Pharmacogenomics

Recommendations for Ontario

PROVINCIAL GENETICS PROGRAM
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Pharmacogenomics Working Group

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Executive Summary

Pharmacogenomics (PGx) examines the effect of genetic variation on drug response. PGx has been extensively studied for several decades and the benefits of personalized therapies based on PGx differences are widely accepted (1).

In a publicly funded health care system, genetic tests should be cost-effective, easy to use, accessible, broadly applicable, and supported by evidence. Although there are PGx tests that fit some or all of these parameters, clinical implementation has been challenged by lack of expertise in the field, limited availability of specialists, testing turnaround times, and cost. There is also limited pharmacogenetic data aggregated at a population level to make public funding and policy decisions. Within this environment, the availability and access to self-pay PGx testing has exploded, marketed broadly to the public, patients, clinicians, and health insurance/group benefits companies.

The Provincial Genetics Program (PGP) at Ontario Health was established in 2021 to ensure the provision of comprehensive, coordinated, evidence-based genetic services for Ontarians. There is currently no formal organization of PGx testing in Ontario. Expertise primarily exists within a small and highly specialized group of clinical pharmacologists, pharmacists, and clinician scientists in the province; and outside of the traditional scope of laboratory and clinical genetics clinicians.

The PGP, at the request of the Ministry of Health's Laboratories and Diagnostics Branch and with advice from the Provincial Genetics Advisory Committee (PGAC), convened the Pharmacogenomics Working Group (Working Group) in September 2022 to develop a roadmap for PGx testing in Ontario. The Working Group, in collaboration with health care clinicians, laboratory scientists, administrators, and patient and caregiver advisors, developed five core recommendations to guide the direction of PGx testing in Ontario:

1) Utilize a systematic process to develop guidance for pharmacogenomic testing.
2) Enable clinical service delivery pathways that facilitate timely, equitable access.
3) Standardize pharmacogenomic laboratory testing and reporting across Ontario.
4) Optimize utilization with education for patients, the public, and health care professionals.
5) Monitor performance through measurement of quality indicators.

Within these recommendations, the Working Group designed planning and evaluation tools that can be used to support the generation of advice and clinical guidance products for PGx tests in Ontario. These include a process map, outlining the pathway from intake to implementation and evaluation of new PGx testing; and an evaluative framework, used to guide decision making within this process. The Working Group also proposed that a standing provincial PGx expert group be established to utilize these processes and tools; and provided an initial ranked list of drug-gene pairs that could help identify priorities for evaluation by this committee (see Appendix A: Drug-Gene Pairs of Interest).

NOTE: This report recommends that a standing PGx expert group be formed. At the time of publication (October 2024), a standing PGx expert group has been formed under the Provincial Genetics Program.

Introduction

Background

Many drugs today are prescribed according to standard dosing recommendations or established clinical guidelines. However, a drug/dose that may help one patient may not help another. For some, the drug/dose may even cause harm. Only a proportion of patients respond to a given drug "as expected." Diverse responses to the same drug dose may be partly due to **genetic variability**. Variability in drug response can lead to serious consequences such as treatment failure or adverse drug reactions (2, 3).

Pharmacogenetics is the study of how genetic variability in a single gene can impact the response to a drug. The study of how genetic variability in multiple genes affects drug response is called **pharmacogenomics** (**PGx**). Some use the terms interchangeably (2, 4, 5). In this report, the acronym PGx will be used to represent both terms.

Depending on the genetic variant a patient carries, the drug prescribed and other factors, the patient may (2):

- Respond **effectively** to the drug
- Respond **ineffectively** to the drug (e.g., treatment failure)
- Experience an **adverse reaction** to the drug

The process by which drugs are absorbed, distributed, metabolized, and eliminated from the body is called **pharmacokinetics**. This process is often mediated by enzymes and transporters. Not surprisingly, genetic variation that affects these processes can result in an altered concentration of a drug in the body. Similarly, genetic variation in drug targets, such as receptors, can modulate the effect of a drug by altering the action of the drug in the body. This is called **pharmacodynamics** (2, 3, 6).

Well-studied genetic variants in pharmacokinetic and pharmacodynamic genes tend to be common across populations. They also tend to have large effect sizes. Most genes that are currently hypothesized to influence drug response are pharmacokinetic genes (2, 7).

PGx phenotypes can vary depending on the allele(s) each person carries. For pharmacokinetic genes, typical phenotypes include (2):

- **Poor metabolizer**: Two loss-of-function alleles
- **Intermediate metabolizer**: One loss-of-function allele
- **Normal metabolizer**: Normal-function alleles
- **Ultrarapid metabolizer**: Gene duplications or gain-of-function alleles

It is important to note that an individual's response to a drug is complex. Some genetic variants may not impact the function of receptors, transporters or enzymes that play a role in drug response. On the other hand, multiple genetic variants and proteins may interact to impact drug action or drug concentration in the body. Moreover, drug response may be dependent on factors beyond genetic variants. These can include other drugs that a patient may be taking, dietary constituents such as grapefruit juice, and other clinical factors (2, 8).

PGx Testing to Guide Drug Selection

PGx testing involves the assessment of genetic variants to predict their impact on drug response. The results of a PGx test may help practitioners prescribe a drug and/or dose that is personalized to their patient. Applying PGx to patient management is therefore an example of **precision medicine** (9).

PGx testing can be utilized as a broad testing approach before a specific diagnosis or drug therapy is identified (**pre-emptive testing**). The results of this testing can be consolidated into the Electronic Medical Record (EMR), where it is made available to prescribers. PGx testing can also be utilized as a targeted approach after a drug therapy is indicated (**reactive testing**). This type of testing can be conducted prior to the prescription of a high-risk drug or after the occurrence of an adverse drug reaction. Pre-emptive testing may help prescribers make timely decisions that maximize the effectiveness of a drug and minimize potential adverse reactions. It may also limit periods of trial and error of drugs and/or doses during treatment and thus decrease health care burden. However, test volumes and associated costs of a pre-emptive approach may be higher compared to reactive testing (9-11). PGx testing should not be used for the renewal of a medication that a patient is already benefiting from and tolerating well.

Numerous PGx tests are already available for purchase by Canadians. Examples, at present, include Pillcheck, Genecept Assay, and TreatGxplus. Some of these tests are offered direct-to-consumer, while others require a practitioner requisition. Similarly, the results of some of these tests are delivered directly to the patient, while others are first delivered to the practitioner (12-15). The cost to the patient for self-pay PGx testing can range from about $150 CAD to $2,300 CAD per test. Although the tests are not covered by public funding in Ontario, some insurance companies subsidize test costs (15-17). Companies offering PGx testing may require a cheek swab, saliva sample, or blood sample. The turnaround time for these tests ranges from 2 to 40 days (15, 18). When patients or families present these results to a practitioner who has not requisitioned the test, the practitioner could have difficulty understanding and applying these results to the care of the patient.

PGx testing is conducted by analyzing single genes or a panel of genes. An algorithm is then used to predict and report the corresponding PGx phenotype(s). Reports geared toward practitioners may also offer decision-support tools, such as a list of drugs that should be avoided or dosage changed based on genotype (8). Some companies focus on drug-gene pairs in the context of specific conditions, such as depression. Others include a wide variety of drug-gene pairs in their algorithms related to a variety of indications, including pain, cardiac conditions, and more (2, 13, 19).

Guidelines that provide prescribing recommendations based on genotype are currently available for some drugs. These include guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG). The Food and Drug Administration (FDA) offers similar dosing recommendations in drug labels for some approved drugs

(20-22). It is important to note that there may be discordance between various published clinical guidelines, which can lead to variability in implementation.

Current State

The multidisciplinary nature of PGx testing presents challenges for its widespread implementation (23). Currently in Ontario, there are no formal frameworks or guidance on how to integrate PGx testing into existing health system operations beyond singular institutions. This situation is similar across Canada, where there is a lack of system-level guidance for effectively implementing PGx into clinical practice. While there is very limited literature on decision-making frameworks or processes for implementation, there are existing initiatives in Canada dedicated to advancing the awareness and science of PGx. For example, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) was established to monitor and reduce serious adverse drug reactions in children and adults (24-26). In Ontario, London Health Sciences Centre (LHSC), The Hospital for Sick Children (SickKids), Sunnybrook Health Sciences Centre, and the Centre for Addiction and Mental Health (CAMH) are learning health systems that have successfully implemented a pharmacogenomics-based Personalized Medicine service for their patients (27, 28). A high-level summary of their PGx service offerings is provided below.

Pharmacogenomics Learning Health Systems in Ontario

- **London Health Sciences Centre (LHSC)** provides pharmacogenomics-based personalized medicine services, both for inpatients and outpatients. A large proportion of the patients seen relate to pharmacogenomic testing for certain chemotherapy medications used to treat cancer.
- At **The Hospital for Sick Children (SickKids)**, specialists from the Division of Clinical Pharmacology and Toxicology provide pharmacogenomics consultations in a collaborative setting with the responsible health-care professional. Referred patients are tested for a multi–gene panel consisting of genetic variants which can be used to predict responses to medications in the areas of pain management, mental health, cardiology, gastroenterology, infectious diseases, oncology, autoimmune disorders, and neurological disorders.
- **Sunnybrook Health Sciences Centre** offers pharmacogenetic testing for *TPMT*, *DPYD*, and more through the Precision Diagnostics and Therapeutics Program (Laboratory Medicine) to patients and external clients.
- The **Centre for Addiction and Mental Health (CAMH)** is home to the Tanenbaum Centre for Pharmacogenetics which acts as a hub from which lab-based discoveries are translated broadly into clinical care specifically in medication prescription for mental illness.

The Canadian Agency for Drugs and Technologies in Health (CADTH) and the Ontario Health Technology Assessment Committee – Ontario Genetics Advisory Committee (OHTAC-OGAC) have conducted a limited number of assessments on the use of PGx testing. Based on evidence gathered from available studies, both groups concluded that PGx testing for drugs used to treat major depression may not be clinically useful or cost-effective at this time. OHTAC-OGAC made positive recommendations for *DPYD* testing, concluding that *DPYD* testing in patients who have planned

cancer treatment with fluoropyrimidines may help prevent serious adverse drug reactions and may be cost-effective (8, 29, 30).

Ontario Health analyzed two administrative data sets to determine the volume and type(s) of PGx tests currently being requested for in-province and out-of-country testing. Based on the Ministry of Health's Laboratory Information Licensing System (LILI) dataset for 2021, four Ontario laboratories offer select PGx tests that are licensed to be performed in Ontario. The availability of these tests at select labs primarily supports institution-specific testing, as there is a lack of provincially-coordinated eligibility or access to these tests. An analysis of the Ministry of Health's Out-of-Country & Out-of-Province Prior Approval Program data for Laboratory and Genetics Testing, showed that there were fewer than 50 requests made for out-of-country PGx testing over the 2020-2021 fiscal year. The most common clinical indication listed was related to mental health/depressive disorders, however these requests were denied based on insufficient evidence for clinical utility, aligning with the findings concluded by the CADTH and OHTAC-OGAC studies.

An online search of international, publicly available sources reveals a considerable lack of published information on how jurisdictions prioritize PGx tests for review or make associated funding decisions. Select relevant resources were found in a variety of jurisdictions including the United States, the Netherlands, Switzerland, France, Japan, Australia and the United Kingdom (21, 31-36).

In Europe, the Ubiquitous Pharmacogenomics (U-PGx) Consortium, comprised of 16 health and university organizations in 10 countries across the continent, is working to study and improve PGx clinical implementation practices (37). The U-PGx Consortium recently published the results of an implementation study of a pre-emptive 12-gene PGx panel across 7 European countries (Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK). Patients aged 18 years or older receiving a first prescription for a drug clinically recommended in the guidelines of the Dutch Pharmacogenetics Working Group (i.e., the index drug) as part of routine care were eligible for inclusion. They found implementation of genotype-guided treatment using this panel was feasible, and significantly reduced adverse drug reactions in the eligible patient population (38). In the United States, the Teachers' Retirement System of the State of Kentucky partnered with Coriell Life Sciences and the Know Your Rx Coalition to improve member health by offering pharmacogenomic testing and comprehensive medication management to eligible members. Evaluating member outcomes over several years showed multiple real-world economic and clinical outcome improvements (39). Both studies demonstrated positive economic considerations for pre-emptive PGx testing.

The pathways to PGx implementation vary across different jurisdictions (40, 41). However, each international jurisdiction that mentioned clinical guidance referenced the Pharmacogenomics Knowledgebase (PharmGKB) or one of their annotation sources, such as DPWG and CPIC. This correlates with the data found in Canada and the United States. It appears that globally, these three sources form the foundation of pharmacogenomic clinical guidance.

Guiding Principles

The Provincial Genetics Program, at the request of the Ministry of Health's Laboratories and Diagnostics Branch and with advice from the Provincial Genetics Advisory Committee (PGAC), convened the Pharmacogenomics Working Group (Working Group) in September 2022 to develop a recommendation report to guide the implementation and delivery of pharmacogenomic testing[1] in Ontario.

To support the development of recommendations, the Working Group advised on the following guiding principles for PGx testing:

- The contribution of genetic variation to drug response is complex, highly multifactorial and can be impacted by other drugs (polypharmacy), diet and other patient-specific factors. Complex clinical scenarios, including polypharmacy, may require specialized consultation.
- Before a PGx test is requested, clinicians should consider the aim of the test and have a clear understanding of how the result will be interpreted and how the patient's management will be affected by the result.
- PGx testing should be focused on drugs for which adverse effects (including toxicity) or treatment failure can be predicted and prevented/avoided.
- PGx tests should be widely applicable to a broad pan-ethnic population. Clinical utility and applicability of PGx testing in diverse populations should be considered in the design and/or implementation of new PGx tests (42, 43).
- PGx tests should have prescribing actionability and associated clinical guidelines for use.
- If alternate drug therapies are not approved by Health Canada, funded and/or available for use, planning for this should occur concurrently with planning for PGx test implementation.
- Participating laboratories should offer testing that is standardized, comprehensive, evidence-based and coordinated across the province.
- PGx testing should not be funded if there is an equivalent drug (i.e., drug actionability and cost) that could be prescribed that does not have PGx implications.
- PGx testing should not be used for the renewal of a medication that a patient is already benefiting from and tolerating well.
- The clinical utility of proactive population based PGx screening in the absence of a clinical indication is not supported by evidence at this time.

[1] In this context, pharmacogenetics is defined as genetic variants affecting drug metabolism and kinetics (e.g., CYP450 enzymes).

Recommendations

Recommendation 1: Utilize a systematic process to develop guidance for pharmacogenomic tests.

The Working Group recommends that a PGx expert group be established within the Provincial Genetics Program (PGP) at Ontario Health. The expert group model utilizes a multidisciplinary approach to horizon scanning, priority setting and advice development to improve quality and standardize service delivery. In partnership with the PGP, the Pathology and Laboratory Medicine Program (PLMP) at Ontario Health provides oversight of laboratory genetic testing, including planning, budgeting, implementation, and performance monitoring.

The PGx Expert Group would consist of a Clinical Lead and a multidisciplinary group of experts from across the province. Ad hoc participation by a diverse group of clinical experts may be required based on the PGx tests being discussed. Subspeciality groups relevant for ad hoc membership might include oncology, gastroenterology, rheumatology, immunology, and complex pediatrics.

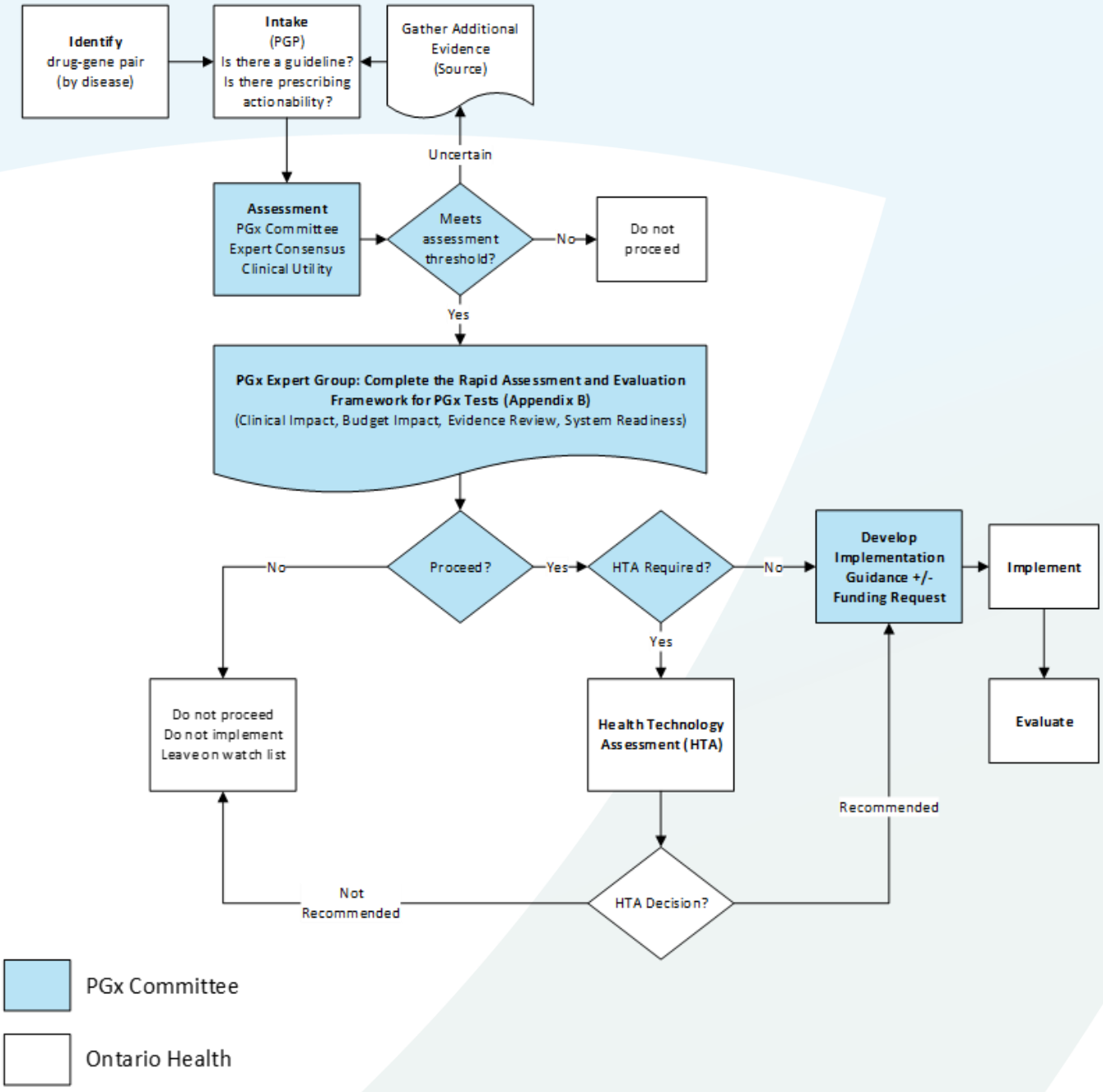
The core members of a PGx Expert Group should include:

- Pediatric and adult clinical pharmacologists
- Community and/or clinical pharmacist
- Primary care clinician
- Clinical molecular geneticist
- Genetic counsellor and/or clinical geneticist
- Clinical biochemist
- Health informatics specialist
- Ontario Health staff

The development of guidance from the PGx Expert Group would be supported by existing Primary Care Genetics Reference Table and Patients and Caregivers Genetics Reference Table. The PGP would also ensure alignment of Expert Group activities across all PGP Expert Groups. Case-by-case review, supported by clinical expert advice, may be required for rare clinical scenarios involving a PGx test that is not associated with an existing clinical guideline. There is a mechanism through the Ministry of Health's Out-of-Country & Out-of-Province Prior Approval Program to evaluate these requests and make funding decisions for out-of-country/province testing.

The PGx Expert Group would be tasked to review and evaluate existing guidelines, relevant scientific literature, and clinical appropriateness of PGx tests. This group would provide consensus recommendations regarding clinical utility and public funding, as well as develop clinical guidance and technical and analytical requirements of testing to support implementation. The recommended activities of the PGx Expert Group are outlined in Figure 1. The activities outlined in Figure 1 are designed to coordinate with other implementation pathways established at Ontario Health.

Figure 1: Process Map for Pharmacogenomics Expert Group Activities



Process Map for Pharmcogenomics Expert Group Activities - Summary of Steps:

1) **Identify:** A drug-gene-syndrome is identified and a PGx test is submitted to **Intake** through a transparent process for provincial implementation. Tests may be identified broadly from health sector partners that may include clinicians, PGP Expert Groups, industry, patients/public, Ministry of Health or Ontario Health programs.

2) **Intake:** The PGP becomes the landing site/group for formal intake. The submitter is responsible for providing the following supporting evidence with their submission:

    a. Summary of existing clinical guidance (e.g., CPIC, PharmGKB, DPWG, CPNDS, RNPGx)
    b. Associated PGx-related drug labelling information (e.g., Health Canada or FDA)
    c. Applicable professional clinical society recommendations
    d. Summary of prescribing actionability
    e. Summary of clinical need and utility
    f. Summary of recommended steps for implementation and potential challenges

    The PGP will assess the evidence provided, consider any equity and access issues, triage submissions for assessment by the PGx Expert Group, and engage health system partners (e.g., Ontario Public Drug Programs) as needed.

3) **Assessment:** PGx Expert Group will be established to perform assessment of PGx tests that have been through the formal intake process. Initial assessment includes expert consensus of PGx Expert Group members, and a representative from specialty area(s) if applicable/as needed.

    a. **Rapid Assessment and Prioritization Framework** – an evaluative framework would ensure a documented and standardized process is followed to answer a set of questions/criteria for each PGx test. PGx tests should be evaluated based on the patient population, the drug(s), the gene variant(s) and the disease/condition for which drug therapy is required. Using a rapid evidence synthesis and review process, the framework would consider the clinical impact, high level budget impact, equity/access issues, and system readiness factors (see Appendix B).

        - **Proceed? Decision:** The decision coming out of the prioritization framework determines if the PGx test should be prioritized for further evaluation and/or provincial implementation. Ministry of Health will be briefed at this stage.
        - **HTA Required? Decision:** If the PGx testing has one or more high-cost, high-complexity, conflicting pieces of evidence, the PGx Expert Group may decide that a full formal HTA and/or cost-effective analysis is required to support decision making. The PGx Expert Group could decide that a formal HTA is not required based on the evidence review and expert consensus.

    b. Develop implementation guidance (including clinical guidance) and a volume-based funding request (~4-8 month process).
        - This process would be led by Ontario Health staff with input from the PGx Expert Group, Primary Care Genetics Reference Table, and Patients and Caregivers Genetics Reference Table members.

4) **Implement:** Initiate implementation following required approvals of the guidance (Ontario Health/PGx Expert Group) and funding (Ministry of Health/Ontario Health). Implementation would require:

    a. Laboratory test validation and licensing
    b. Harmonizing PGx test reporting and interpretation among participating laboratories

c. Knowledge transfer and exchange activities in consultation with appropriate clinical groups
d. Communication plan
e. Measurement strategy
f. Primary Care Genetics Reference Table engagement
g. Patients and Caregivers Genetics Reference Table engagement

Implementation may include designing and piloting the PGx test in learning health systems to collect real world data and evidence for the purpose of measuring impact in Ontario and revising and refining the implementation as required. Measurement will require linking PGx test results data to administrative health datasets. The PGx Expert Group would help to define performance metrics related to health outcomes, health system value, patient satisfaction, and clinician experience. These metrics would be used to inform data collection, evaluation, and improvement initiatives. By defining a clear method for prospective assessment, a pathway to broader implementation (or disinvestment) could then be mapped.

5) **Evaluate:** Monitor and evaluate performance and quality measures and outcomes, and implement modifications based on the results as required.

Recommendation 2: Enable clinical service delivery pathways that facilitate timely, equitable access

The integration of PGx tests into clinical pathways is vital to ensure timely and equitable access to testing that informs treatment planning and management. Clinical implementation considerations may vary considerably for individual PGx tests, patient age, and disease/condition.

While most medications for an individual patient are prescribed through primary care clinicians, PGx testing may provide benefits for patients across the health care system. For example, genetic testing of tumour specimens (biomarkers) is common in oncology populations, used to individualize systemic chemotherapy planning. PGx analysis for the purposes of medication usage and dosing, however, is far less common across other hospital and ambulatory clinic settings. The availability of PGx consultation services staffed by clinical pharmacologists or pharmacists with expertise in PGx is highly limited.

To support equitable access to PGx testing for eligible patients, the Working Group recommends the following:

1) Decisions about PGx testing and subsequent prescribing should ideally be made in a team-based model of care for individuals who meet established eligibility criteria. PGx testing can be ordered by various prescribers on the health care team if it is within their scope of practice. This can include clinical pharmacologists, primary care clinicians, specialists, and pharmacists. Dosing and/or prescribing actions should include full medication reconciliation and consultation with the prescriber who has relevant and current knowledge of the patient's full medical history.
2) Access to a consultation with a clinical pharmacologist or pharmacist with expertise in PGx, should be provincially available to the prescriber. Access could be facilitated through various

communication methods including eConsult, virtual consultations and/or provincial multidisciplinary care rounds.

3) A provincial digital strategy should be implemented to ensure the PGx lab report is available in the EMR of all locations where a patient receives their care and is supported by Clinical Decision Support Tools.

The need for a pre-emptive vs. reactive approach to PGx testing will vary depending on the clinical indication, however, the Working Group recommends that the following circumstances warrant consideration of a pre-emptive approach to PGx testing:

1) Medically high-risk populations, including complex pediatric patients, patients with cancer, patients who are immunocompromised and/or those requiring organ transplant. A PGx gene panel or PGx test could be offered that includes gene variants that impact metabolism of commonly prescribed drugs for the patient population in question (e.g., treating fungal infections in immunocompromised patients).
2) PGx tests that impact prescribing actionability but require an urgent turnaround time as the drug cannot be prescribed safely without the test result.
3) PGx testing combined with genetic testing done for other purposes with informed consent of the patient and/or caregiver. Examples could include:
    a. Reporting out PGx variants as secondary findings for patients eligible for diagnostic whole-exome or whole-genome sequencing
    b. Reporting out relevant PGx variants for patients eligible for disease-specific gene panels (e.g., PGx variants for anti-epileptic drugs in a patient eligible for a hereditary epilepsy gene panel)
4) Where a pre-emptive approach improves efficiency and cost-effectiveness for lab operations, this potential benefit needs to be weighed against the potential risks associated with generating information that is not needed for the immediate treatment of the patient and may cause distress and/or confusion for the patient, and/or may require additional clinician time/resources.

Conversely, the Working Group recommends that pre-emptive PGx testing may not be necessary in the following circumstances:

1) Initiation of drug therapy that can safely wait until PGx results are available within a routine lab turnaround time.

2) Initiation of drug therapy prior to PGx results when the benefits of therapy outweigh the potential side effects to drug response.

Recommendation 3: Standardize pharmacogenomic testing and reporting across Ontario.

Ontario laboratories have a long and successful history of providing genetic testing services for the people of Ontario. One of the earliest examples is the implementation of newborn screening in the 1960s, with more recent examples including the implementation of the Provincial Genetics Program, Hereditary Cancer Testing, and Genome Sequencing Ontario. Ontario labs are accustomed to the guidelines and standards required for successful implementation of genetic testing programs, and the approach to PGx testing should be no different (44).

Currently, implementation of PGx testing in Ontario has been driven at the institutional level, mainly through research programs offering testing and associated clinical services. The exception to this has been the recent provincial approval of publicly funded *DPYD* testing for individuals prior to starting fluorouracil chemotherapy. At the time of this report, implementation planning is in progress for this testing. When considering how institution-level PGx implementations could be scaled provincially, collaboration between participating labs and establishing best practices for PGx testing and reporting is required. The Working Group recommends that Ontario laboratories should:

- Comply with the PGx lab testing criteria set by Ontario Health, which includes the licensing requirements determined by the Ministry of Health, and accreditation standards set by Accreditation Canada Diagnostics.
- Endorse and follow the American College of Medical Genetics (ACMG) technical standard: Clinical pharmacogenomic testing and reporting: A technical standard of the American College of Medical Genetics and Genomics (ACMG) (45).
- Utilize genetic testing technologies that enable re-analysis of genomic data as new knowledge emerges.
- Participate in provincial pre- and post-implementation planning, in collaboration with Ontario Health and testing laboratories, to standardize reporting requirements and incorporate feedback from prescribers. Genetic reports should provide evidence and interpretation that clinicians can use to make treatment decisions.
- Commit to continuous quality improvement initiatives, which may include contributing to educational programs and/or PGx discussion boards/rounds.

Recommendation 4: Optimize utilization with education for patients, the public, and health care professionals.

Prescribers may have limited knowledge and confidence in utilizing PGx testing, despite recognizing the potential benefits to patients and the health care system. There is a gap in the availability of clear, trusted resources and tools to support education for the public, patients, and health care professionals. While it is important to include pharmacogenomics curriculum in formal education pathways for clinicians, the need for “just in time” education to prescribers is significant. Clinical decision support should be integrated into EMRs, and peer to peer consultation pathways should be

established. To optimize appropriate uptake and utilization of PGx testing, the Working Group recommends the following strategies:

- Advocate for embedding PGx education in post-secondary education curriculums for physicians, pharmacists, geneticists, genetic counsellors, and any prescribing clinicians as appropriate.
- Plan for continuing education offerings for prescribers who are already licensed in their field, including a centralized resource that includes educational information for clinicians and patients. This resource should include clear and concise language with accompanying visuals/infographics to minimize barriers related to language and/or genetics jargon, and continually updated information on publicly funded PGx tests, including:
  - Patient eligibility
  - Rationale and evidence for testing
  - Instructions on ordering and interpreting tests
  - Clinical guidance for medical management based on the results
  - Information on who to contact with questions of any of the above
- Promote colleague to colleague collaboration by encouraging the identification of an onsite 'champion' or utilizing eConsult (or similar service) for expert advice.
- Develop a Frequently Asked Questions (FAQ) document to educate the public and providers on the risks, benefits and limitations of PGx testing, including self-pay options. High-quality information on clinical utility of PGx testing can support decision-making for individuals who are considering paying privately for the service.
- Plan and deliver knowledge transfer and exchange activities through presentations at conferences and communities of practice, regulatory colleges and professional associations, and through scientific publications.
- Include broad representation of people with lived experiences in the development of educational tools and resources by requesting their participation through existing Ontario Health consultation mechanisms.

Recommendation 5: Monitor performance through measurement of quality indicators.

System-level quality assurance through measurement and evaluation should drive ongoing improvements in PGx testing, including consideration of disinvestment of testing where evidence of clinical utility has not been demonstrated following implementation. The Working Group recommends that measurement should be tailored to the test in question, as the implementation pathway of provincially funded PGx testing might be different depending on the drug-gene pair. For example, if an implementation pilot is recommended, the collection and analysis of real-world data might be needed to support more broad-based province-wide implementation. For all tests, measurement and evaluation should include processes for data collection that enable reporting on patient access to testing, with metrics for timeliness, safety, and equity. Once these metrics are established, the focus should shift to setting targets for performance management.

The need to collect test result data provincially extends beyond the scope of PGx testing to include all genetic testing. A broader strategy for the collection, storage and use of this data is under development at Ontario Health. While the time-limited collection of real-world data may initially be feasible in a pilot setting without the larger data strategy in place, it is not a sustainable solution on a provincial scale. Ontario's genetics digital strategy must be implemented to support ongoing performance and quality measurement of all genetic testing performed in Ontario, including PGx testing.

Discussion

PGx testing has been available for decades in Ontario, demonstrating its potential to improve prescribers' ability to change patient outcomes, and enhance decision making for drug therapy through institutionally based research and clinical pharmacology programs. At a provincial level, knowing what PGx testing should be available to patients is challenging. At an institutional level, implementation can be targeted to specific patient populations, tailored to the expertise of the available ordering and managing clinicians, and enabled through defined physical and digital infrastructure. Scaling the learnings from these local models adds complexity, and a methodological approach to the decision-making process is required, along with an evaluation of system-level clinical readiness.

The recommendations within this report propose a way forward for a provincial approach to PGx implementation in Ontario, led by Ontario Health's Provincial Genetics Program. The PGx Working Group advised that these recommendations be applied initially to PGx testing that is targeted to a specialized group of prescribers within clearly defined systems of care to ensure the clinical infrastructure is in place to support it. A good example of this is *DPYD* testing, which is currently planned for provincial implementation in the oncology setting for patients with cancer prior to initiation of fluoropyrimidines. The Working Group prioritized *TPMT* and *NUDT15* testing prior to initiating azathioprine and mercaptopurine as the priority for provincial implementation for similar reasons (i.e., prescription initiated by a specialist). Consensus was gained through the outcome of drug-gene pair voting results (Appendix A) and working group discussion. Over time, lab and clinical PGx knowledge in the province will grow through the application of these recommendations and establishment of the PGx Expert Group, broadening opportunities for PGx implementations within additional clinical models of care and testing technologies. Ongoing evidence generation could be strengthened through implementation pilots in learning health systems and strategic collaborations with research partners.

Appendix A: Drug-Gene Pairs of Interest

The list of drug-gene pairs below was presented to the Working Group as potential options for provincial implementation, simulating the "Identify" and "Intake" steps of the Process Map (Figure 1). The list was formatted into a voting tool for the Working Group members to cast their vote on each drug-gene pair, to initially prioritize the options. Working Group members could vote to endorse (yes), not endorse (no), or abstain from voting. Below is a summary of the voting results and background information on each drug-gene pair.

Gene(s)	Drug(s)	# Votes	# Endorsed	% Endorsed	Summary of Comments
TPMT, NUDT15	Azathioprine and mercaptopurine	9	9	100%	No comments
CYP2C19	Clopidogrel	9	9	100%	No comments
CYP3A5	Tacrolimus	9	9	100%	No comments
CYP2C19	Proton Pump Inhibitors: lansoprazole, dexlansoprazole, pantoprazole, omeprazole	9	8	89%	• Major implementation challenges as so commonly prescribed • Might test only in selected instances of therapeutic failure • Yes, but will require a lot of education on the part of the major prescriber group
CYP2C9, VKORC1, CYP4F2	Warfarin	8	7	88%	• Only if timeline permits • *CYP4F2* may have very limited effect on warfarin • How often will this test be of relevance in the future given the use of direct oral anticoagulants?
SLCO1B1, ABCG2	Rosuvastatin	9	7	78%	• Selected instances only • Published clinical guidance available for *SLCO1B1* and *CYP2C9* but not available for *ABCG2*
SLCO1B1	Atorvastatin	9	7	78%	• Selected instances only
SLCO1B1	Simvastatin	9	6	67%	• No reason to prescribe this drug
CYP2D6	Codeine and tramadol	9	4	44%	• Major implementation challenges as so commonly prescribed • Testing not needed, many therapeutic alternatives • Note that *CYP2D6* testing may be more technically challenging as it includes genotype testing, and copy number testing

Gene(s)	Drug(s)	# Votes	# Endorsed	% Endorsed	Summary of Comments
CYP2D6	Ondansetron	9	3	33%	• Note that *CYP2D6* testing may be more technically challenging as it includes genotype testing, and copy number testing

TPMT AND *NUDT15* – AZATHIOPRINE AND MERCAPTOPURINE

Azathioprine and mercaptopurine are immunosuppressants used to manage inflammatory bowel disease, other autoimmune conditions and childhood leukemias. They are also used to prevent kidney transplant rejections (46-48).

The active metabolites of azathioprine and mercaptopurine are thioguanine nucleotides (TGNs). TGNs are metabolized and inactivated by the enzymes thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) through its nucleotide diphosphatase activity. However, certain genetic variants of the *TPMT* and *NUDT15* genes have been associated with reduced TPMT and NUDT15 enzyme activity. In people who carry these variants, conventional doses of azathioprine or mercaptopurine may result in a buildup of TGNs. This accumulation can increase the risk of bone marrow toxicity (46-48).

CYP2C19 – CLOPIDOGREL

Clopidogrel is an antiplatelet drug used to reduce the risk of heart attack and stroke. The enzyme cytochrome P450 2C19 (CYP2C19) helps convert clopidogrel to its active metabolite (49).
Certain genetic variants of the *CYP2C19* gene have been associated with reduced enzyme activity. People who carry these variants convert clopidogrel to its active metabolite less effectively. This may reduce the effectiveness of clopidogrel (49).

CYP2C9, *VKORC1,* AND *CYP4F2* – WARFARIN

Warfarin is an anticoagulant used in the management of thrombotic conditions. It acts by blocking clotting factors that are dependent on vitamin K for their synthesis (50, 51).

Genetic and dietary factors interact to alter the dose of warfarin needed to effectively reduce coagulation. Incorrect blood concentrations of warfarin may decrease its effectiveness or lead to adverse reactions. Therefore, the dose prescribed must be tailored to each patient (50, 51).

Genes that may influence warfarin dosing include *VKORC1*, *CYP2C9,* and *CYP4F2*. The enzymes they encode support vitamin K function and warfarin metabolization (50, 51).

CYP2D6 – CODEINE AND TRAMADOL

Codeine and tramadol belong to a class of drugs known as opioid analgesics. The cytochrome P450 2D6 (CYP2D6) enzyme converts codeine and tramadol to their active metabolites (52, 53).

Some genetic variants of the *CYP2D6* gene may reduce CYP2D6 enzyme activity. In people who carry these variants, most frequently due to the presence of additional copies of the *CYP2D6* gene, a conventional dose of codeine or tramadol may limit analgesia (52, 53).

Other genetic variants in the *CYP2D6* gene may increase CYP2D6 activity. In people who carry these variants, a conventional dose of codeine or tramadol may increase the risk of serious adverse reactions. These can include respiratory depression (52, 53).

CYP3A5 – TACROLIMUS

Tacrolimus is an immunosuppressant commonly used after organ or stem cell transplantation. The enzyme cytochrome P450 3A5 (CYP3A5) helps metabolize tacrolimus (54).

In many people, CYP3A5 is inactive due to the presence of common loss-of-function genetic variation in this gene. However, some people possess a genetic variation that enables CYP3A5 to become active. In such patients, tacrolimus is metabolized more rapidly. This affects the concentration of tacrolimus in the body. In people who carry these variants, a conventional dose of tacrolimus may be ineffective (54).

CYP2C19 – PROTON PUMP INHIBITORS (PPIS)

Proton pump inhibitors (PPIs) are drugs used to reduce gastric acidity. Examples of PPIs include omeprazole, lansoprazole and pantoprazole (55, 56).

The enzyme CYP2C19 helps metabolize various PPIs. In some people, gain-of-function genetic variation in the *CYP2C19* gene may increase the rate of PPI metabolism. In these people, a conventional PPI dose may not be as effective, because the drug rapidly breaks down in the body. Other variants of the *CYP2C19* gene are associated with loss of enzyme function. This loss may decrease the rate of PPI metabolization. In these people, a conventional PPI dose may reduce gastric acidity more effectively (55, 56).

CYP2D6 – ONDANSETRON

Ondansetron is a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist. It is used to help prevent nausea and vomiting from chemotherapy, radiation or surgery (57).

CYP2D6 is an enzyme that helps metabolize ondansetron. Some genetic variants of the *CYP2D6* gene may increase ondansetron metabolism. In people who carry these variants, a typical dose of ondansetron may be ineffective (57).

SLCO1B1 AND *ABCG2* – STATINS

Statins are drugs that help reduce cholesterol. Some commonly prescribed statins include rosuvastatin, simvastatin and atorvastatin (58).

The uptake of all statins into the liver is dependent on a hepatic transporter encoded by the *SLCO1B1* gene. The absorption of rosuvastatin is dependent on an efflux transporter encoded by the *ABCG2*

gene. Genetic variants of these genes may alter the concentration of statins in the body and increase the risk of statin-associated musculoskeletal symptoms (SAMS) (58).

Appendix B: Rapid Assessment and Evaluation Framework for Pharmacogenetic Tests

GENERAL INFORMATION

- Source of intake
- Date of review
- Review panel members
- Drug-gene pair (including gene variants)
- Condition/Indication (including prevalence/incidence in the general population)
- Summarize the need for testing.
- The submitter is responsible for providing the following supporting evidence:
  - Summary of existing clinical guidance (e.g., CPIC, PharmGKB, DPWG, CPNDS, RNPGx)
  - Associated PGx-related drug labelling information (e.g., Health Canada or FDA)
  - Applicable professional clinical society recommendations
  - Summary of prescribing actionability
  - Summary of clinical need and utility
  - Summary of recommended steps for implementation and potential challenges

CLINICAL IMPACT

- How common is/are high-risk genetic variants? (# of people in Ontario)
  - General population in Ontario
  - Specific condition/indication
  - Specific ethnic groups
- Are the genetic variants associated with adverse drug reactions? Specify.
- Do the genetic variants impact drug efficacy? Specify.
- How commonly is the drug prescribed? (# of people in Ontario who had had prescriptions dispensed)
- Is there prescribing actionability?
  - Are all PGx directed drugs publicly funded? (Privately funded?)

- What are major non-genetic sources of drug response variability?
  - List known drug-drug interactions
  - Patient health status (e.g., liver function, kidney function, etc.)
  - If known, indicate proportion of drug response that is PGx-related.
- What are the potential incidental findings and/or implications of testing? For example, visit: ncbi.nlm.nih.gov/pmc/articles/PMC8517135/#!po=22.7273
- What are the ethical, legal, or psychosocial implications of testing?
- What are the access and equity implications of testing?

BUDGET IMPACT

- Cost of testing will be calculated using the per-test cost and the expected number of people eligible for the test
- Budget impact of changes to drug usage
  - Cost avoidance + cost of alternate therapy
  - Current case costing

EVIDENCE SYNTHESIS AND REVIEW

- Published guidelines from CPIC, DPWG, PharmGKB, FDA, CPNDS, and RNPGx will be considered and assessed for:
  - Evidence rating
  - Clinical guidance
- Additional evidence sources if available:
  - Position statements from professional medical societies
  - Systematic reviews
  - Published economic or cost-effectiveness analyses
  - Randomized control trials
  - Real world evidence
  - Health Technology Assessments (HTA)
- Evidence assessment (Note: further work is required to define the evidence assessment groupings)
  - Strong
  - Moderate
  - Weak

SYSTEM READINESS

- Are there any laboratories currently licensed for this test in the province (and/or running a research panel)?
- Are alternative drugs available and/or funded?
- Are there clinical decision support tools available?
- Are clinician education resources available?
- Are patient education resources available?
- Are there potential challenges associated with the recommended approach to implementation?

PANEL DECISION SUMMARY

Panel Recommendation:

- Recommend full HTA
- Recommend cost-effectiveness analysis
- Implement
- Implement Pilot for Evidence Generation
- Do not implement
- Leave on watch list
- Other, please describe

Priority Level:

- Essential for drug safety/efficacy
- Beneficial to guide drug and dose selection
- Potentially beneficial on a case-by-case basis
- Unclear benefit/ insufficient evidence to support clinical utility

FINAL RECOMMENDATION

Include the Panel Recommendation and Priority Level.

Acronyms

ACMG	American College of Medical Genetics
CADTH	Canadian Agency for Drugs and Technologies in Health
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
DPWG	Dutch Pharmacogenetics Working Group
EMR	Electronic medical record
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
HTA	Health technology assessment
LILI	Laboratory Information Licensing System
MOH	Ministry of Health
OGAC	Ontario Genetics Advisory Committee
OHTAC	Ontario Health Technology Advisory Committee
PGAC	Provincial Genetics Advisory Committee
PGP	Provincial Genetics Program
PGx	Pharmacogenetics/Pharmacogenomics
PharmGKB	Pharmacogenomics Knowledgebase
PLMP	Pathology and Laboratory Medicine Program
PPI	Proton pump inhibitor
RNPGx	French National Network of Pharmacogenetics (Réseau National de Pharmacogénétique)
SAMS	Statin-associated musculoskeletal symptoms
U-PGx	Ubiquitous Pharmacogenomics

Glossary

Adverse drug reaction - An unwanted, harmful reaction to the typical use of a drug.

Allele - One or more variations of DNA at a particular location of the genome.

Gene - Fragments of DNA that contain instructions for making molecules necessary to support life.

Genotype - The alleles found at a particular location of the genome.

Pharmacodynamics - The actions of a drug in the body.

Pharmacogenetics - The study of how genetic variability in a single gene can impact the response to a drug.

Pharmacogenomics - The study of how genetic variability in multiple genes affects drug response.

Pharmacokinetics - The process by which drugs are absorbed, distributed, metabolized, and eliminated from the body.

Phenotype - The characteristics or clinical presentation that result from a particular genotype.

Polypharmacy - Multimorbidity and the associated use of multiple medicines.

Precision medicine - A personalized approach to patient management that considers genetic variation, lifestyle factors, and environmental differences.

Pre-emptive testing - PGx testing that is utilized before a specific diagnosis or drug therapy is identified. The results of this testing can be consolidated into the Electronic Medical Record (EMR), where it is made available to prescribers.

Reactive testing - PGx testing that is utilized after a drug therapy is indicated. This type of testing can be conducted prior to the prescription of a high-risk drug or after the occurrence of an adverse drug reaction.

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