The 3-I Framework: a framework for developing public policies regarding pharmacogenomics (PGx) testing in Canada

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**The 3-I Framework: a framework for developing public policies regarding
pharmacogenomics (PGx) testing in Canada**

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Abstract

The 3-I framework of analyzing the “ideas”, “interests”, and “institutions” around a topic has been used by political scientists to guide public policy development. In Canada, there is a lack of policy governing pharmacogenomics (PGx) testing compared to other developed nations. The goal of this study was to use the 3-I framework, a policy development tool, and apply it to pharmacogenomics testing to identify and analyze areas where current policy is limited and challenges exist in bringing pharmacogenomics testing into wide-spread clinical practice in Canada. A scoping review of the literature was conducted to determine the extent and challenges of PGx policy implementation at federal and provincial levels. Based on the 3-I analysis, contentious ideas related to PGx are (i) genetic discrimination, (ii) informed consent, (iii) the lack of knowledge about PGx in health care, (iv) the value of PGx testing, (v) the roles of health care workers in the coordination of PGx services and (vi) confidentiality and privacy. The 3-I framework is a useful tool for policy makers, and applying it to pharmacogenomics policy development is a new approach in Canadian genomics. Policy makers at every organizational level can use this analysis to help develop targeted PGx policies.

Key words: pharmacogenomics, pharmacogenetics, health policy, 3-I framework, genetic testing

Introduction

The notion of utilizing personalized medicine and pharmacogenomics to improve health outcomes in Canada is now becoming a reality. Recently, a family practice clinic, in partnership with the Center for Addiction and Mental Health (CAMH) became the first primary care center to offer genetic testing in Canada to determine how patients will respond to psychiatric medication (Center for Addiction and Mental Health, 2013). The current Canadian government has announced an investment of \$67.5 million for research in personalized medicine and \$165 million in 2014–15 to support Genome Canada's multi-year strategic plan (CIHR-IRSC, 2012; Industry Canada, 2013). While personalized medicine has just begun to be incorporated into clinical practice and funding for research is increasing, policies are lacking to enable personalized medicine and pharmacogenomics testing as a routine service in the Canadian health care system. Who will be providing and financing services, who should be able to requisition the technology and how the information will be used are questions that do not have defined answers today at a federal or provincial level. Not having clear guidelines and policies in place before the technology permeates extensively into clinical practice may have detrimental economic, ethical and operational effects, but also gives health care providers, consumers and service providers free reign in the procurement and use of testing.

Pharmacogenomics (PGx) is defined as the study of variations of DNA and RNA characteristics as related to drug response. PGx includes pharmacogenetics which is defined as the study of variations in DNA sequence as related to drug response (Health Canada, 2008). The ultimate goal of PGx is reflected in the statement, “the right treatment to the right patient at the right time” or, “therapy with the right drug at the right dose in the right patient” (Mancinelli et al.,

2000; Redekop and Mladsi, 2013). An example of PGx in Canada includes testing for genetic variants causing deficiency in the drug metabolizing enzyme thiopurine methyltransferase prior to treatment with thiopurines – a common class of drugs used to treat patients with inflammatory bowel disease, acute lymphoblastic leukemia and other conditions (Donnan et al., 2011).

Another example is the testing of genetic variants in the gene that codes for the enzyme responsible for the metabolism of warfarin, an anticoagulant drug prescribed to prevent thromboembolic events (Ontario Health Technology Advisory Committee, 2011).

Pharmacogenomic testing can be particularly useful in providing information on the variability in drug response among different people. Therefore, it can be a useful tool in predicting who will be better responders to certain drugs and predicting who may suffer certain adverse reactions to a certain drug treatment. Effective treatment without adverse events is a universal aspiration for health care. However, getting there with PGx raises new concerns about existing values surrounding genetic information, its value and its use.

Adverse drug reactions (ADR) are the seventh leading cause of death in Canada after cancer, heart disease, stroke, pulmonary disease and accidents and prolong hospital stay by an average of 4.6 days and cost \$300 million per year (1995 statistics) (Squires et al., 2005). Other data suggest that 3.1% of hospitalized patients experienced any type of ADR and 3,600 hospital deaths occur annually due to an ADR in Canada (Rawson, 2013). It is anticipated that PGx testing could reduce adverse drug reactions and the associated costs of treating ADRs.

Most drugs are only effective within 50-75% of the treated population and cancer chemotherapies are only effective in 25% of those treated (Spear et al., 2001). PGx testing prior

to drug treatment may therefore help to avoid the current trial and error approach to treatment and get the right treatment to the right patient. PGx is unique as a new technology since it requires the incorporation of a new technological platform in our health care system, requires a new knowledge base for its use, and has begun to be offered directly to consumers in certain cases. This is in contrast to the existing panel of available clinical chemistry tests. PGx is a new and rapidly-expanding technology. Fully realizing its potential to improve healthcare brings with it ethical, regulatory, economic and delivery challenges which can be addressed through adequate policy implementation. In the case of PGx this means creating policies where they currently don't exist, at all appropriate levels of governance. The goal of this study was to use the 3-I framework of examining ideas, institutions, and interests and apply it to pharmacogenomics testing to identify and analyze areas where current policy is limited and challenges exist in bringing pharmacogenomics testing into wide-spread clinical practice in Canada.

The 3-I Framework

The 3-I framework of examining the ideas, institutions and interests related to a political topic was originally described separately by renowned political scientists H. Heclo and P.A. Hall (Hall, 1997; Heclo, 1994). “Ideas”, “Interests” and “Institutions” are three basic building blocks of politics and it is the analysis of their interdependencies which facilitates policy analysis. The notion of “Ideas” refers to the evidence, knowledge and values of all the policy makers, stakeholders and general public surrounding an issue. The notion of “Interests” refers to who will benefit from and who will suffer from a particular policy, and refers to the interests and agendas of all stakeholders. The notion of “Institutions” refers to the policies in place or past policies

influencing the development of new policies. It also encompasses government structures and policy networks that influence policy development. Heclo has stated that, “interests tell institutions what to do”; “institutions tell ideas how to survive”; and “ideas tell interests what to mean” (Heclo, 1994).

The 3-I framework has been used previously to examine policy development in the social arena such as in examining social security policy in Ireland and in explaining social policy change in welfare states (Humpage, 2010; Murphy, 2008). However it has been used in a very limited capacity in exploring policy development in health care. For example it has been used in exploring national HIV policy in various countries (Dickinson and Buse, 2008), in explaining the model to government officials as part of a briefing note (Gauvin, 2014), in providing guidance in developing evidence-informed health system policies (Lavis et al., 2012) and in examining barriers encountered by palliative care teams (DeMiglio and Williams, 2012). Since pharmacogenomics policy development is in its infancy in Canada, the 3-I framework provides a good starting point for framing the ideas, interests and institutions surrounding PGx testing in Canada and identifying the areas where current policy is limited and where gaps in policy development exist at the national and provincial levels in Canada.

Materials and methods

A scoping review of the literature and legislation about PGx was conducted to determine the extent of PGx policy implementation at the federal and provincial levels and to highlight prominent issues related to PGx testing. The following databases were searched: ProQuest Genetics Abstracts, ProQuest Health & Medical Database and ProQuest Health Management

Database, Ovid MEDLINE (1946-July 2015), EMBASE (1980- Week 30 2015), HealthStar (1966-June 2015) and HumGen International (<http://www.humgen.umontreal.ca/database-laws-policies#box-A-C>). In addition, Google Scholar and organizations such as the University of Montreal Pharmacogenomics Centre (<http://www.pharmacogenomics.ca/>), Genome Canada (<http://www.genomecanada.ca>), and federal and provincial websites were searched for papers related to pharmacogenomics policy and legislation. English language abstracts were obtained using the search terms of “pharmacogenomics”, “pharmacogenetics” and “health policy”. Abstract titles were reviewed for relevance followed by a review of the abstracts. Articles applicable to a Canadian context and outlining issues surrounding pharmacogenomics implementation were considered in this review. The 3-I framework was used to identify stakeholder values, interests, issues, and policy gaps surrounding PGx. The 3-I tool served to identify areas of agreement and contentious issues among stakeholders and provided a framework to consolidate issues related to pharmacogenomics implementation into the Canadian health care system.

Results

The search strategy of the scoping review resulted in 761 hits and 211 abstracts relevant to this topic based on title review. The abstracts were reviewed and the common themes that emerged addressed either the “ideas”, “interests” or “institutions” aspect of the 3-I framework. Out of the 211 abstracts reviewed, 101 were directly relevant in examining the issues of PGx in Canada for the purposes of this paper. The stakeholders whose interests are outlined were: patients, health care workers, pharmacogenomics service providers, pharmaceutical companies, private payers (such as insurance companies) and provincial ministries of health.

Ideas

Following the scoping review, the common emergent ideas that were of concern were: 1) genetic discrimination; 2) informed consent and the traditional model of clinical trials; 3) confidentiality and privacy; 4) knowledge about PGx; 4) stakeholder roles in PGx; and 5) the value and clinical utility of PGx testing.

Genetic Discrimination

Genetic discrimination occurs when people are treated differently due to their genetic make-up with some definitions specifying that discrimination would occur as a result of genetic testing (Joly et al., 2013). A contentious idea related to genetic discrimination is the use and possible misuse of genetic information by insurance providers (such as private insurers offering life, travel, additional health, mortgage, or disability insurance), or employers (Caulfield et al., 2013; Epps, 2003; Joly et al., 2010; Joly et al., 2013; McClellan et al., 2013). Inequitable access to care as a result of the genetic testing is also a concern (Bombard et al., 2013a; Hayeems et al., 2013; McClellan et al., 2013). Recently an Alberta court ruled that a woman who had sued a landlord for damages would have to undergo genetic testing to prove that her medical symptoms were not part of an inherited disease (Brean, 2013). The lady in the court case and other people with the potential of carrying the gene for Huntington's disease have had first-hand experience with genetic discrimination (Bombard et al., 2012; Erwin et al., 2010). Had legislation prohibiting genetic discrimination in this situation been in place prior to this ruling, perhaps the courts would not be able to force the woman to undergo testing. While the above examples illustrate genetic discrimination as a result of genetic testing for inherited diseases, the fear of genetic

discrimination could exist regardless of whether the genetic test is for the possibility of disease or for genetic variants in PGx testing.

Informed Consent and the Traditional Model of Clinical Trials

Obtaining informed consent and not harming trial participants are basic tenets of clinical research. Genomic biomarkers, which are measurable DNA and/or RNA characteristics that are indicators of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions, are now being researched in tandem with drug targets for companion diagnostics or for companion therapeutic monitoring. Therefore clinical trials are likely to have a pharmacogenomic, or genetic testing component. Hence those individuals participating in the clinical trials (and also those having PGx testing done outside of trials) would have to give informed consent for their genetic information to be collected. The challenges of conducting PGx clinical research arise when patients aren't adequately knowledgeable about genetic testing, about why their genetic information is collected and about what will be done with the results and samples or what social or emotional impact the results may have on their future (H. Howard et al., 2011; Jaitovich Groisman et al., 2014; Kerath et al., 2013; Ormond and Cho, 2014; Rothstein and Epps, 2001). Participation in a trial where PGx information is collected may lead to finding out that the individual is likely to develop a particular disease or not respond to therapy which in turn may not only have a negative emotional effect on the person's well-being, but may also may oblige the clinician to treat participants differently and provide care not provided to non-participants (Hayeems et al., 2013; Miller et al., 2012). The issue of informed consent as it relates to requesting children's genetic tests is also a concern. One issue is the testing of children's genetic information by third parties or by the minors themselves from direct-to-

consumer testing companies that do not comply with professional guidelines of not testing minors without parental consent or until the child is old enough to make the decision for themselves (H. C. Howard et al., 2011). The other issue is as it relates to consent for child genetic testing is the parental consent by proxy and whether this reflects the desire of child and whether the child is old enough to understand the nature and implications of the testing should participate in the consent process. Some clinicians feel that a child as young as twelve should be involved in the consent process (Avard et al., 2009).

The traditional concept of the multi-centre randomized controlled trial as the gold standard for clinical trials could also change because of PGx (Mancinelli et al., 2000). Robust randomized clinical trials (RCTs) have traditionally been thought to require a large sample size and show statistically significant differences between treatment groups. PGx statistical analysis is likely to be more complex. With PGx, sample sizes within trial arms will likely be smaller since patients would be stratified depending on their potential for response based on their genetic variance (A. Issa, 2002; Kraft and Hoffmann, 2012; Mancinelli et al., 2000). In PGx trials statistical power would depend on the minimum allele frequency of the variants of interest, the type of gene action, the number of variants examined, and the variability among and within patients (Glickman et al., 2009). The statistical challenge would be to reconcile statistical power while considering small sample sizes and individual variability in drug response (Glickman et al., 2009). Overall patient recruitment may need to increase to ensure sufficient statistical power, thus increasing clinical trial costs and feasibility which may in turn be reflected in increased drug costs. The traditional model of clinical trial design may have to shift to incorporate smaller trials

stratified by patient response. Regulatory agencies would need to consider guidelines to accommodate these new trial designs as part of pharmaceutical regulatory submissions.

Confidentiality and Privacy

Maintaining the confidentiality of our health information is a basic social expectation in Canada. The privacy of genetic information has been reported as a concern for consumers of direct-to-consumer PGx tests (Goldsmith et al., 2012). While laws protecting health information in Canada exist, issues regarding the enforcement of privacy and confidentiality laws can arise when testing is done outside of Canada (Caulfield and Ries, 2004; Gurwitz and Bregman-eschet, 2009). Currently, very few Canadian pharmacogenomics commercial companies exist, so PGx testing is occurring mainly in Canadian research institutions or outside of Canada. Hence, Canadian patients may seek out direct-to-consumer testing where Canadian privacy laws cannot be enforced. Out of 11 personalized medicine service providers listed as members of the Personalized Medicine Coalition, an organization of innovators, scientists, patients, providers and payers promoting the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system, (<http://www.personalizedmedicinecoalition.org/members/member-list>), none were primarily Canadian based. Adequate policies should be addressed to ensure that our personal information is protected even if testing is done outside of Canada.

Knowledge about PGx

Patients have varying knowledge and attitudes about genetic testing which may influence their opinion on the utility of genetic testing and pharmacogenomics testing, whether it is for

therapeutic, diagnostic, or for informational purposes such as direct-to-consumer testing (Etchegary et al., 2010; Garfield et al., 2015; A. M. Issa et al., 2009). Healthcare professionals generally perceive themselves to have limited knowledge regarding pharmacogenomic testing in general (Dodson, 2011) and a concern about training of health care professionals adequately to execute and understand PGx testing has been raised (Hopkins et al., 2006; M. McGowan et al., 2014; Williams et al., 2006).

Stakeholder roles in PGX

The direct-to-consumer PGx testing gives the patient the ability to become more pro-active in their health care decisions which is an idea that is increasingly popular in our health care system. “Patients as partners” is a philosophy adopted by the British Columbia Ministry of Health in which patients are considered partners in their own health care (British Columbia Ministry of Health, 2007). The challenge related to PGx arises when patients get tested through direct-to-consumer PGx facilities and demand health care follow-up which would not have otherwise been recommended. This could put added financial strain on an already over-burdened health care system and raises the issue on whether restrictions should be imposed on who should be allowed to request testing (Goldsmith et al., 2012).

The delivery of PGx services can involve multiple health care providers. Medical geneticists, genetic counselors, pharmacists and primary care physicians have all expressed an interest in participating in PGx testing implementation (Bartlett et al., 2014; Callard et al., 2012; Machini et al., 2014; Mills and Haga, 2013). However the coordination of services among all types of

providers and the development of PGx practice guidelines require more work (Amstutz and Carleton, 2011; Bartlett et al., 2012; Blancquaert, 2000; McMaster Health Forum, 2012).

The value and clinical utility of PGx testing

Due to the relative infancy of PGx testing, its clinical utility in therapeutics is being debated (Burke et al., 2010; Rogowski et al., 2009). The term “clinical utility” can refer to the benefits and risks accrued from positive and negative tests results, the accuracy with which an assay measures a particular genetic characteristic, the accuracy with which a genetic characteristic identifies a disease condition or risk, as well as the health care value of a particular test (Burke et al., 2010). Some PGx tests can demonstrate cost-effectiveness while others may not (Phillips and Van Bebber, 2004). Standardized methods of assessing the clinical utility and value of PGx need to be developed and further refined (Husereau et al., 2014; Van Rooij et al., 2012; Veenstra et al., 2000; Vegter et al., 2008; Yang et al., 2013). While PGx tests may help to identify favourable drug-responders, overall drug prices may increase if a drug’s target market is decreased and clinical development costs are increased. This could, in turn, reduce the overall health care value attributed to PGx (Shah, 2003).

Interests

As with many health care interventions, PGx involves multiple players, each with their own interests. There are the patients, the health care providers such as primary care providers, specialists, pharmacists and genetic counsellors, the PGx service providers such as the testing labs, the payers and regulators such as insurance providers and government, and the manufacturers such as diagnostics and pharmaceutical companies. The following section will

examine the perspectives and concerns of these stakeholders with respect to implementing PGx into widespread clinical practice.

Patients

Patients are interested in effective and timely care with minimal out-of-pocket expenses. They are also concerned with confidentiality and do not want to undergo discrimination based on their health (Bombard et al., 2013a). Patients welcome the benefits of PGx for improved diagnosis and care, but have concerns about the emotional burden of additional information (M. L. McGowan et al., 2013), the value of the testing and whether testing could be used to ration care (Bombard et al., 2013b; Etchegary, 2014). Patients also have a preference for tests with a high sensitivity rather than a high specificity when dealing with a cancer diagnosis (Najafzadeh et al., 2013).

Health care Providers

As stated previously, a major concern of health care providers is the lack of knowledge and training regarding PGx. The majority of physicians report a limited knowledge of PGx while some nurses reported no knowledge of pharmacogenomics (Dodson, 2011) (26). Some physicians are apprehensive about the clinical utility of PGx (Dodson, 2011; Pirmohamed, 2010). This concern raises the need for adequate training of healthcare providers in understanding and interpreting PGx tests. It also raises the question of who should actually provide this information to the patient. Genetic counselors were open to providing the PGx services and interpretation but also raised concerns of adequate training and the lack of information provided by direct-to-consumer tests (Callard et al., 2012; Sturm and Manickam, 2012). The Canadian Association of Genetic Counsellors also supports legislation against genetic

discrimination. Similarly, pharmacists are open to be involved in providing PGx services but feel the need for adequate education and an apprehension about genetic discrimination (De Denu et al., 2013; Mills and Haga, 2013; Tuteja et al., 2013).

Currently in Canada, there are no specific fee codes for interpreting PGx tests. For example, in the Ontario Schedule of Benefits for Physician services there are general codes for genetic consultations which may or may not be an appropriate representation of interpreting PGx testing results and patient consultation. Physician professional associations, other professional health care workers' professional associations, and provincial health ministries may want to consider entering into negotiations to discuss PGx consultation fees, scope of practice and clinical practice guidelines (Amstutz and Carleton, 2011). As clinical practice changes towards a more team-oriented approach, PGx testing may also benefit by having the appropriately qualified providers performing the appropriate roles for PGx.

PGx Service Providers

Acceptance and increased use of PGx will increase activity for PGx service providers. However, apprehensions about the clinical utility and value of PGx remain a barrier for the progress of PGx service providers and test manufacturers (Faulkner et al., 2012). PGx providers have to demonstrate value in testing, particularly because PGx testing is more costly than traditional tests (Ansari, 2013). As the testing technology evolves toward next generation sequencing, the role of the bioinformatician who filters and synthesizes the findings also becomes more prominent (Wright et al., 2011). Direct-to-consumer testing companies have shown to provide limited information and may not always comply with professional recommendations (Goddard et al.,

2009). At the moment, direct-to-consumer testing is available but if limitations or a requirement to provide increased information is imposed through policy, then PGx service providers may have to re-think their services for Canadian consumers (Ogbonna, 2011). From an operational standpoint, PGx service providers may also have to consider how best to incorporate their systems of reporting into already established e-health or lab reporting systems (Wilke et al., 2011).

Private Payers (Insurance companies)

Private insurance companies are concerned with providing high quality products, profits and sustainability. For private insurers, until genetic discrimination laws are in place, there is nothing stopping them from including a patient's genetic information in their calculation of risk and coverage level. The Canadian Life and Health Insurance Association Inc., maintains that it will not request genetic testing but will require the disclosure of testing if it has been done.

As drug coverage is largely through private insurers in Canada, insurance providers need to anticipate the costs of re-imbursement and demand evidence of value for money for recommended tandem PGx testing if certain tests are not covered by provincial health care plans (Towse and Garrison, 2013). In 2011, eight drugs (primarily oncology-related) had recommended adjunct PGx tests by Health Canada and this number is expected to grow rapidly. Currently the U.S. Food and Drug Administration has listed over one hundred drugs with pharmacogenomic testing in their labelling (U.S. Food and Drug Administration, 2015). Physician adoption of testing is also projected to increase with increased demonstration of utility of the tests (Bonter et al., 2011; Faulkner et al., 2012).

Pharmaceutical companies

PGx has a large impact on pharmaceutical companies, biotech companies and diagnostic manufacturers. Ninety-four percent of pharmaceutical companies are investing in personalized medicine and thirty percent require that all products in development also incorporate the development of an associated biomarker test (Redekop et al., 2013). There is an increased burden on pharmaceutical companies (or PGx manufacturers) to demonstrate the utility of parallel PGx tests associated with pharmaceuticals (Singer and Watkins, 2012). Companies will have to adjust their economic forecasting to incorporate reduced treatment populations, modified clinical trials and regulatory changes (Faulkner et al., 2012). In the interest of sustained profitability pharmaceutical companies are likely to make adjustments to their business strategies (Redekop et al., 2013).

Provincial Health Ministries

Provincial ministries of health are concerned with cost-effective and efficient delivery of health care (McMaster Health Forum, 2012). Health Canada has recommended PGx testing for a handful of drugs such as warfarin and Herceptin^{TM}. Provincial ministries would have to consider adding these tests as part of their coverage schedule if they have not already done so. As PGx becomes increasingly valuable in the treatment of disease, provinces will have to continually update policies dictating what is covered and what is not based on evidence of value.

Regarding cost, provinces are currently able to take advantage of bulk purchasing discounts on some drugs (Bell, 2013). With personalized medicine, bulk numbers could be reduced because

of tailored treatments resulting in drug price increases. While there may be savings through the reduction of health care costs associated with the treatment of adverse events, these may be offset by a reduction in bulk discounts and the cost of PGx testing itself. The actual net cost and incremental cost-effectiveness due to PGx remains to be seen.

Institutions

For the purposes of this paper, the term “Institutions” refers to the rules and policies in place as they relate to pharmacogenomics testing in Canada. The main issue concerning PGx testing is the lack of policies and guidelines governing the implementation of pharmacogenomics despite rapid advancements in technology. Policies are lacking at federal and provincial levels most likely because PGx is still in its infancy as a technology, is not well understood by practitioners and policy makers, and because only a few tests have shown clinical utility so far (Husereau, 2012). Confusion about which organization has jurisdictional oversight for policy development may also exist.

Genetic Discrimination and Genetic Testing

There are currently no laws in Canada that prohibit genetic discrimination while other G8 countries do have laws in place to prohibit genetic discrimination (Walker, 2014). Legislation has been proposed at the federal and provincial level in Canada however it remains to be seen whether these proposed changes will address patients’ concerns about genetic discrimination. The Hon. James Cowan tabled a private members bill in April 2013 (Bill S-201) proposing to create the Genetic Non-discrimination Act and amend both the Canadian Human Rights Act and the Canada Labour Code. As of May 2015, this bill is still being debated by a Senate Committee

(Parliament of Canada, 2015). Bill S-201 was originally proposed to provide legal protection for a person having undergone genetic testing against someone, such as an employer or an insurance company, gaining access to genetic information and using it against him or her. The transcript of the last Senate debate in May 2015 provides a comprehensive account of case studies (such as the apprehension of parents in having their child receive beneficial testing for fear that the child will experience genetic discrimination later in life), and dialogue around the issue of genetic discrimination (Parliament of Canada, 2015). Issues arising in the debate include the fact that the insurance industry does not fall under federal regulation like banks and that other legislation such as the Personal Information Protection and Electronic Documents Act (PIPEDA) or other provincial Health Information Acts (such as the Personal Health Information Protection Act in Ontario) can provide protection of health information if genetic information is included within these definitions. To date, the Canadian government has only introduced legislation to address discrimination on the basis of a predisposition to a disability as inferred from genetic test results for organizations that fall under federal authority such as the federal government and First Nations governments and industries such as banks and telecommunication companies. There is also a proposed amendment to PIPEDA that information from genetic testing would be among the types of personal information protected (Department of Justice Canada, 2015). While these proposed changes may address privacy issues related to genetic information of employees, protection from discrimination against insurers remains to be seen. From a health care perspective, Canada's public healthcare system already provides basic coverage to all permanent residents without discrimination (Department of Justice Canada, 2015). However, the discrimination causing concern is from private insurers that operate outside the public health care

system such as those providing additional health care coverage for drugs, life insurance or disability insurance.

In Ontario, Bill 127 includes changes to the Ontario Human Rights Code proposed to prohibit genetic discrimination (14). The Human Rights Code has been amended by adding “genetic characteristics” after “age”. So far the first reading of the bill has been carried. However, there are caveats to the proposed changes as stated in the explanatory note, “In addition to other amendments, various sections are amended to provide that every person has a right to equal treatment, without discrimination because of genetic characteristics, with respect to services, goods and facilities, the occupancy of accommodation, the right to contract, and employment and membership in various types of organizations. This includes the right to equal treatment if a person refuses to undergo or disclose the results of a genetic test. High value insurance contracts are permitted to differentiate or make a distinction, exclusion or preference on reasonable and bona fide grounds because of genetic characteristics.” (Legislative Assembly of Ontario, 2013).

The current position of the Canadian Life and Health Insurance Association Inc., and the Canadian Institute of Actuaries is that, while companies will not require genetic testing of applicants for insurance, they will ask whether the applicant has been genetically tested in the past, and they will require disclosure of those test results where they exist as the genetic tests provide the insurance companies with information so that they can adequately assess a potential customer’s risk similarly to other medical information (Canadian Institute of Actuaries, 2014; Canadian Life and Health Insurance Association, 2010). Potential problems can arise when people refuse to get potentially beneficial tests or parents refuse to test their children for fear of

later discrimination by insurers (Feze and Joly, 2014; Joly et al., 2013; Parliament of Canada, 2015).

PGx In Practice

With respect to the implementation of PGx testing, Health Canada has thus far produced a guidance document, entitled “Submission of Pharmacogenomic Information” stating that PGx test results as part of clinical trials be submitted with the Clinical Trials Application and that when PGx testing is part of the clinical research that research subjects must be specifically informed that PGx will take place and that specific informed consent for the PGx testing be obtained. The document also suggests the appropriate use of labelling when PGx testing is used for the management of a drug or drug response (Health Products and Food Branch, 2007).

A lack of coordinated services is also an area of concern in accommodating the rapid expansion of PGx technologies (McMaster Health Forum, 2012). How PGx services will be implemented, requisitioned, delivered and reimbursed are all issues that have been noted by governments, but actual policies have not yet been put in place in Canada. Canada Institutes for Health Research (CIHR), and the governments of British Columbia, Ontario, Alberta and Quebec are the current leaders in Canada in establishing committees and research groups to discuss PGx (Ferrari, 2013; Husereau, 2012; McMaster Health Forum, 2012; Ontario Health Technology Advisory Committee, 2011). The consensus among these groups is that: 1) adequate health technology assessments of PGx tests are needed to establish clinical and cost-effectiveness, 2) service coordination needs to be addressed and aligned to determine who, where, when and how PGx testing is implemented and used, and 3) knowledge gaps need to be filled among stakeholders

regarding the use of PGx. As we stand today, policy makers have identified these three areas of improvement within their own committees. The provincial groups are aligned with each other and the next steps would be to address these three issues through policy changes at every appropriate organizational level, whether this is at a provincial government level or at the level of the professional licensing body responsible for ensuring the appropriate education of its members.

Analysis and Next Steps

Three broad areas of contention have been identified through the analysis of the 3-I framework: genetic discrimination reform, direct-to-consumer testing and the potential for cost-savings through PGx. Based on the analysis of ideas and interests of patients and health care providers, patients and health care providers support laws prohibiting genetic discrimination, but insurance providers may challenge these laws if they prove to be detrimental to their sustainability. Another contentious issue is direct-to-consumer testing. Imposing restrictions on direct-to-consumer testing may undermine the idea of the patient as a partner in health care. While consumers may feel empowered by taking a pro-active stance in their health care in requesting PGx tests, they may be ill-equipped from a knowledge or emotional standpoint to handle the results. Direct-to-consumer testing may also be difficult to regulate in terms of quality of care and may create an increased demand for follow-up health care resources. The third area of contention is the idea that PGx could result in cost-savings for the health care system by averting adverse drug responses and realizing more efficient treatments. While averting costly adverse events may be averted with PGx, the costs of policy reform, service coordination and delivery,

commissioning health technology assessments, training resources, and potential reductions in bulk drug discounts may offset any true cost-savings.

The 3-I framework was found to be a useful tool in highlighting and categorizing the issues, policies and stakeholders related to PGx. The issues, stakeholders and policies discussed in this article are summarized in Table 1. Table 1 also describes some suggestions on moving forward with policy and operational improvements in the implementation of PGx into clinical practice in Canada. It is suggested that policies be addressed among stakeholders within the jurisdiction with the most oversight in the field. It is recommended that professional health care worker governing bodies take the initiative of training its members on PGx testing and that they begin a dialogue with each other and with the provincial ministries of health to define the scope of practice as it pertains to PGx testing. It is also suggested that regulatory bodies and governments anticipate the economic and scientific implications of PGx and personalized medicine in relation to changes in clinical trial design and drug costs and require evidence of test effectiveness and cost-effectiveness.

Discussion

For the first time the 3-I framework political science policy development tool has been used to explore the policy issues surrounding PGx testing in health care. Through the lens of the 3-I framework, a consolidated review of the policy issues for fully implementing pharmacogenomics into clinical practice in Canada has been presented. The 3-I framework has highlighted the interdependencies and sources of contention among stakeholders as pharmacogenomics testing becomes more widespread. In examining policy gaps around PGx testing, the 3-I framework tool

has served to remind us that policy development in the Canadian health care system is multi-jurisdictional and that for further PGx policy development to progress, the appropriate organizational levels need to be mobilized. Policy makers and leaders at any organizational level can use this tool and analysis in assisting the development of policies for the implementation of PGx technologies within their jurisdiction. Numerous articles have been published that advocate for policy improvements and policy development in the field of pharmacogenomics, however few have moved beyond just stating a lack of policy. More recently, and as presented within this article, evidence eliciting stakeholder perspectives on PGx implementation supports a desire for policy change, increased education and a demonstration of the value of PGx tests. The key message is that the onus of PGx policy change or addressing the issues surrounding PGx implementation may be at the level of the organization or individual, and not necessarily the government. One such example is the multi-disciplinary approach of the Sick Kids Genome Clinic in which clinicians, researchers and genetic counsellors work in a pro-active and coordinated fashion to address the clinical, economic and social concerns related to PGx testing as it is translated into clinical practice (Bowdin et al., 2014). As individuals participating in our own health care it may also be beneficial for us to take charge and ensure that we are sufficiently educated about testing repercussions that can affect us beyond our physical health (Juengst et al., 2012). As with all medical interventions, there is weighing of risks and benefits. The only difference is that PGx may have social and economic risks that we as individuals may not be fully cognizant of or made aware of by our health care or PGx service providers.

Canada may appear to lag behind other countries in some areas such as enacting genetic discrimination legislation and in the number of approved drugs with associated PGx testing labelling, but PGx is still in its infancy globally. Other countries are making advances in implementing PGx into clinical practice, but uptake is still slow owing to the paucity of scientific evidence, policy development and infrastructure. The challenges of implementing PGx, such as the adequate training of health care workers, obtaining informed consent, genetic discrimination, the delivery of testing, and establishing the scientific and economic value of PGx are not unique to Canada. What is unique to Canada is our own unique blend of public and private health care delivery and legislation at provincial and national levels. A thorough comparative 3-I analysis with other countries would have to consider all the various health care delivery mechanisms, policies and stakeholders for each nation. Since this is the first time the 3-I framework has been used to analyze PGx implementation, and there is limited information on each of the “3-I’s” of PGx, this paper focused on the Canadian context as an example and starting point for a 3-I analysis in PGx policy development. While an extensive 3-I analysis comparing Canadian PGx implementation to 3-I analyses of PGx in other countries may be worthwhile in the future and once additional evidence of PGx in practice is observed, some comparisons in PGx implementation are discussed below.

PGx in Other Countries vs. Canada

Genetic Discrimination

In 2008, the U.S. passed the Genetic Information Non-Discrimination Act (GINA) which prevents the use of the genetic information for health insurance or employment purposes, however life, disability, and long-term care insurance are excluded (Green et al., 2015). The

more recent U.S. Affordable Care Act also prohibits discrimination by health insurers on the basis of pre-existing conditions, including genetic test results (Green et al., 2015). Canadian public health insurance plans already prohibit discrimination. In the U.K., while there is no specific law prohibiting genetic discrimination, there is an agreement between the Association of British Insurers and the British Government called the Concordat and Moratorium on Genetics and Insurance (Association of British Insurers and HM Government, 2014). This agreement outlines that insurance companies will not request the disclosure of genetic testing results for the purposes of insurance unless the customer seeks insurance coverage over a certain amount of funds outlined in the agreement such as coverage over £500,000 for life insurance during the period of the moratorium which is currently until 2019. Soini (2012) reviews the genetic testing legislation in eight Western European countries which use Article 21 of the EU Charter of fundamental rights which bans discrimination based on “genetic features” among other qualities as a foundation (Soini, 2012). Tabled in 2003, the Australian Government’s Australian Law Reform Commission has produced a lengthy and comprehensive report with recommendations on how to handle genetic testing issues within the Australian context (Australian Law Reform Commission, 2003). The report raises similar issues as other countries, such as discrimination, and insurance. The main challenge in enacting genetic testing legislation for all regions including Canada, is determining the scope and overlap among various prior privacy, health, and discrimination laws and whether those laws have adequately covered all the issues regarding genetic testing.

PGx Implementation Initiatives

In Canada, along with local initiatives such as those described at Sick Kids Hospital, larger initiatives to tackle PGx issues, such as PGx research, networking and guideline development are underway. The Canadian Pharmacogenomic Network for Drug Safety (CPNDS) is a national program that aims to reduce serious adverse drug reactions in children, and possibly adults through the exploration of genetic variations in the occurrence of serious adverse drug reactions. CPNDS has been directly involved in the discovery of codeine-related genetic variants that can cause infant mortality in breastfed infants which has resulted in drug labelling modifications by Health Canada and the U.S. Food and Drug Administration (Lam et al., 2013). The program has also spear-headed the discovery of cisplatin-related genetic variants that can cause serious and permanent hearing loss, and the discovery of anthracycline-related genetic variants that cause cardiotoxicity (Aminkeng et al., 2015; Carleton et al., 2014). Genome Canada is a not-for-profit organization that serves to connect various players in the genomics arena to create economic and social benefits for Canadians. The Canadian Pediatric Society and the Canadian College of Medical Geneticists have issued guidelines for genetic testing of healthy children (Arbour and Canadian Paediatric Society Bioethics Committee, 2003). The Canadian Society of Pharmacology and Therapeutics has issued guidelines entitled, “Application and interpretation of pharmacogenetic (PGx) testing: Importance of Clinical Pharmacology as the medical specialty for PGx-based patient care in the 21st century” (Kim, 2015).

The U.S. FDA has over 160 drugs with pharmacogenomic information in their labelling which as of 2012 was about 12% of drugs (Tutton, 2014). In 2013, approximately 11% of the drugs approved by The European Medicines Agency (EMA) had PGx information in their label

(Ehmann et al., 2015). Canada has just over 100 drugs with PGx labelling but the number is increasing (PharmGKB, 2015).

In the United States, the NIH National Human Genome Research Institute is a federally funded organization that is involved in genomic research, has genomics training programs for health care workers, and provides information about genomics to the public (National Human Genome Research Institute, 2015). The U.K. National Health Service (NHS) National Genetics and Genomics Education Centre has developed short courses for health care practitioners on pharmacogenomics (National Genetics and Genomics Education Centre, 2015). The NHS has also established a National Genetic Testing Network to advise the NHS and patients about genetic testing (NHS UK Genetic Testing Network, 2015). Both the U.S. and the U.K. have significantly more federal government involvement in the implementation of PGx initiatives than Canada possibly due to the greater involvement that their federal governments have in their health care systems.

Direct-to-consumer Testing

In Canada, 23andMe, the largest, U.S.-based direct-to-consumer genetic testing company is offering health and ancestry genetic testing. Health Canada considers these tests outside the scope of the Food and Drug Act as they are not diagnostic or therapeutic. 23andMe has recently begun similar offerings in the U.K. However contrary to Canada, in the U.K. there are agreements with insurers to prevent the disclosure of the tests results once they have been performed. The 23andMe website does alert consumers about the lack of genetic discrimination legislation in Canada and potential concern over insurance. France, Germany, Portugal and

Switzerland have legislation stating that genetic testing can only be acquired through a medical professional (Borry et al., 2012). In 2013, the U.S. FDA shut down 23andMe's operations over the lack of compliance to regulatory processes. However over the last two years, 23andMe has worked with the FDA, and the FDA has recently approved 23andMe's carrier screening test for Bloom Syndrome and its procurement without a licensed medical practitioner (23andMe, 2015).

Cost-savings and the Value of PGx

The cost savings and ultimate value of PGx in each jurisdiction remains to be seen as PGx testing is done and resultant adverse events averted data is collected.

Concluding Remarks

Based on our 3-I analysis, Canadian PGx policy development and PGx implementation can start locally at the level of the organization or individual. However, lessons from other countries suggest that federal government involvement can certainly facilitate local PGx implementation efforts through the coordination of networks as well as providing oversight and sponsorship. The challenges for the Canadian PGx landscape are taking initiative, sorting through jurisdictional responsibilities, and sifting through multi-level policy and legislative overlap while ensuring that sufficient evidence is collected to establish the value of PGx.

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Table 1. Summary table of the issues (ideas), stakeholders (interests), and policy status

(institutions) around pharmacogenomics testing. Potential next steps to address policy gaps are also suggested.

Ideas	Interests (Major stakeholders concerned or impacted)	Institutions	Potential Next Steps
Genetic discrimination	Patients, Insurance companies, Employers	Proposed amendments to federally regulated industries and government to protect against genetic discrimination (does not address insurance companies)	At the provincial level, reconcile the provincially regulated insurance industry and address patients' concerns particularly for testing done as a child or that is not reflective of a disability at the time of testing. Consider requesting transparent actuarial risk assessments as they relate to PGx testing
Informed consent and the traditional model of clinical trials	Patients, clinical researchers, pharmaceutical companies, Health Canada, PGx service providers	Amendments to Health Canada submission guidelines	Update Health Canada regulatory guidelines as they relate to medical device/drug/biologic clinical trial design
Confidentiality and privacy	Patients, Health care service providers	Proposed amendments to include genetic information as part of health information to be protected under privacy laws	Direct-to-consumer companies and other PGx service providers should consider addressing the ownership and privacy of cross-jurisdictional test information in their informed consent
Stakeholder roles and knowledge in PGx	Health care workers, patients,	No specific guidelines or limitations on the procurement of PGx testing by qualified individuals and limited education provided about PGx testing, its interpretation, and its utility	Professional bodies representing health care workers should consider initiating training of their members and students on PGx testing and begin dialogue with provincial ministries to discuss scope of practice as it relates to PGx services
The value and clinical utility of PGx testing	Patients, health care workers, PGx service providers, public and private payers, pharmaceutical companies, Health Canada	Limited health technology assessments and clinical evidence supporting emerging PGx tests	Professional and research organizations to update clinical and economic literature with associated knowledge translation