improve quality of care, which could be achieved through personalized medicine approaches. However, hospitals lack the relevant underlying infrastructure to implement PGx and do not have clear clinical guidelines on PGx protocols. Indeed, no comprehensive assessments of PGx implementation challenges for hospitals and primary care practices have been conducted.

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In addition to investment in PGx implementation, investment is required for the development of pharmacogenomic markers to predict the efficacy of new drugs and the risk of adverse drug reactions. The FDA and other regulatory agencies place the onus on pharmaceutical companies to develop predictive biomarkers. However, critics commonly suggest that this presents a conflict of interest within the proprietary pharmaceutical industry. Pharmacogenetic and -genomic stratification, at least initially, reduces the market size for a given medication, so that stratification appears to work against the immediate commercial interests of drug developers and marketers. This conflict has been partially resolved in oncology, where high disease heterogeneity strongly benefits from pharmacogenomic stratification in order to demonstrate a drug's clinical efficacy. With complex chronic diseases, however, pharmaceutical companies may face weaker motivations to develop markers for drug efficiency, because the cost of CCD medications is typically low and many are produced as generic drugs. We will later turn to ways to resolve the apparent conflict of interest (see Section D).

Market penetration of generics is increasing in countries throughout the world (generics account for over 75% of prescriptions in the U.S. and now more than 50% of prescriptions in Canada). While costs for developing markers for generic drugs are at least as high as those for brand names, PGx marker development for generics is the realm of academic researchers, who lack the resources to bring PGx tests through regulatory approval. For example, the pharmacogenomic stratification of warfarin dosing was developed in the early 2000s, but its screening is yet to be implemented in clinical practice in Canada. Lack of funding impedes PGx regulatory test approval for generics, even though substitution of branded drugs with generics ultimately reduces drug expenditure. Indeed, use of PGx with both brand name and generic drugs could substantially reduce costs and improve quality of care.

D. Business strategy as a champion of PGx

One approach to developing PGx would be to put the onus on public agencies and/or academic scientists. Indeed, academia and nonprofit consortia (such as PharmGKB) are currently the main driving forces in pharmacogenetics. However, this approach risks being stranded due to the lack of resources and power to facilitate implementation in clinical practice [18, 19]. Therefore, it is useful to consider how potential corporate players, including pharmaceutical companies, pharmacies, and insurance companies can incorporate PGx in their competitive business strategies. This would serve as an incentive to invest in PGx, helping to bring PGx into the clinic.

PGx as a competitive strategy for branded pharma. Large pharmaceutical and diagnostics companies face disincentives to launching PGx testing due to fear of limiting the blockbuster potential of new drugs. Companies also hesitate due to the need to invest in companion diagnostics and the fear that once a test passes through certification, its use can rapidly become obsolete. This situation often discourages investments in molecular diagnostics. However, thoughtful analysis suggests that incorporating PGx can lend a competitive advantage to business strategies.

Pharma companies aspire to achieve blockbuster drug sales in excess of $1 billion a year, but attempts to attain blockbuster sales positions often fail. Rather than aim for blockbuster status and fail, many potentially effective medications could find profitable

market positions by targeting specific audiences instead. For example, Vioxx (rofecoxib) was marketed as a blockbuster pain medication, but was withdrawn from the market due to identified incidence of heart attacks. Vioxx may have succeeded if it was marketed to a targeted audience, such as patients with lower risk of cardiovascular disease who were susceptible to gastro-intestinal bleeding. Pharmaceutical companies would benefit from investigating the genetic components of severe side effects and drug efficacy. They could then use this information for marketing approaches that screen out high-risk patients and target low-risk patients. In this way, PGx may help position drugs for long-term success.

Success in targeted sales positions often helps a drug retain sales following patent expirations. While there is hesitation to investing in diagnostics, patients' and physicians' perceived value of companion diagnostics allows pharmaceutical companies to sell their medication beyond patent expirations as part of drug-diagnostic test combinations. This allows pharmaceutical companies to regain the money spent on diagnostics through sales. For instance, Eli Lilly, Sanofi, and Novo Nordisk sell not only insulin and insulin delivery systems, but also blood glucose testing systems, which function together as comprehensive care packages. PGx comprehensive care packages can gain significant consumer loyalty due to ongoing use and habit, and can help pharmaceutical companies retain sales for their post-patent drugs.

The antiplatelet drug clopidogrel (Plavix) offers an example of where using PGx could help retain sales after patent expiration. Plavix is co-marketed by Bristol-Myers Squibb and Sanofi; its patent expired in 2012. The drug is highly effective in patients with gain-of-function mutations in the *CYP2C19* gene [15] but is now facing both generic competition and growing market penetration of an alternative blood thinning drug, prasugrel (Effient) from Daiichi Sankyo and Eli Lilly. Prasugrel is marketed as a superior choice because its efficacy is not affected by variations in the *CYP2C19* gene, whereas up to 25% of patients have mutations in *CYP2C19* that may lead to reduced response to clopidogrel. One way Plavix manufacturers could protect against this competition is by offering complementary PGx testing for current Plavix users. Patients who are good metabolizers may choose to stay on Plavix, rather than switching to the more expensive prasugrel. This may allow Plavix manufacturers to retain a substantial share of their customers.

Insurance companies may also benefit from cost savings by offering reimbursement for branded Plavix to good Plavix metabolizers and offering reimbursement for more costly prasugrel only to poor Plavix metabolizers. In negotiations with insurance providers, pharmaceutical companies could seek coverage for PGx testing together with continued reimbursement for the branded versions (such as Plavix) beyond patent expiration, thereby reducing the threat of generic and alternative drug competition. As an example, the pharmacy benefits management provider, Medco, is conducting clinical trials on the pharmacogenomic stratification of clopidogrel (NCT00995514); the trials build on existing cost-effectiveness analysis that demonstrates the superiority of genotype-driven clopidogrel dosing compared with prasugrel [20, 21]. Hence, pharmaceutical and insurance companies can use PGx to inform their business strategies.

Insurance providers. Public and private insurers would benefit from PGx implementation due to reduced expenses of drugs, hospitalization, and rehabilitation costs.

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In the U.S., insurance providers such as Medco and Aetna already incorporate PGx in their strategies and are leading the validation of pharmacogenomic tests through sponsoring controlled clinical trials.

Generic manufacturers and pharmacies in the PGx value chain. Generic pharmaceutical leaders such as Teva, Sandoz, and Apotex, together with pharmacy chains, can also benefit from pharmacogenetics. Generic manufacturers typically offer a large variety of medications. Given their substantial portfolios, genetic testing using expanded genotyping panels can inform physicians, pharmacists, and patients about the metabolic status of numerous drugs. Generic producers could team up with pharmacy chains and provide funding for genetic testing services, while the pharmacies commit to stocking a large number of the producer's medications. The producers and pharmacy chains would offer free or subsidized PGx information to physicians as a package service. Physicians would then refer patients to specific pharmacies for PGx testing, while pharmacies dispense drugs from a specific generic supplier to referred patients, thus offsetting the generic producer's investment in genetic testing through increased sales. Pharmacies could enter long-term deals (e.g., three to five years) with generic producers and physicians, thus ensuring a supply of customers.

E. Practical actions

Developing a strong PGx testing foundation that leads to better healthcare and lower healthcare costs requires both corporate and public actions. Here we summarize the actions required by different stakeholders to achieve this goal, involving business strategy, reimbursement policies, and electronic medical records.

Business strategy. Relevant corporate players in pharmaceutical, diagnostics, insurance, information systems, and other firms need to recognize PGx as a valuable strategic option. This parallels the growing recognition in the pharmaceutical industry that traditional drug development and marketing practices are increasingly challenged. Indeed, the challenge for these players is more a matter of strategic mindset than it is of any inherent technical or organizational barriers to developing PGx strategies.

Reimbursement policies. Within current medical practice, pharmacogenomic testing is most likely to be initiated in hospital settings. Some tests demand rapid turnaround times, such as those required for warfarin dosing, where patients in the first ten days after stroke have higher rates of adverse side effects and stroke recurrence. Yet reimbursement policies in many settings create delays, impeding the use of tests that need fast turnaround. In Ontario, for instance, in order for a patient to receive reimbursement, the use of a genetic test requires pre-approval by the Ontario Ministry of Health. This makes it impractical for testing to be done by hospitals, since patients are often released or transferred by the time test results arrive. Thus, more flexible reimbursement policies should be created to facilitate the uptake of pharmacogenetics.

In addition, the use of PGx in chronic disease management leaves hospitals at a disadvantage, as they are expected to make the necessary investments in testing without additional funding. Genetic testing should not be perceived as an added economical and logistical burden on the healthcare system, but rather as a public health initiative.

Effective use of PGx will require changes in reimbursement policies not only for disease management but also for disease prevention. This has strong potential because the

underlying power of pharmacogenetics, similar to vaccination programs (see Table 3), stems from prevention rather than primary intervention. Current therapeutic strategies typically manage, rather than cure, chronic diseases. Once a severe disease has been manifested and clinically diagnosed, it is virtually impossible to reverse its clinical course. Early behavioral interventions, such as diet and exercise for type 1 diabetes prevention, have been shown to delay disease onset even better than some preventive medications. Using disease prediction and PGx diagnostics to optimize prevention measures can therefore be a powerful way to delay disease onset.

Prevention measures can be implemented for family members of patients with chronic diseases. Genetic testing of individuals with chronic diseases can be used to inform their family members about shared genetic and environmental risks. Genetic counselors or other healthcare professional can motivate family members to make behavioral changes to reduce their risk of developing chronic diseases. PGx test reimbursement by private and public insurers would benefit by including reimbursements for genetic counseling and allow for the expansion of disease prevention programs administered through long-term care facilities. While providing funding for these initiatives, insurance companies will later save on reimbursement costs over patients' life cycles via the reduction in costs of avoidable medical treatments.

Electronic medical records and decision support tools. Effective integration of electronic medical records (EMRs) into clinical practice is essential for PGx uptake and information dissemination across levels of the healthcare system. The need to incorporate additional pharmacogenomic biomarkers and diagnostics into patient records in the future demands for a flexible system that includes electronic medical records, diagnostic laboratory results, and decision-support tools. Effective implementation of PGx requires the use of EMRs that are accessible both to patients and healthcare providers. Increased EMR accessibility, data sharing and better drug information reduce the demand for physicians' time and reduce guesswork and medical errors. Patient access to EMRs can decrease the perception of a power distance between physicians and patients and, in turn, provide patients with a sense of control in their care and greater understanding of the healthcare system. Such advances in EMRs and healthcare technology will require action by private health information systems providers, healthcare providers, and public agencies that set standards and incentives for EMR use.

F. Concluding comments

Personalized medicine is an untapped resource that can significantly improve healthcare outcomes and provide cost savings through the optimization of drug treatments. However, the misalignment of incentives affecting various stakeholders currently impedes extensive PGx implementation. With the use of personalized medicine, public and private actors have a unique opportunity to change current clinical practices. This will occur by implementing evidence-based guidelines that account for genetic variability in disease susceptibility and drug response. The innovations are attainable within current technological trajectories, primarily requiring changes in business strategy, public reimbursement policies, and the availability of electronic medical records.

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Table 1: The distribution of diagnoses among assessed patients in long-term hospital based and residential care in Ontario (2010-2011)

Disease Diagnosis	Hospital-Based Continuing Care		Residential Care	
	N	%	N	%
Endocrine/Metabolic/Nutritional Diseases	**7,242**	**38.3**	**36,288**	**38.2**
Heart/Circulation Diseases	**13,466**	**71.3**	**65,758**	**69.3**
Musculoskeletal Diseases	**8,313**	**44.0**	**51,485**	**54.2**
Neurological Diseases	**10,312**	**54.6**	**70,897**	**74.7**
Dementia	4,912	26.0	53,198	56.0
Amyotrophic Lateral Sclerosis (ALS)	82	0.4	114	0.1
Aphasia	1,626	8.6	5,873	6.2
Cerebral Palsy	121	0.6	544	0.6
Cerebrovascular Accident (Stroke)	4,210	22.3	20,144	21.2
Hemiplegia/Hemiparesis	1,997	10.6	4,861	5.1
Huntington's Chorea	47	0.2	261	0.3
Multiple Sclerosis	343	1.8	1271	1.3
Paraplegia	340	1.8	465	0.5
Parkinson's Disease	807	4.3	6437	6.8
Quadriplegia	506	2.7	276	0.3
Seizure Disorder	1,122	5.9	5,021	5.3
Transient Ischemic Attack (TIA)	749	4.0	4644	4.9
Traumatic Brain Injury	447	2.4	832	0.9
Psychiatric/Mood Diseases	**5,497**	**29.1**	**32,798**	**34.5**
Pulmonary Diseases	**3,576**	**18.9**	**15,679**	**16.5**
Sensory Diseases	**2,597**	**13.7**	**20,831**	**21.9**
Other Diseases	**12,459**	**66.0**	**49,658**	**52.3**
Total Number of Assessed Residents	**18,888**	**-**	**94,939**	**-**

Note: The numbers do not add up to the "Total" line at the bottom, because many residents had multiple disease diagnoses.
Source: Canadian Institute for Health Information (www.cihi.ca)

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Table 2. Examples of gene variations that affect drug metabolism and/or clinical efficacy.

Gene	Encoded enzyme	Drugs affected by variations in the gene
CYP1A2	cytochrome P450 1C2	alosetron, clozapine, flutamide, frovatriptan, mexiletine, mirtazapine, olanzapine, ramelteon, rasagiline, ropinirole, tacrine, theophylline, tizanidine, triamterene, zolmitriptan
CYP2D6	cytochrome P450 2D6	serotonin reuptake inhibitors (SSRIs), tricylic antidepressants (TCA), beta-blockers (Inderal), type 1A antiarrhythmics
CYP2C19	cytochrome P450 2C19	Plavix, carisoprodol, diazepam, Dilantin, Prevacid
CYP2C9	cytochrome P450 2C9	warfarin, Amaryl, isoniazid, ibuprofen, amitriptyline, Dilantin, Hyzaar, THC (tetrahydrocannabinol), naproxen, Viagra
VOCR1	vitamin K receptor	warfarin
CYP3A4	cytochrome P450 3C4	immunosuppressants (ciclosporin, tacrolimus), chemotherapeutics (docetaxel, tamoxifen, paclitaxel, cyclophosphamide, doxorubicin, erlotinib), azole antifungals (ketoconazole, itraconazole), macrolides (clarithromycin, erythromycin, telithromycin)
NAT2	N-acetyltransferase 2	isoniazid, procainamide, Azulfidine
UGT1A1	UDP-glucuronosyltransferase	Camptosar (irinotecan)
DPD	dihydropyrimidine dehydrogenase	fluorouracil (5-FU)
5HTT	serotonin transporter	SSRIs (citalopram, fluoxetine, paroxetine)

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Table 3. Parallels between PGx and vaccination programs

- **Small short-term effects.** Both programs have relatively small immediate effects for vaccinated or gene-tested individuals.
- **Reduction in long-term disease risk.** PGx testing and vaccination both reduce disease risks in the long-term. Risk reduction is often relatively small for individuals but can have enormous impacts on healthcare costs for entire populations. The degree of benefits depends on the scale of deployment: insufficient investment and penetration does not generate enough impact for network effects to take hold.
- **Collective immunity.** The "collective immunity" model applies to both vaccination and genetic testing. PGx-screened individuals tend to become more acutely aware of available disease-risk mitigation options such as pharmaceuticals, changes in lifestyle, and other effective preventive disease-reduction strategies.
- **Impact on social and economic development**. Vaccination programs have played an essential role in improving healthcare systems in developed countries and are increasingly having the same impact in lower and middle income countries. PGx may similarly help transform healthcare systems in Canada and other developed countries. PGx would necessitate the use of evidence-based treatment practices, and lead to better integration of health informatics systems into clinical practice and a greater focus on disease prevention. These advances are equally relevant for social and economic development in lower and middle income countries.
- **Initial investment**. Both vaccination and pharmacogenomic testing require significant upfront investment. The payoff comes later with a reduced disease burden, which improves health and saves money for the healthcare system several years after the investment.
- **Corporate, academic, and public engagement**. Both vaccination and PGx require active engagement by corporate, academic, and public agents in R&D, reimbursement, and supporting frameworks.

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Appendix: Case studies - Cost-effectiveness of personalized medicine

1) **Warfarin**: Warfarin is an anticoagulant medication commonly prescribed to prevent and treat blood clots for stroke patients [11]. The optimal dose of warfarin varies greatly from person to person. A dose that is too high puts the patient at risk of serious bleeding, whereas a dose that is too low increases the patient's risk of stroke. Genetic testing can assess whether or not a patient is a slower warfarin metabolizer and, therefore, whether they would likely benefit from a higher or lower dose. A model evaluating warfarin genetic testing in the U.S. estimated that genetic testing prior to warfarin use could prevent 85,000 serious bleeding events and could avoid 17,000 strokes annually [11]; the estimated cost savings were $1.1B per year, with a range of $100 million - $2B.

2) **Imatinib**: Chronic myeloid leukemia (CML) accounts for 15%-20% of adult leukemia cases [12]. In many instances, patients have an aberrant chromosome called the Philadelphia chromosome, resulting in production of a constitutively active protein. The drug imatinib (Gleevec) targets this protein and can be used for patients who have Philadelphia chromosome-positive CML. A study estimating the cost-effectiveness of imatinib found that, compared to interferon-α plus low-dose cytarabine, imatinib is a cost-effective first-line therapy in patients with newly diagnosed chronic-phase CML [12].

3) **HIV resistance testing**: Drug resistance can limit the effectiveness of highly active antiretroviral therapy (HAART) for HIV treatment [13]. Genotypic antiretroviral resistance testing (GART) is used to determine if the HIV virus has mutations that are associated with drug resistance. This information is used to help select effective HAART regimens after antiretroviral therapy failure. A model estimating the cost effectiveness of GART found that use of GART after treatment failure led to longer AIDS-free survival, an increase in life expectancy and was cost-effective [13].

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