Pharmacogenomics in Pharmacy Practice

by

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Abstract

Background: Pharmacogenomics (PGx) has potential to improve healthcare through personalized drug selection and dosing using genetic predictors of pharmacokinetics and/or pharmacodynamics (PK/PD). Research is uncovering PGx's impact on morbidity and mortality from medication adverse effects and/or inefficacy. Additionally, prescribing guidelines are available from organizations such as the Clinical Pharmacogenomics Implementation Consortium to assist PGx-guided medication assessment. With competency in medication therapy management (MTM) and understanding of PK/PD, pharmacists are proposed to be implementers of PGx. Despite potential benefits and resources for PGx, it is not broadly utilized in Canada. For pharmacists to adopt PGx, it is imperative to evaluate the feasibility and clinical utility of PGx in pharmacy practice, and thus this thesis aims to 1) evaluate prior pharmacy PGx research, 2) improve and assess pharmacist PGx competencies, and 3) implement and observe PGx in community pharmacies.

Methods: A scoping review was conducted to identify non-oncologic pharmacy practices utilizing PGx. Terms were applied to MEDLINE, Embase, Scopus, CINHAL, and Web of Science Core Collection from inception to November 2020. With this review and other literature, a course on PGx was created. Pharmacists in Alberta were invited to participate in 5 hours of didactic lectures and 6 case studies through virtual synchronous, online asynchronous, or mixed method learning. Course efficacy was evaluated through pre- and post-course surveys measuring subjective and objective competency in PGx through 11 Likert-scale and 7 exam-style questions, respectively. Following education, some pharmacists implemented PGx testing in community pharmacies. Data was collected on demographics, PGx indication, PGx results, and identification of drug-gene interactions (DGIs). A feasibility assessment was performed, summarizing mean time of service.

Results: The review found 43 studies between 2007-2020 describing applications of PGx in pharmacy practice. Most occurred in institutional (51.2%) or community pharmacy (23.3%) settings, with others in primary care clinics (11.6%), long-term care (4.7%), pharmacy benefit managers (4.7%), hospice (2.3%), and home-health (2.3%). Cardiovascular, psychiatric, and analgesic PGx applications were most common, with many studies evaluating the use of multi-gene panels in a complex polypharmacy population. Therefore, these topics were of key focus in the PGx education course. Thirty-six pharmacists (10 synchronous, 9 asynchronous, and 17 mixed) were included in the primary analysis. These pharmacists reported experience in community (88.9%), hospital (38.9%), academic (8.3%), and industry (5.6%) settings; 69.4% reported prior education or exposure to PGx. Responses on confidence and opinions in PGx moved from a median of "Disagree" at baseline to "Agree" after receiving PGx education (2-point difference on Likert Scale [1,2]; $p < 0.001$), indicating improved self-rated competency and positive opinions after training. Likewise, participant grades on the knowledge test improved with education (20.8 ± 21.9% pre-course vs. 70.2 ± 19.1% post-course, $p < 0.001$ with a strong correlation between increases in attested and tested competency (mean Likert responses in agreeance with confidence in pharmacogenomics increased by 0.12 ± 0.03 points for every correct answer gained on the knowledge test after education; $r = 0.516$, $p = 0.002$). Pharmacists trained in PGx provided PGx testing to a total of 46 patients among 8 pharmacies across Alberta. Twenty-four test results have been returned with a mean of 1.1 DGIs per patient. Fifteen had care-plans with 26 drug therapy problems (DTPs) identified. DTPs were managed by monitoring without medication changes in 11 DTPs, and through recommendations made to the patient's primary care provider in 11 DTPs. Recommendations were to change medication (27.3% of recommendations), followed by dose increase (27.3%), dose decrease (18.2%), start new medication (18.2%), and stop medication (9.1%). On average, PGx-based services took pharmacists a total of 78.3 ± 12.2 minutes to provide ($n = 9$), with test turnaround times at 60 (30,65) days ($n = 19$).

Conclusion: PGx research in pharmacy has grown over the last decade, with evidence supporting a variety of indications. Pharmacists improved their knowledge in PGx proportional to their own self-assessed ability improvement through a tailored education program. Pharmacists were able to utilize PGx to identify DGIs and DTPs in implementation, collaborating with patients and other healthcare providers to tailor medication therapy in a precision medicine framework. Through evaluating the evidence, educating pharmacists, and observing the use of PGx in practice, we can support broad-scale adoption and future research of PGx in pharmacies across Alberta.

Preface

This thesis is an original work by Meagan Hayashi.

Chapter 2 of this thesis has been published as M. Hayashi, D.A. Hamdy, and S.H. Mahmoud, "Applications for pharmacogenomics in pharmacy practice: A scoping review," *Research in Social and Administrative Pharmacy,* vol. 18, issue 7, 3094-3118. All authors contributed to the methodology and article revisions. I contributed to data curation and interpretation, as well as to the original draft of the article. All authors approved of the final manuscript.

A version of Chapter 3 has been published as M. Hayashi, S.H. Mahmoud, and D.A. Hamdy, "The efficacy of a didactic and case-based pharmacogenomics education program on improving the knowledge and confidence of Alberta pharmacists," *Pharmacogenomics and Personalized Medicine,* vol. 15, 409-427. This research received ethics approval from the University of Alberta Research Ethics Board, titled "Evaluation of the Effectiveness of a Didactic and Case-Based Education Program on Pharmacist Knowledge and Comfort in Pharmacogenomics," Pro00108818, March 14, 2021 (**Appendix A**). All authors contributed to the methodology, article revisions, as well as the conceptualization and delivery of the pharmacogenomics course described herein. I contributed to data collection, statistical analysis, and the original draft of the article. Dr. Sherif H. Mahmoud assisted with the statistical analyses and interpretation. Dr. Dalia A. Hamdy was the supervisory author and was responsible for conceptualization. All authors approved of the final manuscript.

The research presented in Chapter 4 of this thesis received ethics approval from the University of Alberta Research Ethics Board, titled "Pharmacogenomics in the Community Pharmacy Setting: A Prospective Observational Study, Pro00112442, September 9, 2021 (**Appendix B**). This research is in progress at the time of this thesis submission.

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List of Abbreviations

AACP	American Association of Colleges of Pharmacy
ACP	Alberta College of Pharmacy
ADR	adverse drug reaction
CACP	Comprehensive Annual Care-plan
CAD	coronary artery disease
CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP	cytochrome P450
DDGI	drug-drug-gene interaction
DDI	drug-drug interaction
DGI	drug-gene interaction
DNA	deoxyribonucleic acid
DPWG	Dutch Pharmacogenetics Working Group
DRP	drug-related problem
DTP	drug therapy problem
ED	emergency department
ER	emergency room
G6PD	glucose-6-phosphate deficiency
GAD	generalized anxiety disorder
GERD	gastroesophageal reflux disease
HCP	healthcare practioner or healthcare provider
HRU	healthcare resource utilization
I/D	insertion/deletion
IM	intermediate metabolizer
LOF	loss of function
LOS	length of stay
MACE	major adverse coronary event
MDD	major depressive disorder
MTM	medication therapy management
NM	normal metabolizer
OATP1B1	organic anion tranporting polypeptide family member 1B1
PCI	percutaneous coronary intervention
PD	pharmacodynamics
PGx	pharmacogenetics or pharmacogenomics
PharmGKB	Pharmacogenetics Knowledge Base
PHQ-9	Patient Health Questionare 9
PK	pharmacokinetics
PM	poor metabolizer
PPI	proton pump inhibitor
RM	rapid metabolizer
RNA	ribonucleic acid
RT-PCR	real-time polymerase chain reaction
SLCO1B1	solute carrier organic anion transporter family member 1B1
SMMA	Standard Medication Management Assessment
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
TAT	turnaround time
UM	ultrarapid metabolizer

Chapter 1: Introduction

1.1 Pharmacogenetics primer

In 510 BC, Pythagoras first observed what is now understood as glucose-6-phosphate dehydrogenase (G6PD) deficiency when only a portion of the population would develop hemolytic anemia secondary to fava bean ingestion.[1,2] Single nucleotide polymorphisms (SNPs) for this enzyme are now understood to cause a condition known as G6PD deficiency, which is associated with hemolytic anemia following administration of some common medications[2] including nitrofurantoin,[3] primaquine,[4] and gliclazide.[5] SNPs are substituted nucleotide(s) in deoxyribonucleic acid (DNA) sequences among the population, one form of genetic variation that can alter functional proteins such as G6PD, in this case giving rise to an increased risk of drug toxicity. [2,6,7] Individual genetic variation is the crux of the science now understood as pharmacogenetics (PGx), the study of how our DNA affects our responses to medications either by altering their disposition (pharmacokinetics, PK), or their effect on the body (pharmacodynamics, PD).[6] In addition to SNPs, this genetic variation can occur as the addition or removal of nucleotide(s) in a sequence, known as insertion/deletion (I/D) polymorphisms.[6,7] In the coding region of DNA these SNP and I/D polymorphisms can alter functional protein structure thus increasing, decreasing, or even eliminating their activity (**Figure 1.1**).[6,7] Alternatively, polymorphisms in promotor regions may impact the observed effects of genes, referred to as a "phenotype," by increasing or decreasing gene expression,[6,7] as seen with the transcription of the enzyme cytochrome P450 (CYP) 3A4[8] and the serotonin transporter gene, solute carrier family 6 member 4 (*SLC6A4).*[9] Other pharmacogenetic effects are observed with *CYP2D6* gene duplication polymorphisms, wherein the entire gene is duplicated thus increasing enzyme activity.[10] Therefore, through differences in both transcription of DNA into ribonucleic acid (RNA), and translation of RNA into proteins, responses to medications can be considered an inheritable trait through alleles, the pairs of DNA sequences

individuals receive from parents.[11] These alleles can be tested for utilizing in-house or contracted labs, as well as increasingly available commercial test kits that test for a multitude of genes.[12] When a drug is known or suspected to be affected by the allele(s) carried by a person, this is often referred to as a "drug-gene interaction" (DGI). DGIs within the contexts of both medication safety and efficacy are analyzed by a few academic organizations, with the two largest being the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG). These organizations produce guidelines on medication dosing and monitoring in certain allele carriers that are readily accessible for practitioners through websites, scholarly publications, and the Pharmacogenomics Knowledge Base (PharmGKB), a free online resource.[13] Pharmacogenetics, named as such by Friedrich Vogel in 1959, provide some explanation towards the interindividual variability in drug response.[2 6 7 14] Albeit, it is important to remember that a single gene is very rarely the only factor in determining individual drug response: organ function, environment, diet, age, gender, and interacting medications are among many other considerations.[15] Furthermore, a medication's interaction with the protein products of multiple genes may contribute to a polygenic effect, giving rise to the more commonly referenced term, "pharmacogenomics".[6] Generally in the literature pharmacogenetics and pharmacogenomics are used interchangeably, abbreviated as "PGx."[16] PGx is considered a vital component in "precision medicine," (sometimes referred to as "personalized medicine,") a field which strives to consider all of these genetic and non-genetic considerations in delivering optimized pharmacotherapy.[12 17]

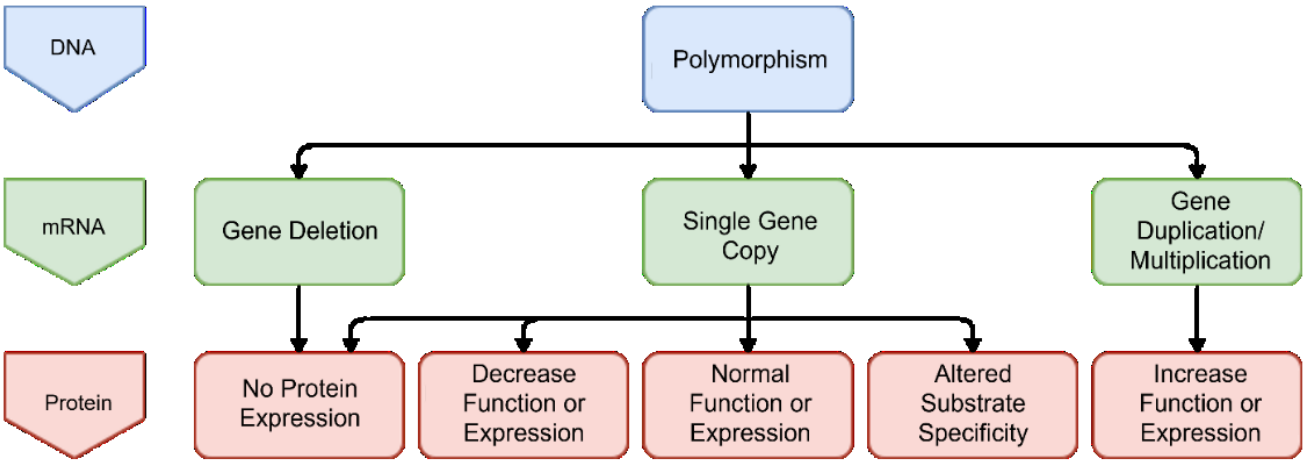

Figure 1.1. Examples of the effects of genetic variation within coding regions for functional proteins.

1.1.1 Pharmacokinetic (PK) PGx

Table 1.1. Examples of select pharmacokinetic pharmacogenes with clinical guidelines available for medication selection or dosing. *Not an exhaustive list of all present in the literature.

Gene (Protein)	Relevance	Medications Affected*	CPIC Guidelines*
CYP2C19 (cytochrome P450 enzyme 2C19)	Drug metabolism (phase I)	Clopidogrel, proton pump inhibitors, antidepressants,	Scott et al. (2013)[111]
CYP2D6 (cytochrome P450 enzyme 2D6)	Drug metabolism (phase I)	Antidepressants, codeine, tramadol	Crews et al. (2021),[31] Hicks et al. (2015)[38]
SLCO1B1 (solute carrier organic anion transporter 1B1)	Drug transporter	Statins, methotrexate	Ramsey et al. (2014)[112]
TPMT (thiopurine S-methyltransferase)	Drug metabolism (phase II)	Azathioprine, 6-mercaptopurine	Relling et al. (2019)[24]

Since the discoveries of Vogel, Pythagoras, and others in between, modern science has uncovered numerous detectable polymorphisms impacting medication response.[6] Many of these "pharmacogenes" are for metabolizing enzymes and transporters involved in drug disposition and pharmacokinetics (PK; **Table 1.1**).[6 18] Significant amounts of research has focused on genes encoding the cytochrome P450 superfamily of enzymes, which are thought to contribute to the elimination of approximately 50% of all medications on the market.[18-20] CYP enzymes, of which many are highly polymorphic among the population,[18] catalyze oxidation to increase the polarity of a medication for excretion via renal or biliary routes in one type of phase I metabolism.[21] This process can also facilitate

further metabolism by phase II enzymes such as uridine 5'-diphospho-glucuronosyltransferases (UDP-glucuronosyltransferases; UGTs) and N-acetyltransferases (NAT), both of which also have known polymorphisms.[22] [23] Other proteins worth mentioning in the context of PK-PGx include thiopurine methyltransferase (TPMT), and the organic anion transporting polypeptide 1B1 (OATP1B1). TPMT is a phase II metabolizing enzyme responsible for the deactivation of the thiopurine class of medications utilized in oncologic and autoimmune indications. Patients with poor function of this enzyme thus are at higher risk of hematological toxicity with these medications.[24] Organic anion transporting polypeptide 1B1 (OATP1B1), encoded for by the gene solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), is a transporter that primarily expedites hydrophilic medication access to the drug metabolizing enzymes within hepatocytes.[25] Medications affected by SLCO1B1 polymorphisms include atorvastatin and methotrexate, where dysfunction with this transporter subsequently reduces their metabolism and elimination, potentially increasing the risk of toxicity.[25] Standardized terminology has been adopted by the CPIC to describe the activity phenotype of these enzymes and transporters (**Figure 1.2**).[26] Most drug metabolizing enzymes can range from "poor metabolizer" (PM) to "ultrarapid metabolizer" (UM) status depending on the two alleles carried by a person.[26] Non-metabolizing proteins, such as OATP1B1, are referred to in terms of their function, from "no function" or "poor function," to "increased function."[26] While most medications at standard doses can be predicted to have a decrease in effect with an increase in metabolism and greater risk of side-effects with a decrease in metabolism, occasionally metabolism can lead to activation, potentiation, or even toxification.[27] Examples include the bioactivation of clopidogrel, a prodrug, by CYP2C19,[28] the potentiation of venlafaxine to the more-active O-desmethylvenlafaxine by CYP2D6,[29] and the toxification of diclofenac after production of an intermediate diclofenac-UDP conjugate by UGT2B7 contributing to hepatotoxicity.[30] These varied effects of metabolism create the need for an awareness not only for the enzymes and transporters involved in drug disposition, but also for a thorough understanding the intricate pathways disposition takes, in

order to correctly understand the impact on the functional proteins produced, or not produced, as a result of genetic polymorphisms.

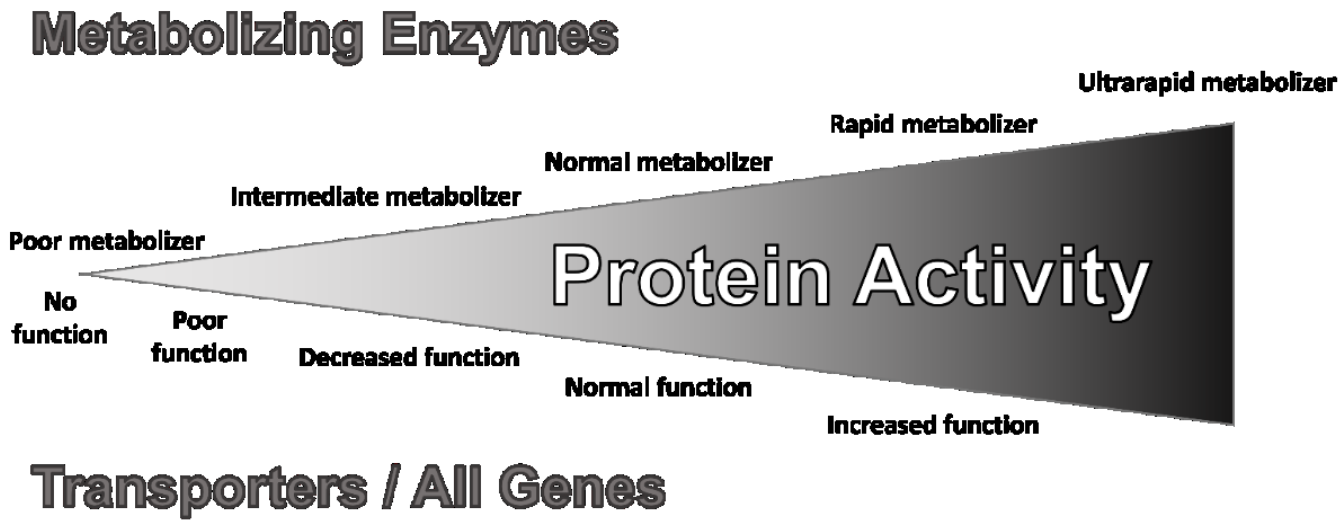

Figure 1.2. Functional classification of phenotype assignments developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC). Caudle, K. E., et al. Genet. Med. 2017; 19(2):215-223.

1.1.2 Pharmacodynamic (PD) PGx

Provided that therapeutic concentrations can be attained in an individual after its interaction with metabolizing enzymes and transporters, the effect of a medication is determined by its interaction with drug targets. This phenomena is often referred to as a drug's pharmacodynamics (PD). These can include the intended target of the medication, such as the μ-opioid receptor encoded for by opioid receptor mu 1 (*OPRM1)* gene. Limited evidence indicates that those carrying the rs1799971 G allele have greater opioid dose requirements, albeit at this time this evidence is not sufficient to recommend increasing initial doses from standard.[31] At times, the susceptibility of a person's diagnosis to treatment is affected by their own production of the drug target, as seen with promotor region variants affecting *SLC6A4*, the gene encoding for the serotonin transporter target of selective serotonin reuptake inhibitors (SSRIs).[9] Those with European ancestry and alleles coding for increased transcription, and thus greater density of serotonin transporters, are more likely to experience remission of major depressive disorder (MDD) when treated with SSRIs.[9] Further PGx implications can be seen with drug binding to

unintended targets, for instance in the increased weight gain observed with certain 5-hydroxytryptamine receptor 2C (*HTR2C*) polymorphisms and antipsychotics.[32] Pharmacodynamic PGx can also involve indirect pathways leading to adverse drug reactions (ADRs). Determining those at risk of ADRs are demonstratively imperative for some DGIs such as the examples provided in G6PD deficiency. Another well-known polymorphic gene with predictable ADRs is human leukocyte antigen major histocompatibility complex, class I, B (HLA-B). Abacavir[33] and carbamazepine[34] labelling include United States Food and Drug Administration (FDA) black box warnings for HLA-B genotyping to determine risk of severe, often fatal, cutaneous ADRs due to an off-target immunologic effect in certain HLA-B allele carriers.[35-37] It is therefore critical to consider both PK and PD effects in determining potential medication efficacy and toxicity in an individual when providing PGx-based personalized medicine.

1.3 Clinical, economic, and humanistic outcomes with PGx

Table 1.2. Clinical benefits observed with pharmacogenetic testing in clinical pharmacy practice. ER: emergency room; IM: intermediate metabolizer; LOF: loss-of-function; MACE: major adverse coronary event; PCI: percutaneous coronary intervention; PM: poor metabolizer.

Pharmacogenomic Test	**Clinical Outcome**	**Source(s)**
Multi-gene panel testing in the elderly polypharmacy population	Reduction in ER visits and hospitalizations	Elliott et al. (2017),[46] Brixner et al. (2016)[47]
Multi-gene panel testing patients with depression	Reduced time to symptom improvement	Papastergiou et al. (2021),[48] Battig et al. (2020)[45]
CYP2C19 genotyping in PCI	Reduction in MACE with genotype-guided prescribing in LOF allele carriers	Cavallari et al. (2018)[40]
CYP2D6 genotyping in chronic pain	Greater pain control with genotype-guided prescribing in IMs and PMs	Smith et al. (2019)[41]

Research to date has demonstrated that the use of PGx testing and precision medicine in pharmacy-developed patient care-plans can improve patient outcomes (**Table 1.2**). Genotyping has been shown to assist in selecting efficacious therapy and dosing in depression,[38] gastroesophageal reflux disease (GERD),[39] coronary artery disease (CAD),[40] and pain.[41] In regions where at-risk G6PD and

HLA-B polymorphisms are prevalent and the need for affected medications such as primaquine[42] and carbamazepine,[43] respectively, are high, scientists and healthcare providers advocate for routine use of PGx. Such testing allows use of more efficacious medications in most, while avoiding drug toxicity in those found to be at risk. In addition to preventing ADRs, PGx testing can also predict the most efficacious therapy, thus preventing treatment failure. This is seen with testing *CYP2C19* in the percutaneous coronary intervention population, as it has been observed that those on clopidogrel with a loss-of-function (LOF) allele that predicts an intermediate or poor metabolizer phenotype are at greater risk of recurrent acute coronary syndromes on clopidogrel, compared to those on alternative antiplatelets and compared to those without LOF alleles on clopidogrel.[40] The impact of such testing is not only observed with patient morbidity and mortality, which can be reduced up to 50%,[40] but with our healthcare system expenditures. Within Alberta, standard of care currently provides ticagrelor, an antiplatelet unaffected by *CYP2C19* variation, at a cost of ~$100 per month, compared to clopidogrel's cost of ~$8.50 per month. Furthermore, there is mounting evidence that clopidogrel may also be a safer choice of therapy with less overall bleeding than alternatives such as ticagrelor.[44] With the knowledge of which patients, as determined by their genetics, should be on clopidogrel and which should be on ticagrelor, we can save costs and more importantly, lives.

Quality of life (QoL) is also valuable to patients, and delays in finding effective drug therapy can impact QoL by increasing time off work, time in hospital, and overall patient frustration. Within Canada, this affects healthcare system costs by increasing the number of emergency room (ER) visits, hospital admissions, length of stay (LOS), and overall resources required to effectively treat a patient. Several studies have demonstrated a reduction in healthcare resource utilization (HRU) with PGx testing. An observational study by Battig et al. showed decreased LOS in MDD admissions with PGx testing compared to without.[45] Two studies have also shown a reduction in overall HRU in the elderly polypharmacy population with panel testing of only 6 genes (*CYP2C9, CYP2C19, CYP2D6, CYP3A4,*

CYP3A5, and vitamin K epoxide reductase complex subunit 1 [*VKORC1*]) by about 50%.[46 47] In addition to reducing patients' need to seek care, it is particularly important that patients feel better. Pharmacogenomics has been shown to provide meaningful improvement in MDD and generalized anxiety disorder (GAD) symptoms as measured on the Patient Health Questionnaire 9 (PHQ-9) and GAD-7 scales, respectively.[48] However, despite the substantial potential to reduce patient morbidity and mortality by improving drug efficacy and/or reducing toxicity, and the subsequent cost-saving effects seen in our healthcare system, PGx adoption into routine clinical practice remains low.[17]

1.2 The potential role of the pharmacist in PGx

There is arguably no healthcare practitioner (HCP) with a greater understanding of the complexities of PK, PD, and the non-genetic factors in interindividual drug response than the pharmacist.[49] This is likely why many other HCPs look to pharmacists as a resource in PGx-based care. [50] [51] Additionally, pharmacists are viewed as one of the most trusted HCPs by patients due to their accessibility, communication skills, and reliability.[52] These qualities allow pharmacists to be in a position to assess, communicate, and act on PGx information at the point of care in a patient-centered approach. With appropriate background knowledge and education in PGx, they are able to collaborate with patients and other members of the patient care team to determine if PGx testing is indicated, interpret results, and select optimal medication therapy based on PGx results in conjunction with other patient-specific factors.[53] This is the foundation of many PGx consult clinics already seen in the United States, described by Arwood et al.,[54] Hicks et al.,[55] and Schuh & Crosby,[56] wherein patients are referred (provider or self-referral) for testing and assessment, followed by medication therapy recommendations that take individual patient factors in addition to genotype/phenotype into consideration.

Ideally, PGx could be incorporated into the existing pharmacist patient care process to enhance the services pharmacists already provide.[57 58] The patient care process is often depicted as a cycle of

continuous assessment and follow-up of a patient's drug and non-drug management of health conditions. The process typically begins with collection of information about a patient's health, medical conditions, medications, lifestyle, family history, laboratory data, and other relevant information. [57 58] With the incorporation of PGx, data collected includes any relevant pharmacogenomic data, or lack thereof. This data is then assessed by the pharmacist, which typically includes an assessment of medication indication (i.e. are conditions treated with appropriate drug therapy, are there any unnecessary medications), efficacy (is the condition effectively treated, is the best drug therapy selected for this indication), safety (are there any side-effects or interactions present), and adherence (can the patient afford the regimen selected, is the dosing frequency appropriate for the patient's lifestyle, do they understand the medication they are taking and why they are taking it). PGx can assist in this assessment by further personalizing drug therapy selection for an indication by ensuring optimal PK and PD parameters for medication efficacy and safety. The additional knowledge towards how and why their medication is effective for them also empowers patients as the driver of their own care, thus enabling improved adherence.[59] If a patient does not currently have PGx data, the pharmacist's assessment can include medications for which there are clinical PGx guidelines available, and other indications for PGx testing, including future need for PGx test results considering a patient's risk factors for illness, age, and other comorbidities. This assessment results in the creation and implementation of a care-plan by the pharmacist, the patient, and other members of the care team. This may include ordering PGx tests, recommending medication changes based on a combination of PGx and non-PGx factors, education of patients or other HCPs on PGx, identifying goals of therapy, and scheduling follow-up. Follow-up often leads the cycle to begin again as goals are reached or adjusted, new data becomes available such as the return of PGx test results, or the patient's health condition changes. While PGx aids this process, it does not replace it. Rather, it is seen to *enhance* this well-defined cycle of care that always puts the patient at the centre.[60]

Pharmacist implementation of pharmacogenomics has increased over the last decade, which will be further discussed in **Chapter 2.** This has occurred primarily in the United States, wherein pharmacists in both community and institutional settings have demonstrated capability in assessing and interpreting PGx information, applying PGx to patient care to provide medication therapy recommendations, and educating patients and other HCPs on PGx applications and results.[61] In addition to the direct clinical roles involved in PGx implementation, pharmacists are often involved within leadership of PGx program development.[62-65] These leadership roles include involvement in committees responsible for developing policies and procedures,[62 63 65-68] creation of documents for patient referral,[54 69 70] curation of literature,[64 65 69 71] development of clinical decision tools in collaboration with information technology (IT),[65 69 72] and provision of education to physicians and other professionals.[69 70 73] With these varied capabilities (**Figure 1.3**), pharmacists, especially those with expanded competencies in leadership, drug therapy management, and advanced practice such as prescribing, are well equipped to lead the advancement of clinical PGx.

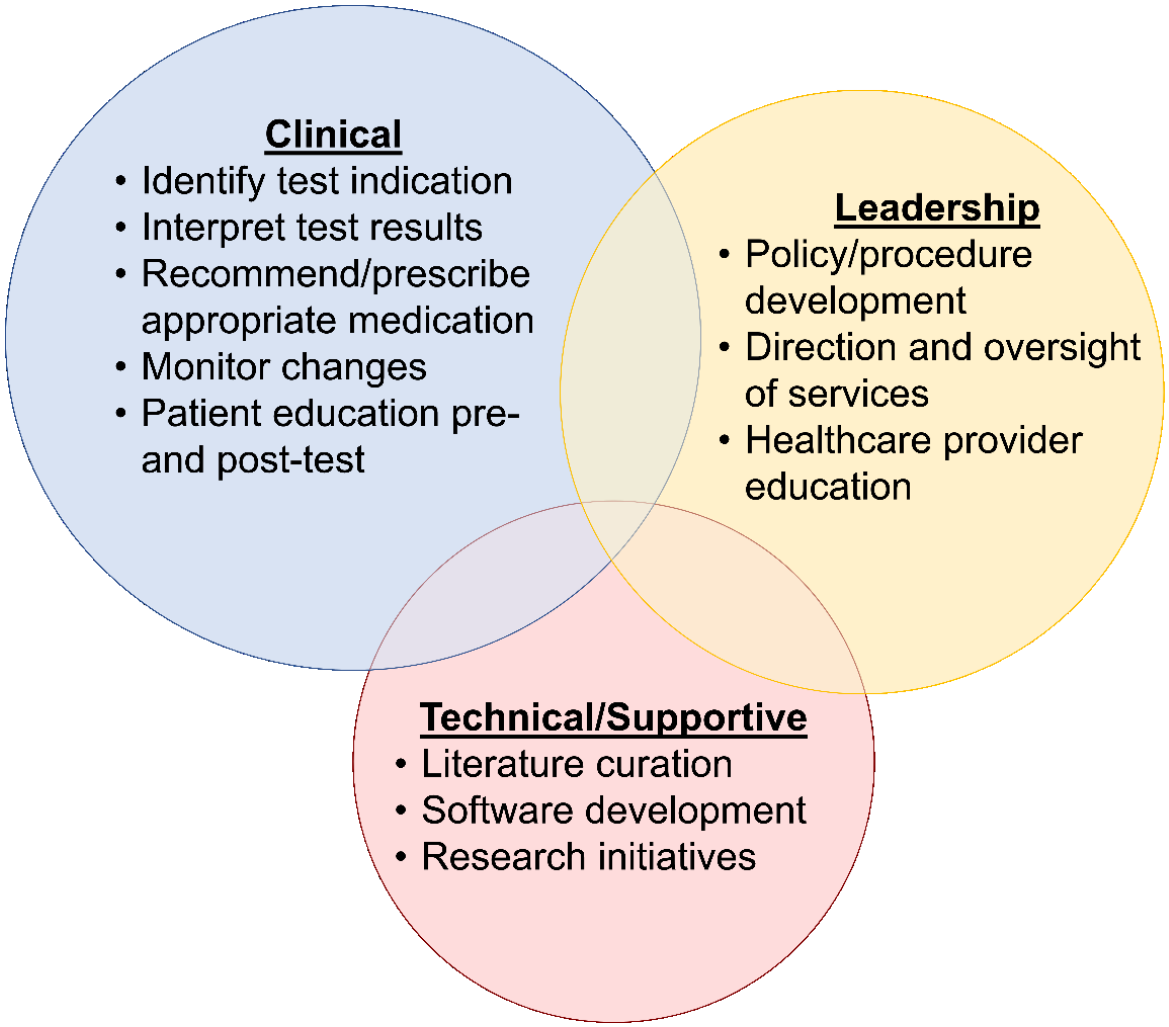

Figure 1.3. Pharmacist roles in clinical PGx implementation are complementary and often overlap within clinical, leadership, and technical domains.

1.2.1 Pharmacy scope in Alberta

Pharmacists in Alberta practice with one of the widest scopes globally that includes authorization to provide comprehensive medication therapy management services, administer injections, and prescribe independently.[74] This authority arose from a consolidation of the various pieces of legislation for each of the individual health professions into the unified Health Professions Act in 2003, which required the identification of each sector's professional competencies.[75] After extensive consultation and advocacy by the Alberta College of Pharmacy (ACP), prescribing was identified as a

pharmacist competency, and pharmacists were granted the authority to prescribe in 2007.[75] Pharmacists in Alberta must have at least one year of clinical experience, demonstrate collaborative relationships with other health professionals, maintain knowledge and skills necessary, and have the supports in place (such as documentation processes) to apply for additional prescribing authorization with ACP.[76] After adjudication by their peers of an application detailing their practice environment and demonstrating clinical judgement through de-identified patient cases, pharmacists are either granted the authority to prescribe within their own competency, or are provided feedback towards gaps in their practice.[76] Even without additional prescribing authority, pharmacists are able to adjust new medications based on organ function or therapeutic equivalency when it is in the best interest of the patient and within the pharmacist's individual level of clinical and therapeutic knowledge.[74 75] Other important aspects of pharmacist prescribing include collaboration with the patient's physician and other relevant healthcare providers, a therapeutic relationship with the patient, sufficient knowledge about the condition prescribed for, and the occurrence of appropriate assessment, follow-up, and documentation by the prescribing pharmacist. It is this framework in which pharmacist prescribing in conjunction with pharmacogenomics assessments can occur as the pharmacist's prescribing decisions must be evidence-based and in collaboration with the patient and other members of the healthcare team. The evidence basis arises from the availability of prescribing and assessment information developed and curated by organizations such as the CPIC, DPWG, and PharmGKB. The other important pearls of prescribing are best supported by the compensation plan for clinical pharmacy services enacted in 2012. In this legislation, pharmacists were provided a framework for compensation for medication therapy management services, referred to in Alberta as Comprehensive Annual Care-plans (CACPs) and Standard Medication Management Assessments (SMMAs) for complex and simple patients, respectively.[77] Within a CACP or SMMA, it is expected that a pharmacist identifies drug-related problems (DRPs, often identified as drug therapy problems, DTPs, in the literature) in collaboration with the

patient and other healthcare providers, documents their activities in the patient care record, and communicates effectively with the patient, their physician, and any other relevant members of the healthcare team.[77] Follow-up on the care-plan developed, including any prescribing decisions, is also covered by this compensatory framework.[77] This expanded scope, with a sufficient legislative, collaborative, and compensatory framework to provide these clinical services, leads Alberta to be an ideal location for clinical pharmacogenomics implementation. With the ability to prescribe, pharmacists in collaboration with the patient and the rest of the healthcare team can implement pharmacogenomic-based precision pharmacotherapy instantaneously rather than experiencing a lag in transition to genotype congruent therapy, as seen in studies utilizing a recommendation-based model.[46] The scope and framework in place also allows pharmacogenomic information to fit seamlessly into the other information that the pharmacist takes into consideration as described in the pharmacy patient care process, thus creating a comprehensive, personalized, precision pharmacotherapy care-plan.[57 58]

1.4 Facilitators and barriers to clinical PGx implementation

1.4.1 Healthcare provider PGx knowledge

One barrier to wide-scale adoption of PGx globally is that healthcare provider knowledge in this field is substantially limited.[78 79] This applies to pharmacist, physician and other healthcare provider confidence in liability, PGx's clinical significance, and how to interpret tests.[51] Most pharmacy and medical schools have only begun to introduce PGx into their curricula within the last decade.[80 81] Therefore within Canada there is a large proportion of the practicing health professional population that PGx education needs to reach before implementation. Often, pharmacists are looked at as a resource towards this knowledge gap for physician groups,[50 51] however their own knowledge in PGx, while slightly higher,[82] is still not at a level required to deliver this service at baseline.[83-85] Therefore it is critical that prior to clinical implementation, pharmacists are knowledgeable and confident in their ability to

assess PGx information, educate patients and other HCPs, and utilize PGx to improve patient care. In other specialties, barriers to HCP education have included time, access, and incentive to learn.[86] There have been several methods used to overcome these barriers with respect to PGx education including residency programs,[87] seminars with exams,[63] board certification,[88] e-learning,[56] and grand rounds.[89] The method of delivery for PGx education is strongly dependant on the target population's geographic location, available time, and baseline knowledge level.

Regardless of the method of delivery of PGx knowledge to HCPs, it would be critical to define precisely what information is necessary to impart onto the target population of education programs. Groups such as the American Association of Colleges of Pharmacy (AACP) Pharmacogenomics Special Interest Group have defined key competencies for pharmacists in PGX within their paper "Pharmacogenomics competencies in pharmacy practice: A blueprint for change,"[90] with a recent update that identifies expanded-scope competencies in clinical pharmacy practice (Gammal et al., 2022, in press). Additionally, a similar statement should be created specific to Canadian pharmacists and other HCPs, given the differences in Canadian and American healthcare systems. The 2017 AACP competencies included knowledge of basic genetic concepts, genetics and disease, PGx, and the ethical, legal and social implications[90] while the 2022 update add to domains of the pharmacist as the patient care provider, interprofessional team member, population health promoter, information master, and practice manager (Gammal et al., 2022, in press). Future competency statements in Canada and elsewhere should include these within the core concepts, while with greater emphasis on pharmacist capabilities in communicating PGx information, identifying indications for PGx testing, prescribing with PGx information in applicable jurisdictions, and incorporating PGx information in concert with other patient factors in developing a comprehensive, personalized care-plan.

1.4.2 Testing logistics

HCPs sufficiently equipped with knowledge and confidence in PGx require access to affordable options for PGx testing for patients and payers, and logistical adaptations that allow PGx to fit into workflow feasibly. The financial burden of pharmacogenomic testing, as with all types of genetic sequencing, has decreased substantially over the years as the technology has advanced and more alternatives have become available.[91] These options include low-cost alternatives such as microarray methods and restriction fragment length polymorphism analysis, and the more sensitive albeit costlier options of real-time polymerase chain reaction (RT-PCR) with Taqman probes and Next Generation Sequencing.[91] However, sourcing of test technology is not the only cost associated with PGx. Depending on the complexities of the genes and medications assessed, PGx testing can take a considerable amount of time for HCPs and patients. In educating the patient, there are often many questions unique to PGx information such as: background information about PGx testing including how it works and how it differs from disease-risk genetics, the rationale behind the recommendation to test, the privacy risks, and protection of information.[92] While test interpretation can also take more of the HCP's time, there are often clinical decision software (CDS) tools that can assist a provider in developing their care-plan, and keep the patient aware of which medications to be cautious with in the future. Examples include the OneOme RightMed® comprehensive test used by one Mayo Clinic study, which categorized medications with major, moderate, or minimal drug-gene interactions into red, yellow, and green "bins" respectively, based on the patient's PGx test results.[71] In addition to this simplification of information to the patient level of understanding, more advanced technology, such as the YouScript® Clinical Decision Support Tool, can even identify complex drug-drug-gene interactions,[46 47] further aiding the assessment process for HCPs.

1.4.3 Ethical, legal, and social considerations

While most PGx tests may only apply to risks regarding medication response, some PGx tests may carry "ancillary" or "incidental" findings of disease risk.[93] For example, angiotensin converting enzyme (*ACE*) I/D polymorphisms that predict treatment response to ACE inhibitors for renal disease that also may indicate a risk of Alzheimer's disease.[93] [94] In the Chinese-Han population, *SLC6A4* polymorphisms that predict treatment response to SSRIs may additionally indicate increased susceptibility to developing schizophrenia.[95] Some CYP genes may even carry increased risk of some cancers, especially when assessed in a pharmacogenomic approach among the presence of other at-risk genes.[96] Within large multi-gene panels, the number of such incidental findings may appear overwhelmingly numerous.[97] However, by adopting strategies utilized in whole-genome sequencing, HCPs can stratify the results by level of evidence, clinical significance, and burden to the patient, in order to focus on only meaningful results.[98] Involvement of genetic counsellors may also mitigate this burden to patients by ensuring informed consent pre-test, and empowering patients post-test to understand the importance of sharing results within their circle of care.[49] Importantly with regards to incidental findings, a genetic counsellor would likely be the best professional to address the implications of such results on family members.[76] Regardless of the definition of a PGx finding as incidental or not, implications towards family members is one of the primary ethical issues within this field. Outside of incidental findings of disease risk, it may be clinically relevant for family members to understand if they may have an inheritable gene for poor treatment response.[99] Additionally direct to consumer DNA test kits have led users to identity crises when they reveal falsely attributed parentage,[100] a revelation that can shatter family relationships. Such complex social issues that can arise from PGx testing make it imperative that HCPs and patients are fully aware of the risks and benefits of testing, and how to securely and appropriately communicate, share, and record PGx information.

The security and privacy of PGx information has consistently been identified as a patient concern as this technology becomes increasingly available.[101] [102] Canadian legislation contains the Genetic Non-Discrimination Act (S.C. 2017, c. 3) that prevents employers and service providers (such as insurers) from requiring genetic testing or disclosure of genetic testing for contract or goods/services, respectively. The United States Genetic Information Nondiscrimination Act of 2008 provides greater clarity, further preventing employers from using any genetic information it may have about an employee in hiring decisions and prohibiting health insurers from using genetic information in eligibility, coverage, underwriting, or premium-setting decisions. However, as of writing only 7 states have further state laws prohibiting the use of genetic information in underwriting other types of insurance policies, such as those for life, long-term care, and disability.[103] Also lacking legislation is guidance and protection for HCPs in accessing, using, disclosing, and sharing PGx information in patient care. While HCPs and researchers are exempt from the prohibitions in the Genetic Non-Discrimination act within Canada, there is no clear guidance on how pharmacists are to document PGx information in the patient care record. Even more unclear are the permissions required to share this information with other members of the healthcare team, such as in sending a recommendation for genetically guided medication therapy to a physician. While most conventional information, such as diagnosis, serum creatinine, and current medications, would be considered reasonable to share within the patient's "circle of care,"[104] the sensitivity associated with genetic information requires clearer lines drawn towards how, when, why, and with whom, this information can be communicated. One solution that has been considered is enabling the patient to be able to communicate their own PGx test results when the need arises,[105] not unlike how a patient would report their own allergies. However, patients may not be aware of all indications in which this information would be needed, thus increasing the risk of duplicate testing or not having this information at the point of care.[105] Thus healthcare providers should be enabled in

future policy and legislation to ensure this information is accessible when needed, by those who require it to make drug therapy decisions.

1.4.4 Technology adaptations

Alberta holds an advantage over many other healthcare jurisdictions in the interconnectivity of technological adaptations already in place for healthcare information. Since its launch in 2006, Netcare has provided HCPs access to critical health information including prescription dispense history, laboratory results, and hospital discharge summaries.[106] Recently, this software has been expanded to allow patients access to some of this information as well, to increase their own ability to monitor their conditions and share information within their circle of care.[106 107] Additionally in Alberta, Netcare is in the process of being integrated with Connect Care, a software by Epic (Epic, Verona, WI) that further expands the potential of health record integration with PGx, as already seen in many American institutions.[108] Such software can be shown to utilize clinical decision algorithms that further aids HCP assessment of PGx information and ensures efficient and accurate application of results.[108] With the right privacy and discrimination protections in place, this technology could be leveraged to facilitate wide-scale PGx adoption. Van der Wouden et al. established in a follow-up to an implementation pilot in the Netherlands that easier access to PGx test results facilitated their re-use in future drug therapy decisions.[109] Another study out of the United States found that 42% of patients had drug-gene interactions found with CYP2C19 substrates after PGx testing for antiplatelet therapy post-percutaneous coronary intervention.[110] These results show the importance of having PGx results accessible well after the incident test, due to the reusability and versatility of PGx test results for a patient's entire lifetime.

1.4.5 Interdisciplinary patient care

At the crux of all these factors in the implementation of PGx into routine patient care is the collaboration between many different healthcare professionals and other players in clinical

implementation. Many studies have demonstrated that multidisciplinary efforts are imperative to implementation as PGx requires the unique knowledge and skills of each profession to fit seamlessly in patient care. These parties include organization leaders, informatics specialists, laboratory technicians, physicians, and pharmacists.[108] As discussed, genetic counsellors may also need to be incorporated into this framework to address the grey areas in ethical and social implications on patients and families.[49] Technology, education, and teamwork can all facilitate adoption by creating a pipeline of communication and information within the patient's circle of care (**Figure 1.4**).

1.5 Research rationale and objectives

PGx can provide insight into a medication's PK and PD properties for an individual patient. Evaluated in concert with other non-genetic information, PGx can potentially be used by pharmacists within medication therapy management (MTM) to improve patient drug therapy outcomes. While pharmacists appear best suited to interpret PGx data due to their base understanding of drug PK and PD, significant barriers remain to feasible implementation in Alberta pharmacies. These include an undefined population for which to direct PGx services, and an observed lack of knowledge among pharmacists in the principles of PGx. Moreover, while several studies have established the feasibility and clinical utility of PGx in the community pharmacy setting, none have done so in Alberta. It would be necessary to establish the use of PGx in this geographic setting, as the expansive pharmacist scope in Alberta includes comprehensive care-plans, and more importantly, pharmacist prescribing. The ability of initial-access prescribing by Alberta pharmacists may in theory lead to improved feasibility due to a reduction in time from PGx test to clinical action taken on results. Within this expanded scope, Alberta pharmacists, are poised to improve patient outcomes through PGx, provided they are equipped with the processes, policies, education, and support required to implement PGx in patient care.

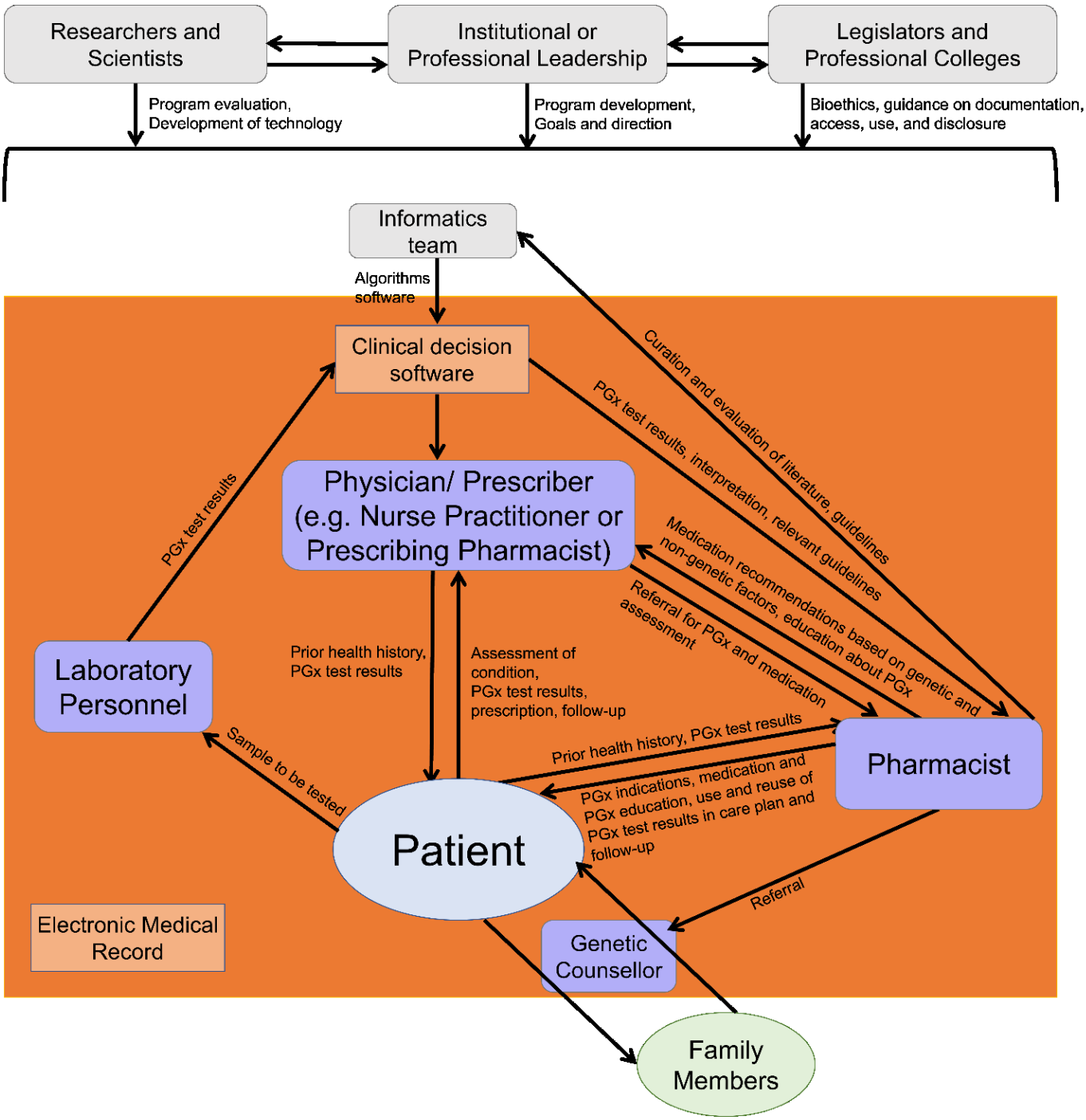

Figure 1.4. A theoretical framework of PGx implementation supported by electronic medical record integration and policies developed by collaboration between researchers, leaders, professional organizations, and legislators. Pharmacists have many key roles to play in PGx adoption including communication with patients, collaboration with other healthcare providers, and evaluation of literature for software algorithm development. Arrows represent flow of information between parties, with information contained in the orange box supported by and included in the medical record. PGx: pharmacogenetic/pharmacogenomic

1.5.1 Scoping literature review

To inform research on pharmacogenomics in pharmacy practice, a scoping literature review on all use of pharmacogenomics by pharmacists, excluding oncology and transplant, was conducted. The objective of this review was to map the evidence of PGx services in the pharmacy setting, to determine:

1. What implementation models for PGx have been studied in pharmacy practice to date?
2. What age groups, conditions, or medication classes should community pharmacists focus on for PGx services?
3. What common themes or processes exist in studied pharmacist implementation models for PGx?
4. What positive clinical, economic, or humanistic outcomes have been demonstrated in the implementation of PGx in pharmacy practice?

By addressing these four research questions, this review aimed to identify patient populations and pharmacy processes that have greater potential to identify drug-gene interactions, drug-therapy problems, and ultimately improve patient medication therapy outcomes.

1.5.2 Education of pharmacists in PGx

Information gleaned from the scoping review, in addition to established competencies published by the AACP[90] were employed in the development of a mixed didactic and case-based educational program for practicing Alberta pharmacists. This program was studied in a live (virtual) setting as a two-day course, as well as an online self-directed set of modules. Course impact on pharmacist confidence/opinions and knowledge were measured using Likert scales and skill-testing questions, respectively, prior to and after attending this program. This study aimed to determine the impact of this

course on the subjective and objective knowledge of Alberta pharmacists in PGx, as well as identify the baseline understanding of PGx among this population, and the most effective delivery of PGx education.

1.5.3 Clinical implementation of PGx in pharmacies

With sufficient pre-implementation education, it has already been established that pharmacists are able to include evidence-based PGx within MTM. This involves identifying drug-gene interactions, i.e., when one medication is determined to be incompatible with one gene, and then using that interaction, integrated with all other patient information, when identifying drug-therapy problems and formulating care-plans. What has yet to be evaluated is the impact of PGx in community pharmacies in Alberta. By quantifying the use of pharmacogenomic testing piloted in pharmacies within our province, we can identify ways to optimize and support PGx use in the patient populations most likely to benefit from this service. Additionally, with grant funding by the Alberta Pharmacists' Association, we will be able to allow this service to be provided to patients who may benefit, regardless of personal finances. The information gained from this study can serve to inform pharmacy policy including guidelines on the use of pharmacogenomics, funding of services, and the direction of future research in pharmacy practice.

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Chapter 2: Scoping Review

Applications for pharmacogenomics in pharmacy practice: A scoping review

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Abstract

Background: Pharmacogenomics (PGx) can provide valuable pharmacokinetic and pharmacodynamic information for the pharmacist's assessment of drug therapy, especially within medication therapy management (MTM) services. However, no review has comprehensively mapped the pharmacists' use of PGx in practice-based research. Doing so would allow future researchers, practitioners, and policy-makers to identify the ideal populations and settings for PGx implementation within the pharmacy.

Objective: The purpose of this review is to identify the evidence to date of PGx use in pharmacy practice.

Methods: A scoping review was conducted to find all studied non-oncologic pharmacy practices incorporating PGx testing. Search terms were applied to 5 databases and relevant journals. Characteristics of patients, pharmacy settings, genetic tests, and outcomes were summarized to determine models most likely to benefit patients.

Results: The search identified 43 studies on the use of PGx by pharmacists published between 2007 and 2020. *CYP2C19* testing with antiplatelets was the most studied model, found in both community and institutional settings. It also was the most actionable test: approximately 30% of patients have polymorphisms indicating a need for alternative antiplatelets, and identifying these patients can reduce morbidity and mortality by more than 50%. As technology shifts, broader studies using multi-gene panel tests within MTM demonstrate an approximate 50% decrease in emergency visits and hospitalizations in elderly polypharmacy patients. Clinical benefit or drug-gene interactions are also found in other cardiovascular, psychiatric, analgesic, and gastrointestinal indications. No evaluations of actual costs or of pharmacist prescribing within pharmacy-based PGx have been performed. Facilitators towards successful PGx implementation included pharmacist education, collaboration with other healthcare providers, and the use of clinical decision software.

Conclusions: Pharmacogenomic testing has demonstrated feasibility and improved medication outcomes in pharmacy practice, including in the community pharmacy. Further PGx research should be directed towards pharmacist prescribing, pharmacist education, and pharmacoeconomics.

2.1 Introduction

Pharmacy practice has made significant advancements in the last several decades by increasing pharmacists' scope of practice and their delivery of direct interventional care towards the betterment of medication therapy outcomes. Some examples of this expansion include the development of diabetic and chronic disease clinics, travel medicine services, and immunizations.[1] At core of all these services are medication therapy management (MTM) frameworks, which are now considered a key component to current pharmacy practice. MTM involves pharmacists holistically assessing a patient's treatment plan and providing appropriate recommendations and monitoring to meet goals of therapy agreed upon by the pharmacist, patient, and other healthcare providers.[2] These services outside of traditional dispensing roles have been informed considerably by pharmacy practice research, grounding MTM in evidence-based medicine. This research is crucial to the development and implementation of feasible services that provide real clinical, economic and humanistic benefits to patients and systems.[3] One of the first studies that revolutionized pharmacy practice was the Asheville Project, an MTM service that began in the late 1990's in 10 community pharmacies in North Carolina, USA. This study demonstrated improvements in blood glucose, cholesterol, quality of life, and costs, from community pharmacist-delivered patient education, assessment, and monitoring.[4 5] This innovation was proceeded by an increase in pharmacy practice research throughout the 21st century and continuing into today. Most studies continued to show positive outcomes in a wide variety of therapeutic areas including diabetes, smoking cessation, hypertension, dyslipidemia, chronic obstructive pulmonary disease, and heart failure.[6 7] Frameworks for providing and funding these services followed in many countries. Such compensation models include the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 in the United States of America (USA).[4] Similar legislation within individual provinces of Canada have also been passed for the provision of cognitive services, medication reviews, laboratory monitoring, and prescribing.[8] Pharmacist prescribing in particular shows promise to improve patient

therapy outcomes through eliminating delays in appropriate medication interventions.[9] [10] Today, pharmacy education emphasizes the patient care processes required for these services: comprehensive patient assessment, accurate identification of drug-therapy problems (DTPs), and effective communication strategies with patients and physicians to act on and monitor these DTPs.[11] [12] The crux of pharmacist-delivered patient care is the Pharmacist Patient-Care Process (PPCP) well described by the Joint Commission of Pharmacy Practitioners (JCPP)[13] and the University of Alberta-based book "Patient Assessment in Clinical Pharmacy."[14] Both publications highlight the continual process that occurs in pharmacy-based patient care, adapted in **Figure 2.1a.**

Leveraging the clinical skill, scope, compensation, and patient benefits associated with MTM with the pharmacist's standing as one of the most trusted and accessible healthcare professionals,[11] [15] puts pharmacists in a position well-suited for the provision of pharmacogenetic and pharmacogenomic (interchangeably used, and collectively abbreviated as "PGx") services.[16] PGx is one of many factors that influence drug response within the spectrum of personalized medicine. Variability in DNA, the sequence of nucleotides coding for proteins, occurs naturally in the population: these may be single nucleotide polymorphisms (SNPs) wherein one or more nucleotides in a sequence differ, or insertion/deletion polymorphisms (I/D) wherein one or more nucleotides are added or removed from a sequence. [17] [18] The specific sequence of DNA is generally referred to as an individual allele, of which a person has two, one inherited from each parent.[19] These variations in DNA can change the structure of proteins, leading to increased decreased, or null activity. Alternatively, promotor regions may be altered, or genes may be duplicated or deleted, leading to altered genetic expression.[17] [18] Functional proteins affected by polymorphisms include metabolizing enzymes, transporters, receptors, and other indirect targets.[17] [20] Thus, a person's alleles to a gene encoding for the above proteins may account for the interindividual variability in medication efficacy and/or toxicity.[17] Such drug therapy problems (DTPs) can have deleterious effects to individuals and healthcare systems. An estimated 20% of patients will suffer an

adverse drug reaction (ADR) in their lifetime, and these may be a cause of up to 30% of all hospital admissions.[21] Inefficacy also can lead to greater healthcare resource utilization and costs. At least a quarter of those diagnosed with depression may be classified as treatment-resistant, and these individuals see 37-44% increases in hospital admissions, and a 63-74% increase in healthcare related costs,[22] not accounting for losses in employment income, or quality of life. When a person has an allele that is known to increase the risk of an ADR or inefficacy to a prescribed medication, this is commonly referred to as a drug-gene interaction (DGI). Some examples of DGIs that can have serious consequences include decreased activation of clopidogrel by CYP2C19 as a result of poor metabolizing *CYP2C19* phenotypes, which has been shown to result in major adverse cardiac events (MACE)[23 24] and increased risk of skin-related toxicity such as Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) to phenytoin with certain alleles for *CYP2C9* and *HLA*.[25] In other clinical scenarios, such as the use of antidepressants,[26] predicting metabolism can avoid the trial-and-error method of prescribing, ideally returning patients to better health sooner. The pharmacist can play a critical role in preventing these ADRs and inefficacies by including pharmacogenomics in their patient care process, in a manner illustrated in **Figure 2.1b**.

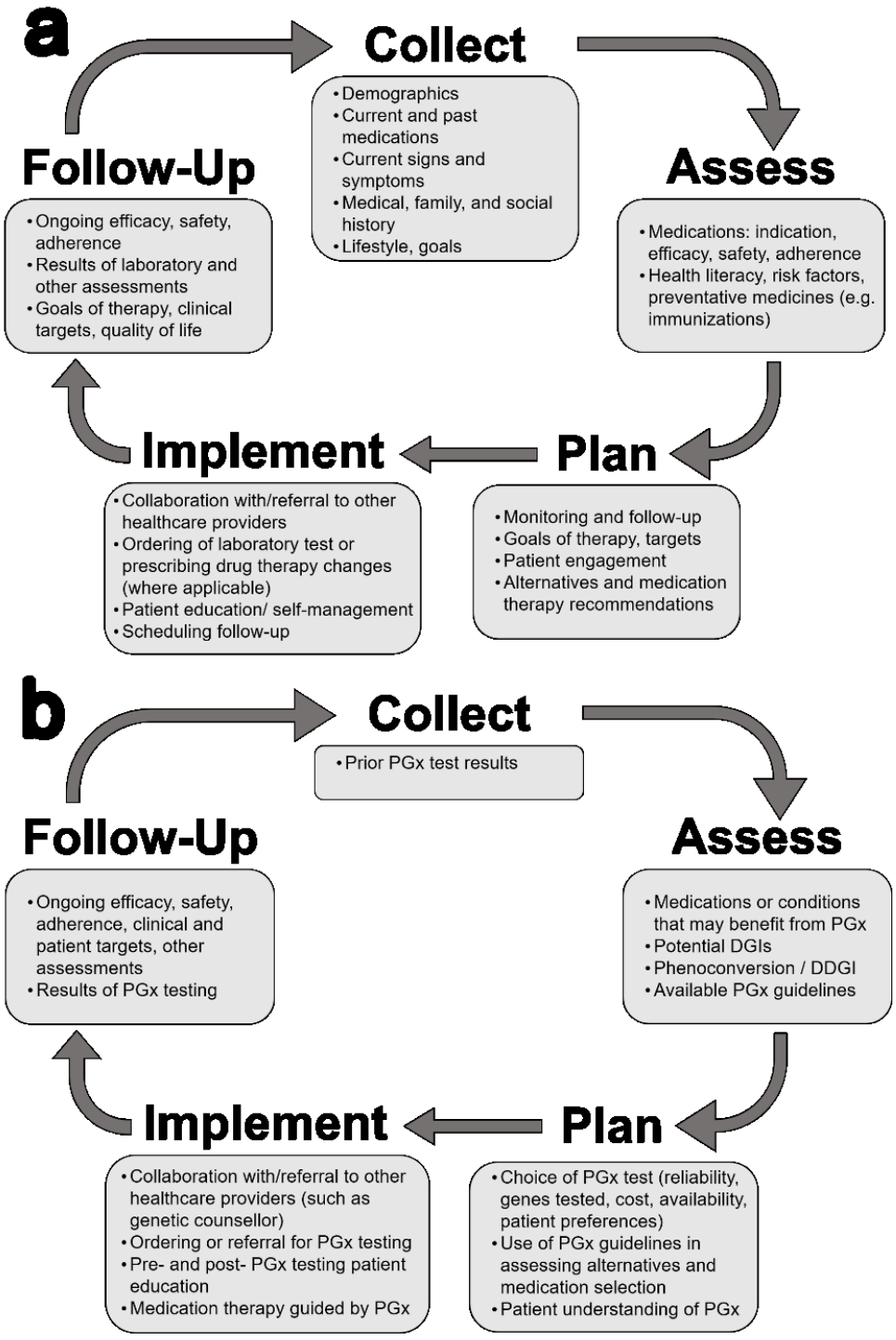

Figure 2.1. The pharmacist patient care process (PPCP), adapted from the Joint Commission of Pharmacy Practitioner's *The Pharmacists' Patient Care Process*, and the University of Alberta's *Patient Assessment in Clinical Pharmacy* (a, top).[14] Pharmacogenomics can be utilized in addition to processes already used by pharmacists (b, bottom). DDGI: drug-drug-gene interaction; DGI: drug-gene interaction; PGx: pharmacogenomics.

In the past decade, the effects of pharmacogenomics on the response of many medications have been elucidated, resulting in the creation of evidence-based practice guidelines that are regularly updated by organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network of Pharmacogenetics (RNPGx). These guidelines, as well as other pertinent information such as drug pathways and gene information, are compiled and presented by a pharmacist-led initiative known as the Pharmacogenomics Knowledge Base (PharmGKB).[27] The access to evidence-based guidelines is critical to clinical implementation of PGx in pharmacy. Another key component to wide-scale pharmacist adoption of PGx is pharmacist knowledge and competency. Lack of knowledge in this field is consistently identified as a barrier to implementation in current literature.[28-30] Competency needs for pharmacists have been identified by the Pharmacogenomics Special Interest Group of the American Association of Colleges of Pharmacy that covers the areas of basic genetic concepts, how genetics impact disease expression and drug response, and the ethical, social and legal implications of PGx testing.[31] While pharmacy schools are beginning to address this by adding these PGx competencies into their curricula,[32 33] the knowledge of currently practicing pharmacists will need to be updated, likely through continuing education programs. With these advancements in PGx knowledge, and with PGx testing becoming more feasible and accessible due to the increase in availability of affordable genetic tests,[34 35] the community pharmacy appears to be an ideal location for the delivery of PGx services. Through established MTM services, community pharmacists may be able to provide the consistency and continuity of care[15] needed to utilize pharmacogenetic test results. While previous reviews have outlined clinical pharmacy PGx implementation models studied mostly in hospital settings,[36 37] none have identified all available literature, and there is an apparent need to translate this information to the community pharmacist.

As with MTM, PGx services in pharmacy practice must be supported by practice-based research. In theory, PGx can reduce morbidity, mortality, and health spending by enabling the selection of medications that will result in better therapeutic outcomes. This occurs by taking into consideration the interindividual variability resulting from patients' genetic alleles. However, to use this in practice both feasibility and clinical utility need to be demonstrated. The objective of this review is to comprehensively map the current evidence of pharmacist-delivered PGx services, and to evaluate evidence sources for patterns in the characteristics of pharmacy practices, patients, pharmacogenetic tests, and clinical indications. Summarizing the evidence currently available from all pharmacist-led PGx services will help identify which patient populations may have meaningful clinical outcomes from similar interventions to those studied. These populations and pharmacy traits could be inferred by which patient and pharmacist characteristics have been shown to find greater frequencies of actionable genotypes/phenotypes, drug-gene interactions, medication interventions, and prescriber acceptance of pharmacist recommendations. While these conjectures are most useful in developing more rigorous investigations into PGx implementation, some studies may already identify real clinical, economic, or humanistic outcomes, and it would be critical to highlight these for current and future practice. Acknowledging that pharmacists practice in a broad range of settings including hospitals, long-term care facilities, medical clinics, and of course community pharmacies,[38] this review will look at all pharmacy implementation practice models to date to develop hypotheses about how PGx in community pharmacies may be able to benefit patient outcomes. Knowing which patients to prioritize for PGx services, and how to accomplish this in a community pharmacy setting will serve to inform future research, policy development, and the practice of pharmacists globally.

2.2 Methods

A scoping review was determined to be the most effective means of accomplishing the objectives of this review due to its ability to map a very heterogeneous body of literature. This scoping

review was developed and conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist and after reviewing publications by Tricco et al.,[39] Arksey and O'Malley,[40] and the Johanna Briggs Institute [41] on the use of scoping reviews.

2.2.1 Identifying the research questions

As the objectives of this review were to identify the currently studied models of pharmacist-led PGx services in the literature, and determine common successful features among pharmacists and patients in these studies, the following research questions were identified:

1. What implementation models for PGx have been studied in pharmacy practice to date?
2. What age groups, conditions, or medication classes should community pharmacists focus on for PGx services?
3. What common themes or processes exist in studied pharmacist implementation models for PGx?
4. What positive clinical, economic, or humanistic outcomes have been demonstrated in the implementation of PGx in pharmacy practice?

2.2.2 Identification and selection of relevant studies

2.2.2.1 Search strategy

MEDLINE (1946 to November 7 2020), Embase (1974 to November 7 2020), Scopus (1842 to November 8 2020), CINHAL (1942 to November 8 2020), and Web of Science Core Collection (1864 to November 8 2020) were searched using keywords developed in collaboration with a medical librarian to identify studies of pharmacists using PGx testing in their practice. The following keywords were used: (pharmacist* OR pharmacy OR pharmacies) AND (pharmacogen* OR personal?ed medicine* OR personali?ed health OR precision medicine* OR genetic medicine* OR genomic medicine* OR pgx) AND

(test* OR implement* OR pilot*). Search was limited to human studies. No restrictions on language were employed due the availability of translating applications, and no restrictions on date were used due to the lack of comprehensive reviews available on the subject, and the relatively recent history of clinical pharmacogenomic research. Additionally, key journals were searched for publications that may be missed by indexing, and bibliographies of included articles were scanned for additional sources of evidence. Grey literature was not searched due to the focus on peer-reviewed research in this review.

2.2.2.2 Inclusion and exclusion criteria

Peer-reviewed journal articles and conference abstracts of original research involving pharmacists implementing PGx services in their practice were considered for inclusion, regardless of the practice setting. Studies of PGx implementation in oncology or transplant were excluded due to the highly specialized nature of these therapeutic areas and therefore lack of feasible application to a typical community pharmacy practice. Implementation models that had minimal pharmacist involvement, or the role of the pharmacist was not clear, were excluded as well due to the inability to infer these results to pharmacy practice. Theoretical models, research proposals, and research in progress with no reported results were excluded due to lack of evaluation of outcomes or processes.

For the purposes of this review, "implementing" refers to studies that recruit patients as participants (as opposed to practice surveys, which recruit providers), and "PGx services" refers to methods of the study including any part of the following: identification of eligible patients, provision of PGx testing after obtaining consent, pre- and post-PGx testing education, identification of drug-gene interactions and drug-therapy problems related to PGx test results, recommendations made to the patient's prescriber or other means of implementing changes to medications based on PGx results, and follow-up after PGx testing. For a source of evidence to be included, pharmacists must be the healthcare personnel providing the majority of the PGx services described in the study, and the PGx testing must be used in the delivery of care to patients. "PGx testing" in this review specifically refers to testing for

genes that affect drug pharmacokinetics and/or pharmacodynamics, and for the purposes of inclusion criteria will only include the Tier 1 Very Important Pharmacogenes (VIPs) listed on www.pharmgkb.org/vips as these are genes that have strong evidence in available literature of a significant effect on drug response.[42 43]

2.2.2.3 Selection of sources

All articles from searches were uploaded into Endnote X9 (Clarivate, Philadelphia, PA) using the software's function of excluding duplicate references. Title and abstract screening was performed using the inclusion and exclusion criteria described, and any potentially relevant sources were filed for full text review. Any sources of uncertain inclusion were also marked for full text review. At the full text review stage, articles were selected for inclusion into the review if they satisfied the inclusion and exclusion criteria.

2.2.3 Data extraction

For included articles, data was extracted on source characteristics (e.g. year, country, aim), pharmacy characteristics (e.g. setting of practice, pharmacist role, use of a clinical decision support software (CDSS)), PGx considerations (e.g. genes tested, pre-emptive vs. reactive testing, therapeutic aim of testing), patient demographics (e.g. average age, most common diagnoses, most common medications), and results (e.g. genotyping results, frequency of DGIs and pharmacist recommendations, prescriber acceptance of recommendations). Any important outcomes, barriers or facilitators of implementation, and conclusions were also qualitatively summarized.

2.3 Results

A total of 1,285 records were identified through database, journal, and bibliography searching (**Figure 2.2**). Of these, 195 articles were determined to be suitable for full text review. Three sources were duplicates missed in the initial screening. Reviews and commentaries were excluded but were

utilized for completion of the discussion (n = 21). The PRISMA reporting framework identifies that multiple articles may present on the same research study.[44] In this review, other publications of an included study, such as conference proceedings, sub-group and later analyses, or additional descriptions of the pharmacy practice, were excluded in the final count of publications but may be referenced in addressing the research questions (n = 33). After full text review, a total of 43 studies were selected for analysis, with select characteristics and results reported in **Table 2.1**. Included studies consisted of 34 full-length manuscripts in peer-reviewed journals, and 9 conference abstracts.

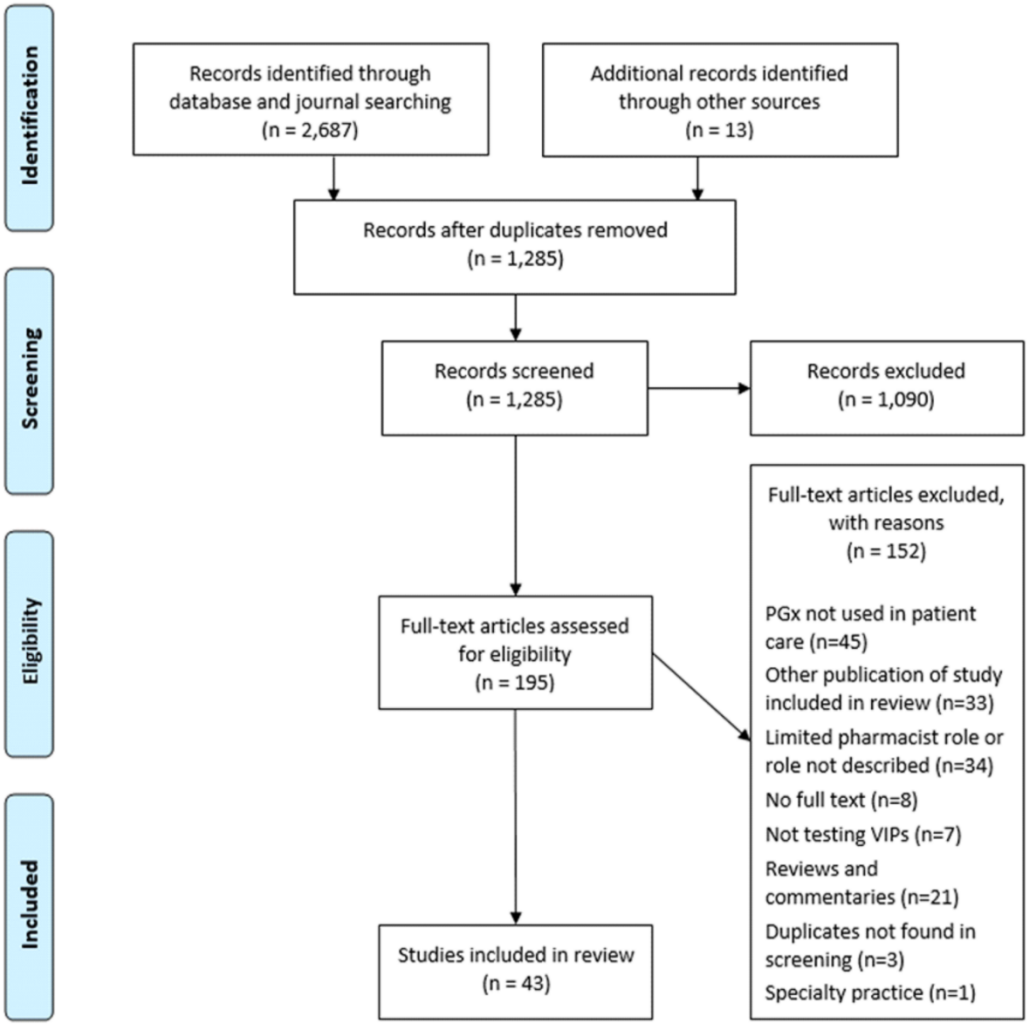

Figure 2.2. Study PRISMA flow diagram. PGx, pharmacogenomics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VIP, very important pharmacogenes.

Table 2.1. List of included studies, select characteristics, and results of pharmacogenetic testing (n = 43).

Reference	Study focus or patient population	n of PGx tested	n (%) female of PGx tested	Mean ± SD or median (IQR) age of PGx tested (years)	Number of genes evaluated	Average DGI per patient (multi-gene) or proportion of patients with actionable results (single-gene)	% of pharmacist-recommendations accepted by prescriber
Umbreit et al. (2020)[91] *	Psychiatric medications	51	NR	NR	17	NR	NR ‡
Smith et al. (2020)[109]	Cardiology and perioperative polypharmacy	667	339 (51)	70 (61,76)	12	0.19	NA
Rodríguez-Escudero et al. (2020)[63]	Psychiatric polypharmacy	29	26 (90)	49.9 ± 15.0	3	2.7	NR
Patel et al. (2020)[101]	Opioids / pain	43	25 (58)	60 (37,77)	9	0.35	NR ‡
Papastergiou et al. (2020)[98]	Cannabis / psychiatric patients	20	13 (65)	47 (SD NR)	3	0.55	NR
Marrero et al. (2020)[64]	Supportive medications in cancer	1	0	73	8	2	100%
Kerskes et al. (2020)[125] *	CKD polypharmacy	61	NR	NR	8	1.1	NR ‡
Dorfman et al. (2020)[100]	Elderly polypharmacy (LTC)	90	NR	80.1 ± 10.2	18	1.3	Less than 18%
Brown et al. (2020)[95] *	MDD or GAD	37	22 (60)	40 (SD NR)	NR	NR	NR
Battig et al. (2020)[65]	MDD	49	23 (47)	41.27 ± 14.15	31	NR	NA ‡
Arwood et al. (2020)[59]	Psychiatric, cardiovascular, gastrointestinal dx, or opioids	78	61 (97)	57 ± 18	1 to 8 (single gene or panel)	0.82	87%
Schuh, Crosby (2019)[124]	Rheumatoid Arthritis/Polypharmacy clinic	1	NA	76	27	1	100%
Sandritter et al. (2019)[96]	Pediatrics with psychiatric, neurologic, or GI dx	221	125 (41) †	12.4 ± 5.9 †	10 total, selective	NR	63% ‡

Reference	Study focus or patient population	n of PGx tested	n (%) female of PGx tested	Mean ± SD or median (IQR) age of PGx tested (years)	Number of genes evaluated	Average DGI per patient (multi-gene) or proportion of patients with actionable results (single-gene)	% of pharmacist-recommendations accepted by prescriber
					testing		
Kasi et al. (2019)[62]	Supportive medications in cancer	155	64 (41)	56 (IQR NR)	27	4.4	NR
Cicali et al. (2019)[97]	Opioids (3 studies), PPIs (2 studies), and SSRIs (1 study)	469	297 (63)	see study breakdown	1 or both	NR	varies: 93% - 100% reported
Bank et al. (2019)[71]	Statins, antidepressants	200	103 (52)	62 ± 11	8	0.31	89%
Kim et al. (2018)[85]	General polypharmacy	58	17 (29)	74.17 ± 6.34	6	NR	Less than 30%
Empey et al. (2018)[67]	Clopidogrel	6340	NR	NR	1	NA	57% §
Davila-Fajardo et al. (2018)[75] *	Clopidogrel	1163	NR	NR	1	NR	NR
Crown et al. (2018)[94] *	antidepressants or antipsychotics	65	30 (60)	47 ± 13	NR	NR	68%
Bain et al. (2018)[87]	Elderly polypharmacy (PACE)	296	208 (70)	74.5 ± 10.0	11	1.5	89%
Schwartz et al. (2017)[66]	General polypharmacy	50	23 (46)	69.5 (65.0,75.8)	14	0.88	91%
Reynolds et al. (2017)[86] *	Palliative polypharmacy	372	NR	NR	14	2.5	NR
Papastergiou et al. (2017)[99]	General polypharmacy	95	62 (62)	56.7 (SD NR)	10	1.3	59%
Johnson et al. (2017)[55]	Clopidogrel	6	2 (33)	64 (SD NR)	1	0.17	100%
Haga et al. (2017)[68]	Single gene testing for: atomoxetine, carbamazepine, celecoxib, clopidogrel, codeine,	63	NR	NR	7 (single-gene tests)	0.29	NR ‡

Reference	Study focus or patient population	n of PGx tested	n (%) female of PGx tested	Mean ± SD or median (IQR) age of PGx tested (years)	Number of genes evaluated	Average DGI per patient (multi-gene) or proportion of patients with actionable results (single-gene)	% of pharmacist-recommendations accepted by prescriber
	esomeprazole, fluoxetine, imipramine, metoprolol, nortriptyline, simvastatin, or warfarin						
Elliott et al. (2017)[120]	Elderly polypharmacy (home-health)	57	32 (56)	76.5 ± 9.4	6	1.49	77%
Wirth et al. (2016)[69] *	Clopidogrel	34	9 (26)	66 (SD NR)	1	0.38	NR
Sugarman et al. (2016)[119]	Elderly polypharmacy (LTC)	112	64 (57)	74.2 (SD NR)	15	NR	NR
Hicks et al. (2016)[110]	abacavir, carbamazepine, thiopurines	211	NR	NR	3	0.08	100% §
Dunnenberger et al. (2016)[45]	General polypharmacy	76	NR	NR	10	NR	NR ‡
Moaddeb et al. (2015)[53]	Simvastatin or clopidogrel	205	118 (58)	NR	2 (single-gene tests)	0.34	0%
Brixner et al. (2016)[118]	Elderly polypharmacy	56	NR	75 ± 6.9	6	NR	46%
Kim et al. (2015)[78] *	Warfarin	389	NR	NR	NR	NR	NR
Haga et al. (2015)[47]	Cardiovascular polypharmacy	30	7 (23)	66.6 (SD NR)	5	0.2	50%
Bright et al. (2015)[52]	Clopidogrel	29	NR	NR	1	0.172	40%
Weitzel et al. (2014)[51]	Clopidogrel	1097	NR	NR	1	0.278	70%
Ferreri et al. (2014)[50]	Clopidogrel	18	5 (28)	77 (SD NR)	1	0.389	83%
Hoffman et al. (2014)[49]	Pre-emptive testing in pediatrics with catastrophic dx	1559	NR	9.8 (SD NR)	4 (single-gene tests)	NR	NR

Reference	Study focus or patient population	n of PGx tested	n (%) female of PGx tested	Mean ± SD or median (IQR) age of PGx tested (years)	Number of genes evaluated	Average DGI per patient (multi-gene) or proportion of patients with actionable results (single-gene)	% of pharmacist-recommendations accepted by prescriber
Rodríguez-Arcas et al. (2013)[84]	Antihypertensives	37	NR	NR	2	0.5	64%
Condinho et al. (2012)[58] *	Fibromyalgia	1	1 (100)	50	NR	4	100%
Crews et al. (2011)[46]	Opioids (codeine) / acute lymphoblastic leukemia / pediatrics	65	NR	NR	3 (single-gene tests)	NA	100%
Anderson et al. (2007)[76]	Warfarin	101	51 (51)	63.2 (SD NR)	2	NA	NA

* denotes conference abstract; † aggregate data of PGx tested and untested; ‡ pharmacist care/recommendations provided on an integrated healthcare team; § adherence to genotyping prescribing set up in institutional database. CKD: chronic kidney disease; dx: diagnosis; GAD: generalized anxiety disorder; GI: gastrointestinal; LTC: long term care; MDD: major depressive disorder; NA: not applicable; NR: not reported; PACE: Programs of All-Inclusive Care for the Elderly; PPI: proton pump inhibitor; SSRI: selective serotonin reuptake inhibitor

2.3.1 Characteristics of included studies

2.3.1.1 Study designs

There were 3 randomized controlled trials (RCTs) among included articles comparing pharmacogenetics-based services to usual care. Observational designs included prospective (n = 24) and retrospective (n = 6) analyses. Also included were descriptive studies with the primary aim of describing the implementation of PGx (n = 7), and 3 case reports highlighting PGx use in patient care. All but 15 sources shared at least some genotyping data as either alleles identified or assigned phenotypes. Thirteen included studies had evaluated meaningful clinical outcomes such as symptoms or hospitalizations. Furthermore, four excluded publications presented results pertaining to included articles, and thus were utilized in identifying outcomes of pharmacogenomic testing by pharmacists, as reported in **Table 2.2**.

2.3.1.2 Pharmacy settings

Research taking place in the United States of America (USA) accounted for 72.1% of all publications (n = 31), while the remainder of studies took place in Canada (n = 4), the Netherlands (n = 2), Spain (n = 2), Germany, Puerto Rico, Portugal, and Malta (n = 1 each). Within these countries, implementation models were identified in community pharmacies (n = 10), ambulatory and inpatient institutions (n = 22), non-pharmacy clinics (n = 5), long-term care (LTC; n = 2), pharmacy benefit managers (n = 2), one home-health agency, and one hospice. **Figure 2.3** outlines the growth in pharmacogenetic research within each practice setting. Community pharmacy has consistently produced an average of 1-2 publications annually between 2012-2020 (apart from 2016), and accounts for nearly a quarter of the papers included in this review. It is clear by its early and consistent contribution to the body of literature, that the local pharmacy is considered by researchers to be a viable option for the delivery of pharmacogenetic services.

Table 2.2. Clinical and hospitalization outcomes found by pharmacists using PGx testing (n = 17 studies).

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
Patel et al. (2020)[101]	Adult patients with uncontrolled cancer pain	All patients: baseline and f/u pain and symptom RPh assessments, review of medications with labs, assess DDIs, provide recommendations. PGx only: Panel PGx testing for 9 genes, interpret PGx results, identify DGIs	1) Historical controls (no RPh or PGx) vs. RPh-managed; 2) PGx vs. no PGx in RPh-managed	Reduction of pain by 2 or more points on a 10-point scale	• more patients with improved pain control in RPh-managed groups vs. control (53% vs. 30%, p<0.001) • no difference in pain control in PGx vs. no PGx (56% vs. 52%, p = 0.72) • trending significance to improved pain control in PGx-actionable vs. PGx-no actionable genotypes (73% vs. 46%, p = 0.12)	Smaller difference in both RPh-managed groups may be due to effect of pharmacist alone; likely underpowered for differences in PGx-actionable vs PGx-not actionable (n = 15 actionable)
Marrero et al. (2020)[64]	A 73-year-old male with advanced urothelial cancer	Panel PGx testing for 8 genes followed by identification of DGIs with use of CDSS. Review medications and provide recommendations to prescriber.	Pre/post assessment	Subjective symptom assessment	• GERD symptoms resolved with PGx-guided dosing of PPI • Sertraline was effective and tolerated despite DGI	DGIs do not always necessitate medication change. This case report highlights the need to treat the patient as a whole.
Brown et al. (2020)[95] *	Dx of GAD or MDD with history of inefficacy or side effects, or treatment naive	PGx testing (not specified) followed by interpretation, patient education, and recommendations to prescriber.	Pre/post assessment	PHQ-9 and/or GAD-7	• PHQ-9 decreased by 2-14 points in 69.2% of patients • GAD-7 decreased by 1-4 points in 46.2% of patients	Limited analysis due to abstract presentation

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
Battig et al. (2020)[65]	Adults admitted to hospital for severe MDD without psychosis	Panel PGx testing for 31 genes, followed by test interpretation and identification of DGIs. Recommendations made to MD at weekly rounds.	Patients admitted during specified timeframe prior to PGx implementation (no PGx)	LOS, BDI-II and GAF scores at baseline and at discharge	• Shorter corrected LOS in PGx vs. no PGx (36.3 ± 19.3 d vs 46.6 ± 19.1 d, p = 0.003), with effect more pronounced in treatment-naïve (LOS corrected 24.7 ± 13.5 d, p<0.001). • greater reduction of BDI-II per day (corrected) in PGx group (-0.626 ± 0.762 points per day vs -0.38 ± 0.33 points per day, p = 0.038), though no difference in BDI-II scores at discharge (p = 0.283) • no difference in GAF scores	uncorrected outcomes worse for PGx group due to delay in test result and change in therapy: TAT (17.8 ± 13.6 days), medication changes only made at once-weekly rounds.
Schuh, Crosby (2019)[124]	A 76 year old female with RA on methotrexate, with new onset cognitive dysfunction.	Panel PGx testing, face-to-face assessment, assessment of DTPs, DGIs, and DDIs, provide recommendations to prescriber.	Pre/post assessment	Subjective symptom assessment	• Resolution of CNS ADR with genetic-guided medication review	Case report from setting of polypharmacy PGx clinic.[48]
Smith et al. (2019)[103] †	Adults with chronic pain on tramadol, codeine, or oxycodone at baseline	PGx testing with *CYP2D6* followed by test interpretation (including phenoconversion), and recommendations to prescriber for pain therapy via EMR.	Usual care (no PGx, unclear if RPh)	1) composite pain score (current pain and worst and average pain in the past week) at 3 months 2) proportion with clinically significant	• In baseline tx tramadol or codeine, IM/PMs PGx arm had greater pain reductions than non-PGx arm (-1.01 ± 1.59 vs. -0.40 ± 1.20; p = 0.016) • In baseline tx oxycodone, less pain reduction in PGx vs. non-PGx (-0.02 ± 1.09 vs. -0.87 ± 0.67; p = 0.024) • No difference in pain score in NMs in PGx vs. non-PGx	PGx-guided opioid therapy may improve pain in those on tramadol or codeine, but not those on oxycodone.

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
				(≥30%) decrease in pain	with any drug treatment • More clinically significant reductions in pain in PGx vs. non-PGx (24% vs. 0%)	
Cicali et al. (2019)[115] †	Children with GERD or other gastric indications for PPI, experiencing inefficacy or treatment naive	Genotype-guided adjustment to weight-based PPI dosing	Weight-based PPI dosing (prescriber blinded to genotype)	1) H. pylori infection rate 2) sino-nasal symptoms of GERD (5-point scale); after 12 weeks of PPI	• Trending significance to less H. pylori in PGx vs no PGx group (20% vs. 44%; p = 0.07) • decrease in sino-nasal symptoms in PGx group vs. no PGx (2.6 (2.0, 3.4) vs. 1.8 (1.0, 2.3), p = 0.031)	
Mosley et al. (2018)[102] †	Adults with solid tumor with metastasis and pain 4 out of 10 or higher	PGx testing for *CYP2D6* and genotype guided pain treatment recommendations via EMR	conventional pain management	Baseline and at 2, 4, 6, and 8 weeks: 1) BPI-SF, 2) MDAS, 3) assessment of previous 24-hr medication use, 4) quality of life	• Research in progress. • In single patient presented, a decrease in pain scores observed with genotype-guided opioid (average 7/10 prior to medication change, and 2/10 after)	Only one IM (of 6) was changed to congruent opioid

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
Cavallari et al. (2018)[24] ‡	Adult patients with PCI and *CYP2C19* genotyping	Patients prescribed genotype-congruent therapy: LOF-carriers on alternative antiplatelet (n = 346), non-LOF carriers on clopidogrel (n = 1050)	Patients prescribed genotype-incongruent therapy: LOF-carriers on clopidogrel (n = 226) non-LOF carriers on alternative antiplatelet (n = 193)	MACE (defined as first occurrence of myocardial infarction, ischemic stroke, or death)	• Greater risk of MACE for LOF-carriers on clopidogrel vs. on alternative therapy (23.4 vs. 8.7 per 100 patient-years, HR = 2.26, p = 0.013) • no difference in LOF-carriers on alternative therapy vs all non-LOF carriers on either treatment (HR = 1.14, p = 0.60) • no difference in MACE in non-LOF patients on clopidogrel vs. non-LOF patients on alternative therapy (HR = 1.01, p = 0.98)	Number needed to genotype = 3.2 to determine one patient needing alternative antiplatelet and = 93 to prevent one MACE outcome
Crown et al. (2018)[94] *	Patients starting, changing, or with history of inefficacy or side-effects to an antidepressant or antipsychotic	PGx-trained pharmacists in community pharmacies provided pre-test education and recommended testing when appropriate, provided PGx testing (not specified), interpreted results and provided medication recommendations and ongoing follow-up.	Pre/post assessment	Side effects by Clinical Global Impression (CGI) rating	• 46% of patients who attended final study visit (n = 29/65) had a clinically significant decrease in side-effects.	Limited analysis due to abstract presentation
Reynolds et al. (2017)[86] *	Hospice patients with a life expectancy of over 2 weeks on pain, psychotropics, and/or cardiovascular drugs	Panel PGx testing for 14 genes, followed by test interpretation and recommendations to prescriber	Pre/post assessment	Average pharmaceutical costs	• Average drug cost decreased by $317 per patient (unclear timeframe).	Limited analysis due to abstract presentation

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
Elliott et al. (2017)[120]	Patients 50 years or older discharged from hospital and referred to home health services on PGx-indicated medication(s)	Panel PGx testing for 6 genes, MTM review, assessment for DDI and DGI using CDSS, recommendations to prescribers	MTM without PGx or CDSS, assessment for DDIs (using "standard" resources), recommendations to prescribers	hospital readmissions and ED visits (primary outcomes)	• No difference in readmission at 30 days • less readmissions per patient at 60 days in PGx+CDSS group vs. standard care (0.33 vs. 0.70, RR 0.48, p = 0.007) • No difference in ED visits at 30 days • less ED visits at 60 days per patient in PGx+CDSS group vs. standard care (0.39 vs 0.66, RR 0.58, p = 0.045).	Delay in test turnaround and physician response reduced impact of 30-day outcomes
Brixner et al. (2016)[118]	Patients 65 years or older taking 3+ medications including one affected by CYP-PGx.	Panel PGx testing for 6 genes, followed by assessment for DDIs and DGIs using CDSS and recommendations to prescriber	Historical controls (matched) from the Inolvalon MORE2 database (no PGx or RPh)	Hospitalizations, emergency department (ED) and outpatient visits.	• Decrease in hospitalization for PGx tested vs untested (9.8% vs 16.1%, RR = 0.61, p = 0.027) • Decrease in ED visits in PGx tested (4.4% vs 15.4%, RR = 0.29, p = 0.0002) • Increase in outpatient visits in PGx tested vs untested (71.7% vs 36.5%; RR = 1.97, p<0.0001)	Authors speculate increase in outpatient visits as implementing and following up on changes
Kim et al. (2015)[78] *	Patients started on warfarin in hospital.	Pre-emptive PGx testing (not specified) followed by warfarin dosing instructions using a PGx guided algorithm	Historical controls (no PGx, unclear if RPh)	Warfarin-related hospitalizations (bleeding and embolic) at 30 and 90 days	• Decrease in bleeding and embolic events at day 30 (p = 0.04) • No difference at day 90 in PGx tested vs. untested (p = 0.08) • Fewer overall hospitalizations/events in PGx tested vs. untested (6 vs. 15, IRR 0.45, p<0.05)	Limited analysis due to abstract presentation; see review discussion re: Anderson et al. [76] initial vs. maintenance dosing

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
Rodríguez-Arcas et al. (2013)[84]	Patients with hypertension and refilled antihypertensives metabolized by CYP2C9 or CYP3A4	PGx testing for *CYP3A4* and *CYP2C9* followed by review of medications to identify DTPs, provide recommendations to physicians, and ongoing follow-up on medication adherence, BP, and HR.	Pre/post assessment	Blood pressure, heart rate, and medication adherence prior to and after intervention	• Difference in heart rate (bpm) for TC 2C9*2 carriers vs. wildtype (73.4 ± 10.0 vs. 66.2 ± 10.6; p = 0.048) • Improved adherence to medications after vs. before PGx testing (83.9% vs. 54.8%, p = 0.015) • Decrease in systolic blood pressure (mmHg) after vs. before PGx testing (145.6 ± 21.8 vs 135.7 ± 19.5, p = 0.043)	High risk of biases (observation bias, confounding) affecting adherence and blood pressure outcomes. Unclear relevance of heart rate findings.
Condinho et al. (2012)[58] *	A 50-year-old female with chronic depression and new onset fibromyalgia and history of multiple treatment failures for depression and anxiety	Panel PGx testing for at least 10 genes (not specified), patient assessment with physician geneticist including test interpretation and recommendations to patient's prescriber	Pre/post assessment	Subjective symptom assessment	• Subjective decrease in pain symptoms after duloxetine increased based on PGx results.	Limited analysis due to abstract presentation
Anderson et al. (2007)[76]	Adults starting warfarin with a target INR of 2-3	PGx testing for *CYP2C9* and *VKORC1.* RPh provided PGx-based warfarin dosing instructions	RPh (unblinded) provided warfarin dosing using standard algorithm	Serious adverse clinical events (INR ≥4, use of vitamin K, major bleeding events, thromboembolic events, stroke (all	• No significant difference in clinical endpoints or INR ≥4.0 between PGx and untested groups	Composite combines meaningful outcomes with surrogates; dilution of impact over 90 days as only initial dose different in PGx arm, maintenance dosing follows same algorithm. Subgroup analysis of primary outcome of out-of-range INRs better for wild-type and >1 polymorphic

Reference	Population	RPh-provided intervention	Comparator	Outcome measure(s)	Summary of outcomes	Review notes
				cause), myocardial infarction, and death over 90-day study period) (secondary outcome, primary is a surrogate measure)		allele patients (combined) vs. patients with singular polymorphic allele.

Most patients with actionable pharmacogenetic test results see an improvement in clinical or hospitalization outcomes. No studies assessed real economic outcomes, however a few estimate substantial savings from optimizing medications and/or reducing emergency department and hospitalizations. * denotes conference abstract; † included study: Cicali et al. (2019)[97]; ‡ included study: Empey et al. (2018)[67]. ADR, adverse drug reaction; BDI-II, Beck's Depression Inventory-II; BPI-SF, Brief Pain Inventory (Short Form); bpm, beats per minute; CDSS, clinical decision support system; CNS, central nervous system; d, days; DDI, drug-drug interaction; DGI, drug-gene interaction; DTP, drug therapy problem; dx, diagnosis or disorder; ED, emergency department; EMR, electronic medical record; GAD, generalized anxiety disorder; GERD, gastrointestinal reflux disease; GI, gastrointestinal; HR, hazard ratio; hx, history; IM, intermediate metabolizer; INR, international normalized ratio; LOF, loss-of-function LOS, length of stay; MACE, major adverse cardiovascular event; MDD, major depressive disorder; MDAS, the memorial delirium assessment scale; mmHg, millimeters of mercury; MTM, medication therapy management; NM, normal metabolizer; PCI, percutaneous intervention; PGx, pharmacogenomic or pharmacogenetic; PHQ-9, Patient Health Questionnaire; PM, poor metabolizer; PPI, proton pump inhibitor; RPh, pharmacist; TAT, test turnaround time.

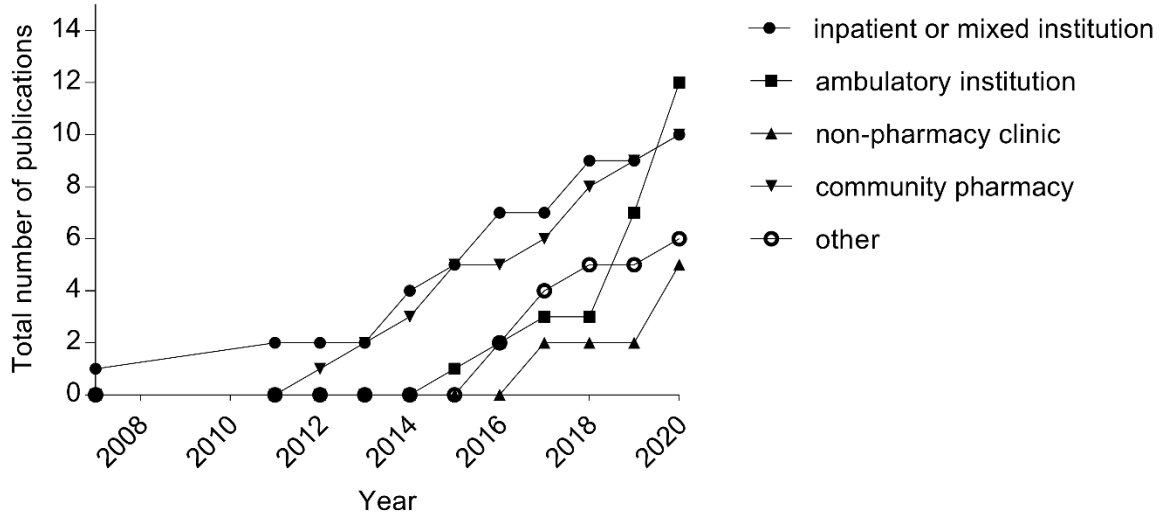

Figure 2.3. Pharmacy practice research in pharmacogenomic applications other than cancer and transplant has increased exponentially over the last 10 years, driven by an increase in the ambulatory pharmacy setting. Other, pharmacy benefit manager (n = 2), long-term care (n = 2), hospice (n = 1), home-health (n = 1).

2.3.1.3 Participant demographics

A total of 14,758 patients received PGx-based services among these investigations, though one multi-center report accounted for 43% of the total patient count. The median number of participants PGx-tested was 65 (IQR: 37,213.5). There were 2 studies reporting an average (PGx-tested) participant age under 18 years, 5 studies with an average age between 18 to 49 years, 8 between 50 to 64 years, and 13 studies with an average participant age of 65 years or greater within those PGx tested. Fourteen studies did not report an average age, and one included manuscript reported the individual results of six different studies: two which had a mean age under 18, and the remaining four with an average age between 54 to 63 years.

Only 15 sources reported the average number of total medications, despite this information being a critical component to applying these results to future populations. There was also inconsistency

observed among included articles in reporting both medications and age: central tendency was reported as mean, median, or occasionally as an "average". At times variance was substituted for a range, or not reported at all, which made comparing study results difficult. Notwithstanding, in the studies reporting an average number of medications, number of genes, and DGIs found (n = 11), a trend of a proportional increase in DGIs to medications was observed within two strata: those with a mean medication count less than 11 drugs, and those with more than 11 drugs (**Figure 2.4**). It is unclear why this trend occurs: these strata may be explained by the number of genes tested, the heterogeneity among included studies, or by another factor not identified.

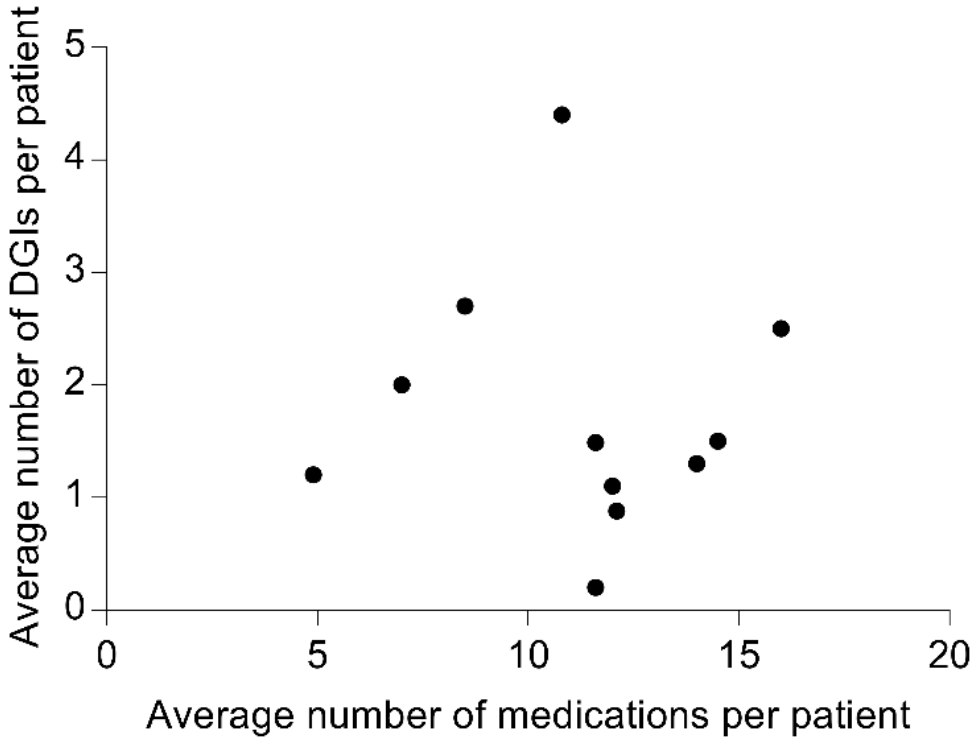

Figure 2.4. Trends in the number of drug-gene interactions (DGIs) found based on the average number of medications per patient (n = 11 studies).

2.3.1.4 Pharmacogenetic testing strategies

Overall, 15 studies used single-gene tests, while 23 used panel tests looking at anywhere from 3 to 31 genes, with over 90% of panel studies occurring in the last 5 years. Some studies used either, depending on the patient (n = 2); and a few conference abstracts did not report genes tested and thus type of testing could not be inferred (n = 3). As noted above, there is a proportional relationship of DGIs found to the number of genes tested (**Figure 2.5a**), as well as an optimal effect of at least one patient with an actionable phenotype found if testing at least 10 genes (**Figure 2.5b**). These tests may be used pre-emptively (n = 9), testing prior to the patient requiring a medication with PGx implications; or reactively, analyzing the patient's current medication profile for drug-gene interactions (n = 20). Fourteen studies employed a mix of reactive and pre-emptive strategies. A wide variety of genes were tested for the provision of clinical services, and these are summarized in **Table 2.3**. *CYP2C19*, *CYP2D6*, and *CYP2C9* were the most frequently analyzed genes, though more than 40 pharmacogenes were examined within the included literature.

2.3.1.5 Pharmacist roles in PGx implementation

In all but one study, pharmacists were directly involved in interpreting pharmacogenomic test results and the application of these results through medication recommendations (n = 39), or initiation of changes in a collaborative practice model (n = 6). The pharmacist role in identifying more intricate drug-drug-gene interactions, also referred to as phenoconversions, was evaluated in 4 studies, and its significance mentioned or discussed in another 8 papers. Other pharmacist roles included identification of appropriate patients or pharmacogenomic tests to be used (n = 18), non-PGx assessments/MTM services (n = 17), patient education before (n = 12), or after (n = 11) PGx testing, and sample collection (n = 10). Interesting roles undertaken in mostly institutional settings included leadership in PGx initiatives (n = 9), education of other healthcare providers in PGx implications (n = 5), curation of literature (n = 4), and development of clinical decision software algorithms (n = 2).

Table 2.3. Genes tested within included studies (n = 38). Studies without this data excluded from analysis.

Reference	*CYP1A2*	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*COMT*	*HLA* gene(s)	*HTR* gene(s)	*OPRM1*	*SLCO1B1*	*TPMT*	*UGT* gene(s)	*VKORC1*	Others
Smith et al. (2020)[109]		X		X	X	X		X					X	X		X	*CACNA1S, DPYD, IFNL3, RYR1*
Rodríguez-Escudero et al. (2020)[63]				X	X	X											
Patel et al. (2020)[101]	X	X		X	X	X	X	X	X			X					
Papastergiou et al. (2020)[98]				X					X								*AKT1*
Marrero et al. (2020)[64]				X	X	X		X					X			X	*CYP2C-cluster, CYP4F2*
Kerskes et al. (2020)[125] *	X	X		X	X	X	X	X								X	
Dorfman et al. (2020)[100]	X	X	X	X	X	X	X	X				X	X		X	X	*ADRB2, DPYD, F2, F5, IFNL3*
Battig et al. (2020)[65]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	*ABCB1, ABCG2, ADRB1, ADRB2, COQ2, DPYD, GNB3, GSTP1, HMGCR, IFNL3, ITPA, MT-RNR1, NAT2, SLC19A1*
Arwood et al. (2020)[59] †				X	X	X		X					X			X	*CYP2C-cluster, CYP4F2*

Reference	*CYP1A2*	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*COMT*	*HLA* gene(s)	*HTR* gene(s)	*OPRM1*	*SLCO1B1*	*TPMT*	*UGT* gene(s)	*VKORC1*	Others
Schuh, Crosby (2019)[124] ‡	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	CYP2C-cluster, CYP4F2, DPYD, DRD2, F2, F5, GRIK4, IFNL4, NUDT15, SLC6A4
Sandritter et al. (2019)[96] †				X	X	X		X			X						*SLC6A4*, serotonin reuptake transporter, *DRD3, DRD4*
Kasi et al. (2019)[62]	X	X		X	X	X	X	X							X		*DPYD*
Cicali et al. (2019)[97] †					X	X											
Bank et al. (2019)[71]				X	X	X		X					X	X		X	*DPYD*
Kim et al. (2018)[85]				X	X	X	X	X								X	
Empey et al. (2018)[67]					X												
Davila-Fajardo et al. (2018)[75] *					X												
Bain et al. (2018)[87]				X	X	X	X	X					X	X		X	*CYP4F2, ATM, F5*
Schwartz et al. (2017)[66]				X	X	X	X	X					X	X		X	*CYP4F2, ATM, F2, F5, MTHFR*
Reynolds et al. (2017)[86] *					X	X											*SLC6A4,* 11 other genes tested not specified

Reference	*CYP1A2*	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*COMT*	*HLA* gene(s)	*HTR* gene(s)	*OPRM1*	*SLCO1B1*	*TPMT*	*UGT* gene(s)	*VKORC1*	Others
Papastergiou et al. (2017)[99]	X			X	X	X	X	X				X	X			X	
Johnson et al. (2017)[55]					X												
Haga et al. (2017)[68] †				X	X	X				X			X			X	
Elliott et al. (2017)[120]				X	X	X	X	X								X	
Wirth et al. (2016)[69] *					X												
Sugarman et al. (2016)[119]	X			X	X	X	X	X	X		X	X	X			X	*SLC6A4, SLC6A2, MTHFR*
Hicks et al. (2016)[110] †										X				X			
Moaddeb et al. (2015)[53] †					X								X				
Brixner et al. (2016)[118]				X	X	X	X	X								X	
Haga et al. (2015)[47]				X	X	X							X			X	
Bright et al. (2015)[52]					X												
Weitzel et al. (2014)[51]					X												
Ferreri et al. (2014)[50]					X												
Hoffman et al. (2014)[49] †					X	X							X	X			
Rodríguez-Arcas et al. (2013)[84]				X			X										

Reference	*CYP1A2*	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*COMT*	*HLA* gene(s)	*HTR* gene(s)	*OPRM1*	*SLCO1B1*	*TPMT*	*UGT* gene(s)	*VKORC1*	Others
Condinho et al. (2012)[58] *	X																at least 9 other genes tested, not listed
Crews et al. (2011)[46] †						X								X	X		
Anderson et al. (2007)[76]				X												X	

* denotes conference abstract; † indicates not all patients tested for all listed genes; ‡ From Schuh and Crosby (2019)[48]

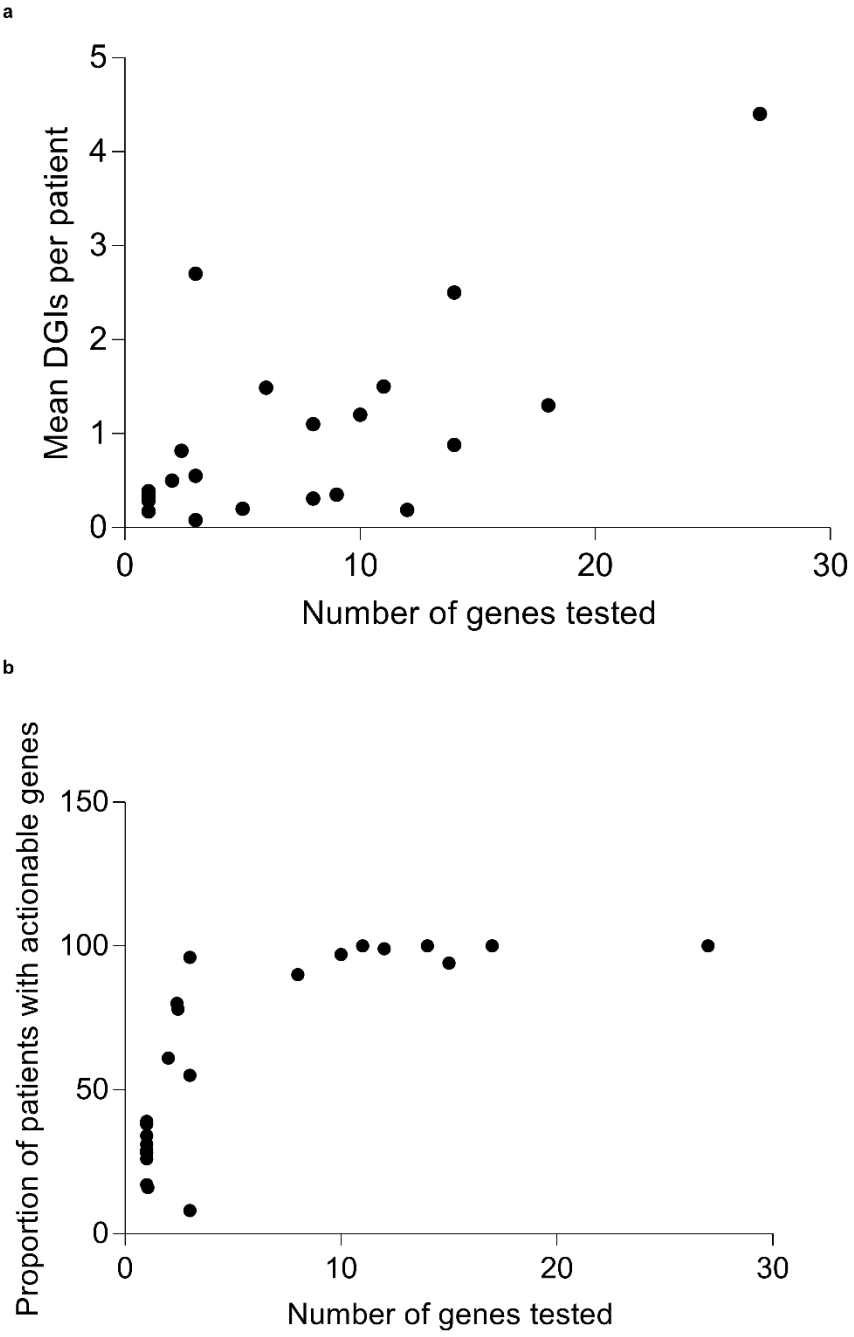

Figure 2.5. Mean drug-gene interactions (DGIs) per patient (a, top, n = 23 studies), and percent of patients with actionable phenotypes (b, bottom, n = 25 studies), by the number of genes analyzed per patient in studies. Excluded case-reports and studies without sufficient data provided.

2.3.1.6 Therapeutics addressed

The focus of pharmacy-based pharmacogenomics services described in **Table 2.1** can be categorized into four domains: cardiology (n = 12), cancer and non-cancer-related pain/other supportive therapies in palliative medicine (n = 5), psychiatry (n = 6), and polypharmacy patients/studies testing multiple drug-gene pairs in different therapy classes (n = 20) (**Figure 2.6**). Overlap in medications was seen among these categories, especially as multi-gene studies evaluated medications within the other three categories. Particularly, there were some specific drug-gene pairs that were identified among the included publications that would be of consideration for the community pharmacist.

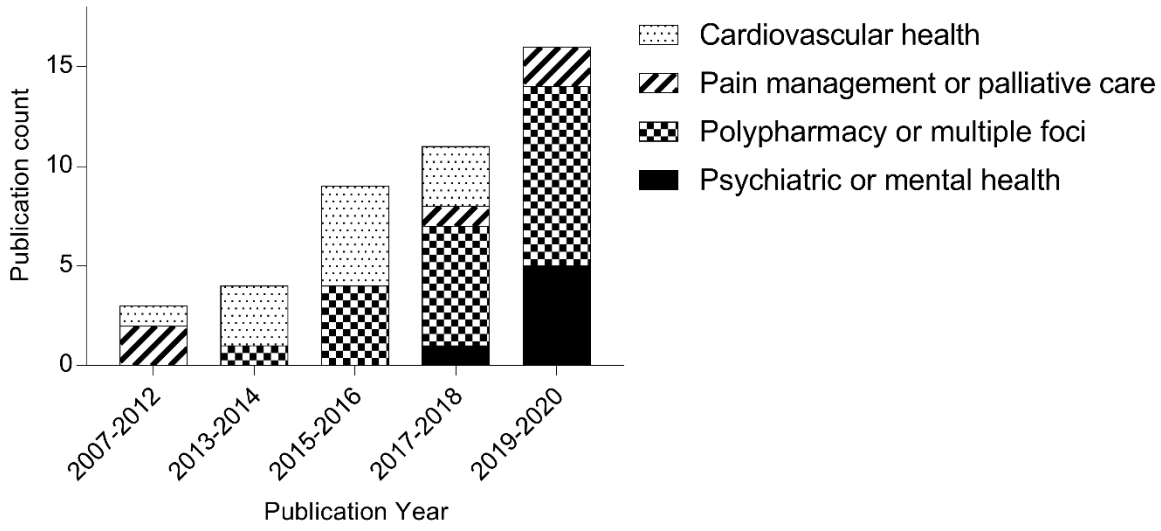

Figure 2.6. Number of studies identified in this review by therapeutic focus of study design (n = 43).

2.3.1.6.1 Cardiology

Clopidogrel was one of the most common medications identified for testing, with 9 studies using single-gene testing of *CYP2C19* to assess antiplatelet therapy, and another 6 panel-based

studies reporting that clopidogrel/*CYP2C19* was one of the most actionable drug-gene pairs. Within cardiology medicine, there were also 3 studies that addressed warfarin pharmacogenomics directly and another 15 that tested the *VKORC1* gene used in initial warfarin dosing algorithms. Fifteen studies tested *SLCO1B1* encoding for the organic anion transporting polypeptide (OATP) 1B1. This is mostly referenced in the included literature as the transporter responsible for hepatic uptake of lipophilic statins for subsequent metabolism, though it is also responsible for the transport of other medications, such as methotrexate, as identified by one case report. Antihypertensives were specifically studied in one paper, though beta-blockers, angiotensin receptor blockers (ARBs), and/or calcium channel blockers were identified in another 4 studies as actionable therapies found in patients tested.

2.3.1.6.2 Psychiatry and mental health

There were 16 studies that either specifically addressed antidepressants or identified these medications as one of the most pharmacogenetically-actionable within testing. In studies focussing on the psychiatric population, three studies analyzed antidepressants in major depressive disorder (MDD), one conference abstract studied unspecified “psychiatric medications”, one polypharmacy protocol included only patients within a psychiatric counselling service, and one study uniquely addressed the pharmacogenomics of cannabis in a patient sample with mental health disorders. While other studies mentioned the pharmacogenetics of benzodiazepines, antipsychotics, and mood stabilizers other than carbamazepine, there was not enough data in the included papers on the use of pharmacogenomics with these medications to analyze these further.

2.3.1.6.3 Pain and supportive therapies in palliative care

Within included literature, there were 3 manuscripts that reporting use of single-gene *CYP2D6* testing for opioids, with one of these identifying three separate studies in both cancer and non-cancer pain, to provide a total of 5 studies among these manuscripts. Another study utilized panel testing and pharmacist assessments in pain management for cancer patients, and 4 panel-based studies identified opioids as frequently involved in DGIs. Two case reports were also included in this category: one on the use of panel testing for supportive, non-chemotherapy medications in cancer patients; and one case report on panel testing in fibromyalgia, in which PGx testing informed an effective titration of duloxetine. Non-steroidal anti-inflammatories (NSAIDs) were mentioned as a commonly actionable medication by one panel study but not elaborated on in any other included research. Additionally, while *CYP2D6* is the most discussed opioid pharmacogenetic target discussed within this review, additional genes analyzed for opioid use in some of these studies include pharmacokinetic genes like *CYP3A4/5* and catechol-O-methyltransferase (*COMT)*, and the pharmacodynamic target of the mu-receptor (*OPRM1*).

2.3.1.6.4 Other therapeutics

Drug-gene pairs not discussed in the above three categories that were analyzed among multi-gene studies included carbamazepine/*HLA-B*1502*, azathioprine/*TPMT*, and proton-pump inhibitors (PPIs)/*CYP2C19.* While this list is not exhaustive for all medications that have pharmacogenomics implications, this list does cover all studied therapeutics specifically in pharmacy practices outside of chemotherapy and transplant areas of medicine. Thus, these medications have some evidence to refer to in considering research or implementation in pharmacogenomics in the community pharmacy.

2.3.1.7 Facilitators to implementation

There were 19 studies that described pharmacist education or expertise as part of the implementation model, with physicians accepting pharmacist recommendations after PGx testing a weighted mean of 61.4% of the time in these programs, compared to 32.7% of the time in studies without described pharmacist education. "Training" included residency programs,[45] seminars with exams,[46] board certification,[47] and e-learning.[48] There were also 18 studies found to have used clinical decision software in the form of drug-gene interaction reconciliation, notifications if a medication is ordered that may benefit from testing, and/or notification of new results available. In some institutions, this program was designed by pharmacists in collaboration with a bioinformatics team. In community settings, this was more frequently identified as the use of YouScript® or similar software that found both drug-drug and drug-gene interactions, enhancing the identification of phenoconversions. A common barrier to PGx implementation identified by the included literature was the time commitment for pharmacists and patients alike. While many studies commented on this, only 10 studies documented time commitments for PGx services. A summary of the time-based results is reported in **Table 2.4.**

Table 2.4. Studies reporting time required for PGx services (n = 10).

Reference	Number of genes tested & evaluated	Time per pt (minutes)	Duration category
Johnson et al. (2017)[55]	1	5.7 (of pharmacist time)	short
Hicks et al. (2016)[110]	3 (single-gene tests)	60 (in ambulatory clinic, unclear if this was also single-gene testing)	long
Moaddeb et al. (2015)[53]	2 (single-gene tests)	3-15	short
Ferreri et al. (2014)[50]	1 (single-gene test, time also included an MTM consult)	76.6	very long
Crews et al. (2011)[46]	3 (single gene tests)	12-120	too varied to categorize

Reference	Number of genes tested & evaluated	Time per pt (minutes)	Duration category
Schuh, Crosby (2019)[124]	27	30 focused or 60 comprehensive consults*	long
Schwartz et al. (2017)[66]	14	30-40 obtaining informed consent. Rest of time not detailed.	long
Dunnenberger et al. (2016)[45]	10	60	long
Haga et al. (2015)[47]	5	79.8 (39.7 visit 1, 16.1 visit 2, 11 chart review, 12 test interpretation)	very long
Arwood et al. (2020)[59]	1 to 8 (single gene or panel)	40-60 (pre-test), 20-30 (post-test)	long

* From Schuh and Crosby (2019)[48]; MTM: medication therapy management

2.4 Discussion

The results provided by mapping the current research in pharmacy-based PGx implementation serves to inform researchers, policy developers, and individually practicing pharmacists. For researchers, gaps in the literature can be identified and highlighted for future protocol development. Legislators benefit from the research available while making decisions on the funding or scope of pharmacists providing these services. Despite the expected decrease in costs as market competition increases for tests, there are still finite resources available. Therefore, it is important to develop a prioritization strategy for both public and private-funded services to obtain the most cost-benefit. Lastly, as pharmacogenomics is a relatively new field in medicine, and so individual pharmacists either planning or expanding a PGx practice can benefit from the collection of knowledge of what has been demonstrated to improve patient outcomes thus far. These more clinically relevant models can be identified by both the testing logistics, including the number of genes tested as well as the timing of testing in relation to therapy initiation, and by the specific medications or therapeutic categories addressed by studies.

2.4.1 Testing logistics

2.4.1.1 Single gene tests

Nearly all early (2007-2015) pharmacogenetic implementation models in pharmacy employed single-gene tests to assess one medication **(Figure 2.7a)**. These preliminary investigations served as pilots that demonstrated the feasibility and clinical utility of PGx testing by pharmacists. Some examples of this include testing *CYP2D6* in opioid use,[46 49] and *CYP2C19* in antiplatelet selection.[49-53] One such pre-emptive testing program at St. Jude's Children's Hospital had an aim of reducing codeine toxicity in children with acute lymphoblastic leukemia.[46] Of the 65 patients tested in this pilot, 4.6% were determined to be CYP2D6 ultra-rapid metabolizers (UMs) and thus at a greater risk of toxicity from an accumulation of active metabolite. Poor metabolizing (PM) status was also found in 6.2%, indicating a reduced ability to activate codeine. Both subgroups were recommended by pharmacists to utilize an alternative analgesic, and these recommendations were 100% approved by prescribers. This program's success allowed it to expand to test pediatric patients with other catastrophic diagnoses, and for more genes, including *CYP2C19* and *SLCO1B1*.[49] While testing for these genes may not be immediately relevant to this patient population, the benefits are deferred to later in life. Heart disease disproportionally affects pediatric cancer survivors, conferring a three-fold greater risk for these patients.[54] Pre-emptively testing this population can lead to more effective and safe selection of antiplatelets and statins if future need arises. These cardiovascular therapies also tend to demonstrate the most actionability for pharmacogenetic testing based on patients with actionable phenotypes and DGIs found, and thus are well-suited for single-gene models in a high-cardiovascular risk population.

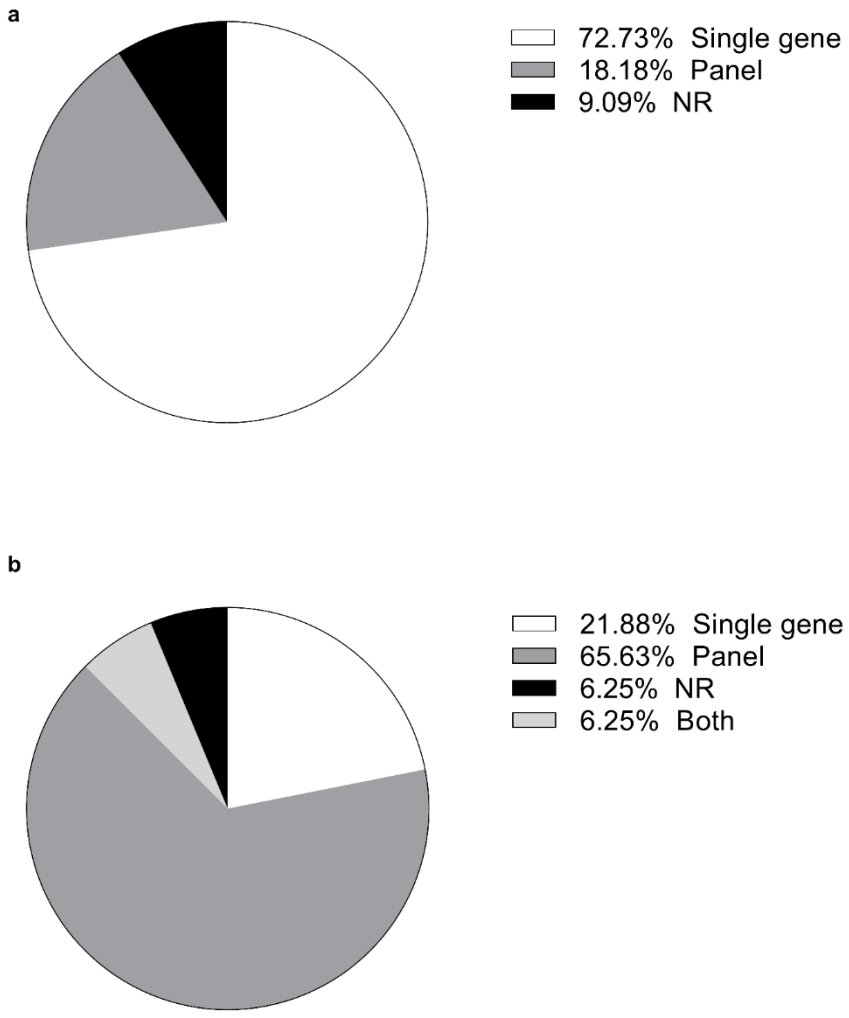

Figure 2.7. A comparison in the distribution of pharmacogenetic tests used in studies between 2015 and earlier (a, top), and after 2015 (b, bottom) (total n = 43 studies). NR: not reported.

In addition to providing a specialized focus to patients, single-gene tests are more feasible for the pharmacist than panel tests, as demonstrated by 10 studies reporting time spent providing PGx services **(Table 2.4)**. All studies testing multiple genes appeared to require at least 60 minutes, usually for a comprehensive consult. Single gene tests, on the other hand, usually needed 15 minutes or less of a pharmacist's time for the entire process. A small study of *CYP2C19*

genotyping prior to percutaneous intervention in an institutional setting noted an average of 5.7 minutes to interpret test results and recommend therapy.[55] Similarly, Moaddeb et al. found pharmacists spent 3 to 15 minutes to provide education, interpretation, and recommendations for either *SLCO1B1* in simvastatin use or *CYP2C19* in clopidogrel use in a community pharmacy setting.[53] However, in the latter study some problems could be identified that included: incorrect interpretations for ~8% of all results, a lack of suggested therapy changes despite of the identified polymorphisms, and some patients reporting disappointment in their physician for prescribing the medication found to have a DGI. While these results highlight the need for ensuring pharmacist competency in the assessment and communication of PGx results, it is not anticipated the time required to improve these parameters would lead to times as high as those observed with panel testing. A time-and-motion simulation reported an average of 9.49 ± 1.38 minutes of time spent providing *CYP2C19* testing in a community pharmacy, in line with the real-world results included in this review.[56] Another included *CYP2C19* study in a community pharmacy did report a longer time than these (mean 76.6 minutes),[50] however some of this increase may be accounted for by components exclusive to research, such as a more thorough consent and/or data collection process, and the included comprehensive medication review. The time for this component ranged from 7 to 55 minutes, with a mean of 23.1 minutes, comparable to other MTM services rather than genotyping alone.[50 57] Albeit panel testing may inherently find more drug therapy problems (DTPs), single gene tests may be more feasible to implement or pilot compared to panel tests, particularly when time or compensation is limited.

2.4.1.2 Panel tests

Aside from a case report presented by Condinho et al. in 2012,[58] multi-gene panels were not used in published pharmacy studies until 2015 **(Figure 2.7b)**, when this technology became

broadly available through institution and commercial laboratories. Arwood et al. identified that these panel tests are considered more cost-effective for patients on multiple medications with PGx implications.[59] Polypharmacy is a prevalent concern worldwide. In the USA, 11.2% of all individuals are on 5 or more medications, and in those 65 years and older this proportion increases to 40.9%. Similarly, in Canada, 65.7% of seniors are on 5 or more medications, and the prevalence of polypharmacy in Germany is seen to increase proportionally with age.[60,61] Therefore, panel PGx testing may have a higher clinical utility measured by an increased number of drug-gene interactions (DGIs; **Figure 2.5a**). In studies reporting on this, a trend is observed as the mean number of DGIs increase proportionally with the number of genes tested**.** The study by Kasi et al. found the greatest number of DGIs per patient among articles in this review (4.4) after testing for 27 pharmacogenes.[62] The number of genes tested is not the only factor contributing to this effect, these patients were also on a mean of 10.8 medications. The effect of polypharmacy contributes to the mean of 2.7 ± 1.14 DGIs per patient seen by Rodriguez-Escudero et al. when analyzing only 3 genes in a psychiatric patient population on a mean of 8.5 ± 2.8 medications.[63] Therefore, it is reasonable to assert that medication burden, breadth of genetic testing, and potentially comorbid diagnoses contribute to the clinical utility of testing, and that these factors should be of consideration in either trial or policy design. Another observation made in this review was that with testing at least 10 genes, a study is likely to find that all patients carry at least one actionable genotype (**Figure 2.5b)**. The frequency of DGIs, as well as the proportion of patients with actionable phenotypes based on the number of genes tested is valuable information in discussing the potential benefits of pharmacogene panel testing with patients and stakeholders.

2.4.1.3 Pre-emptive testing

A variety of approaches in the timing of pharmacogenetic testing are utilized throughout included articles. While pre-emptive testing is useful in avoiding serious adverse effects prior to their occurrence or avoiding the typical trial-and-error method of prescribing, it comes with cost-based disadvantages. In areas with third-party coverage for genetic testing, some may not approve pre-emptive uses. Due to this, it has been identified as not feasible by some studies,[51] and suggested by others to be feasible with specific targeting of patient populations more likely to see benefit.[59 64] The cost-benefit analysis must be weighed with the fact that pre-emptive testing while younger may have deferred benefits as one ages. Clinical utility of pre-emptive panel testing may be enhanced by targeting such services towards those who may be more likely to require more medications in the future, as identified by risk factors like family history, prior illness such as those seen in the pediatric patients of St. Jude's Hospital,[46 49] or smoking status.

2.4.1.4 Reactive testing

Reactive testing generally appears more pragmatic in the reviewed literature as clinicians can target patients on highly actionable medications, or those who have already experienced inefficacies or side effects that may be explained by a polymorphism. These patients are therefore more likely to see immediate benefit from PGx testing in the pharmacy. Reactive testing, however, may not be as useful when a prompt result is required. As identified by many studies in this review,[51 65-68] a fast test turnover time (TAT) is imperative to effective implementation of pharmacogenetic testing in both reactive and pre-emptive models. This issue may be overcome by point-of-care testing. Two studies evaluated the use of point-of-care tests that returned results within an hour for *CYP2C19* genotyping, finding it a feasible model for implementation.[67 69] Additionally, in comparing POC to standard testing, it is seen that patients with rapid-testing were

more likely to be on genotype-congruent antiplatelet therapy on discharge from hospital.[67] These tests could be considered reliable, as one study found that POC testing led to the same result as laboratory testing 97% of the time.[70] Another important pearl to PGx implementation is the ability to recall results for use with future medications in both reactive and pre-emptive methods. A follow-up to the Implementation of Pharmacogenetics into Primary Care Project (IP3 study)[71] found that 96% of pharmacists and 68% of prescribers had PGx test results that could be recalled on their electronic medical record. This documentation is necessary to enable the use of PGx results in assessing future therapies, thus making any pre-emptive or reactive implementation of use in a patient's lifetime.[72]

2.4.2 Therapeutic applications

2.4.2.1 Cardiovascular health

Cardiovascular medication therapy is the most researched in pharmacy-based non-oncologic PGx literature to date. This is primarily driven by testing of *CYP2C19* in antiplatelet selection, *SLCO1B1* in assessing statin therapy, and testing multiple genes for warfarin initiation. The drug-gene pairs discussed in this therapeutic category have been analyzed in both community and institutional settings, supporting the use of PGx testing cardiovascular medications in either setting of pharmacy practice.

2.4.2.1.1 Clopidogrel

Clopidogrel is a prodrug that relies on CYP2C19-mediated metabolism to be able to bind irreversibly to the adenosine diphosphate ($P2Y_{12}$) receptors of platelets.[73] Due to this dependency on metabolism for efficacy, alternative antiplatelet therapy with prasugrel or ticagrelor is recommended by the CPIC guidelines for patients with acute coronary syndromes and those

undergoing percutaneous intervention for coronary disease who carry a loss-of-function (LOF) allele for *CYP2C19*.[23] This is because the consequences of treatment failure with an antiplatelet can be devastating. A recurrent myocardial infarction may lead to significant disability or death, as well as financial strain for patients secondary to treatment costs and loss of income. Unfortunately, without genotyping it is not apparent if a patient is more likely to fail treatment due to inadequate metabolic activation of clopidogrel until the debilitating event occurs. An Implementing Genomics in Practice (IGNITE) Network publication looking at outcomes of major adverse cardiovascular events (MACE) in those treated with clopidogrel found a hazard ratio of 2.26 (95% CI 1.18 to 4.32, p = 0.013) in LOF allele carriers compared to LOF carriers on alternative antiplatelets. This indicates a significantly higher likelihood of clopidogrel failure in LOF-carriers.[24] It is important to note that these results are primarily driven by heterozygous LOF allele carriers, also referred to as intermediate metabolizers (IMs), who accounted for 90.6% of all patients categorized as "LOF allele carriers". The IGNITE publication included in this review found IMs were less likely to be prescribed congruent therapy as per the CPIC guidelines[23] compared to homozygotes, also known as poor metabolizers (PMs).[67] This effect is seen in other studies,[51] highlighting a need to educate prescribers on the evidence basis for the CPIC recommendation for IMs to be placed on an alternative antiplatelet. While confounding may be present wherein the socioeconomic status of a patient may predict both an inability to afford alternative antiplatelets and a higher likelihood of events,[74] a plausible biologic mechanism exists towards the above results, and must be given due consideration.

The importance of *CYP2C19* genotyping is compounded by the high prevalence of polymorphic alleles for this enzyme. Studies in this review analyzing *CYP2C19* genotypes within the current CPIC guidelines for antiplatelet selection [23] found 26% to 38% of all participants should be

on an alternative antiplatelet.[51-53 55 67 69 75] Exceptions to this included a study using older guidelines for phenotype assignment[50] and one where the reason for discordance (10-20% actionable, depending on guidelines) was unclear.[47] Within this review, pharmacists demonstrated leadership within institutions implementing *CYP2C19* genotyping.[49 51 67] The feasibility of this service is also demonstrated in both hospital and community settings when sufficient education is given to pharmacists prior.[49 51 52 67] This is further supported by high acceptance of recommendations to physicians based on this service, reasonably high patient acceptance per study consent rates, and clear guidance provided by the literature.[23] While one could argue all patients should simply be placed on alternative antiplatelets to avoid genetic-related issues, these medications come at a much higher cost compared to clopidogrel despite no difference in MACE for non-LOF carriers.[24] Therefore, the clinical significance, high actionability, and potential cost savings make genotyping for antiplatelets a valuable service for patients and healthcare systems, and a service the included literature shows can be provided by pharmacists.

2.4.2.1.2 Warfarin

Within antithrombotics, pharmacists are also positioned to improve patient outcomes with the use of pharmacogenomics in warfarin dosing. Warfarin acts on the vitamin K epoxide reductase complex (VKORC-1) receptor to inhibit the activation of clotting factors, thus exerting its anticoagulant effect. Warfarin is subsequently metabolized primarily by CYP2C9 for elimination.[73] Thus, there are at least two proteins wherein genetic polymorphisms may lead to a difference in warfarin effect through pharmacokinetic (CYP2C9), or pharmacodynamic (VKORC-1) pathways. Anderson and colleagues used these genes in the earliest study that employed pharmacogenomics in a non-oncologic pharmacy practice (the Couma-Gen study).[76] In this RCT, they compared patients started on a warfarin dose determined by a multi-linear regression equation that included

genetic and non-genetic covariates to patients started on a validated 10mg loading dose algorithm. A pharmacist provided dosing instructions to both arms for both initiation and chronic dosing for a period of 90 days. The study failed to find a difference in time in therapeutic range (TTR) in all patients. However, the subgroup of patients with 0, 2, 3, or 4 polymorphisms among the two gene pairs did see a significant reduction in out-of-range INRs with genetically-guided dosing compared to the non-genetically dosed arm (29.3% vs 39.1%, p = 0.03). There are a few possible explanations for this observation. First, the dosing algorithms only differed in the initial loading dose, as the changes in dose for out-of-range INRs (international normalized ratio) were based on the same percentages as the non-genetic algorithm. If a patient was truly more or less sensitive to warfarin, they in turn should also be receiving proportionally different percentage-based changes for aberrant results. To our knowledge, no such genetically-based maintenance algorithm exists. Secondly, this study saw that patients who had only 1 polymorphic allele within two gene pairs had an average warfarin dose requirement of 37.4mg per week, numerically close to the non-genetic algorithm initiation dosing of 35mg per week. Therefore, patients in the non-genetically dosed arm would be started on a dose numerically close to the same dose they would have been on in the genetic arm. Therefore, it would appear for many patients, the standard dosing arm would be reasonably applicable, as 43% of all patients had a single polymorphism identified. Third, as both arms were managed by a pharmacist unblinded to genotype, some bias may be present as aggressiveness of dosage changes may differ with knowledge of warfarin sensitivity. Fourth, pharmacists have already demonstrated an aptitude for anticoagulation management in other studies.[77] Possibly for this reason, the authors of Couma-Gen observed a smaller difference in TTR between the two arms than they expected in calculating sample size, making the study underpowered to find a significant difference. While this study failed to

demonstrate a difference in clinical outcomes, it did demonstrate the feasibility of a pharmacist providing this service and hinted there may be still a clinical benefit for patients either very sensitive or resistant to warfarin.

This potential improvement in TTR has also been shown to improve real clinical outcomes in another study presented in a conference abstract reporting warfarin management by pharmacists aided by pharmacogenetics.[78] These authors found a decrease in bleeding and embolic events at day 30 ($p = 0.04$) but not at day 90 ($p = 0.08$). This is consistent with the findings by Anderson et al.[76] that the positive effects of genetically guided initial warfarin dosing may be diluted by later undifferentiated maintenance dosing. It was unclear why a decrease in warfarin-related hospitalizations at the endpoint was seen in this study despite no difference in bleeding and embolic events at day 90 (6 vs 15, IRR 0.45, 95% CI 0.12-0.81, $p<0.05$).[78] This could be driven by the first 30 days, or it could be a difference in arms, as it is unclear if patients in the non-genetically guided arm were pharmacist-managed. Therefore in these studies it is shown that pharmacists can use genetics to guide initial warfarin dosing, with at least 32% of variability in warfarin dose requirements predicted by genotype.[76] This method of anticoagulation may lead to improved clinical outcomes, though could be further improved on with a genetically-guided maintenance dosing algorithm.

2.4.2.1.3 Statins

Maintaining adherence to statins is something that has perplexed clinicians for a long time. Their pleotropic effects are difficult to explain to patients, and their side-effect profile can make them less appealing when the user cannot feel benefit in a tangible way. This makes statins a reasonable target for pharmacogenetic-guided medication selection and dosing, as this is a visible way to improve patient confidence in their drug therapy, and thus adherence. Statins are

transported into the liver via the organic anion-transporting polypeptide (OATP) encoded for on *SLCO1B1* for subsequent elimination. It has been demonstrated that patients with the *5 allele have reduced function of this protein and thus do not clear certain hydrophobic statins as effectively.[79] Clinical guidance exists through various organizations for simvastatin[80 81] and atorvastatin[80], with the French National Network of Pharmacogenetics (RNPGx) guidelines, suggesting pre-emptive *SLCO1B1* testing for all statin use.[82] Additional research has also indicated that other statins, including rosuvastatin, can be affected by this gene.[79 83] No clinical guidelines exist for genetic dosing of statins other than simvastatin and atorvastatin, leaving it to clinicians to interpret the primary literature, and researchers to fill that body of evidence by establishing guidelines.

Studies for pharmacy-managed testing for *SLCO1B1* have therefore focused on simvastatin use, and to a small extent atorvastatin use, based on clinical guidelines. In a multi-site community pharmacy pilot in the Netherlands, Bank et al. used a list of medications in their eligibility criteria that consisted of simvastatin, atorvastatin, and 8 psychiatric or central-nervous system (CNS) medications. Most patients were recruited based on statin use (72%), and 19% of all patients had a drug-gene interaction with a statin, indicating these drugs as both commonly prescribed and highly actionable.[71] Even without an active drug-gene interaction, a result indicating normal function of OATP can reassure prescribers and patients of the decision to prescribe simvastatin, as it did in at least one study.[68] Some challenges exist in the clinical utility of testing as results are not generally considered if the current dose is already low.[53] Therefore, reactive testing protocols should consider only those patients on higher doses of medications with clinical guidelines, and/or those experiencing side-effects regardless of dose. Since all statins do not have guidelines, and there are several patient specific factors that can impact drug side effects such as age and

interacting medications,[79 83] a pharmacist is the best provider to interpret *SLCO1B1* results in the context of the individual patient.

2.4.2.1.4 Antihypertensives and other cardiovascular drugs

One study analyzed pharmacogenomics specifically for use of antihypertensives, in conjunction with MTM services.[84] Pharmacists provided on average 1.1 medication-related recommendations to prescribers per patient, with half of all patients having at least one DGI. While improved adherence was seen, and likely contributed to the reduction of blood pressure observed, observation bias can potentially explain both outcomes. While it is plausible that pharmacogenetic testing and MTM can improve patient adherence and therapy optimization, a control group would be advisable to reduce this bias. Randomization with and without PGx can also aid in determining how much effect is due to PGx outside of MTM's established benefits, as seen in other studies.[66 85] The remaining studies assessing antihypertensives among other medications in panel testing identified drug-gene interactions for metoprolol,[66 86 87] calcium channel blockers,[66] and angiotensin receptor blockers.[63] Not much detail is provided in the management of these drug-gene interactions within these studies, aside from referencing the use of clinical guidelines. While some antihypertensives are metabolized by CYP enzymes, and some may have pharmacodynamic effects to polymorphisms in receptors,[73] these medications are typically titrated to effect. This may limit the impact PGx may have to the average patient with hypertension who can be managed based on vital signs. Perhaps subgroups such as treatment-resistant hypertension or those with a high fall risk may see a greater benefit from genetic-guided antihypertensive treatment, however these specific populations were not identified in the current literature.

2.4.2.1.5 Antiarrhythmics

Other cardiovascular medications not explicitly explored in pharmacy-based pharmacogenomics literature to date include antiarrhythmic drugs. Amiodarone is known to be affected by p-glycoprotein and CYP3A4 drug-drug interactions,[73] however there is currently no clinical guidelines on management of polymorphisms in these proteins. Flecainide and propafenone do have clinical guidelines by the DPWG for *CYP2D6*,[80] however they are not studied in the included articles. Given the large number of drug-drug interactions, genetic implications, and the narrow therapeutic range of these medications, antiarrhythmics would be an interesting target for future PGx research.

2.4.2.2 Psychiatry and mental health

Psychotropic drugs are heavily dependent on CYP metabolism,[88] and have multiple pharmacodynamic targets affected by genomics such as dopamine and serotonin receptors.[89] Therefore, PGx testing can help predict response or side-effects to antidepressants, antipsychotics, atomoxetine, some benzodiazepines, and some mood stabilizers like valproic acid and carbamazepine. Inefficacy and side effects to these medications impact many patients, and with costly consequences. In 2011, a research group identified that by 2041 over 20.5% of the population of Canada may be affected by mental health disorders, with costs to patients and taxpayers greater than $2.5 trillion (CAD) within this 30 year time period.[90] Literature that demonstrates the application of pharmacogenomics solely to psychiatric populations in the pharmacy has emerged in the last three years, and it has already been observed that these patients may have a greater number of genetic polymorphisms. One study within this review found that 96% of outpatient psychiatric patients tested for only three gene-pairs had at least one allelic variation indicating altered drug metabolism. Another reported a mean of 6.1 actionable

variants per patient among 13-17 genes tested.[91] This correlation may be related to altered endogenous neurotransmitter metabolism by the same polymorphic enzymes utilized in drug metabolism, or an undetermined linkage disequilibrium with other predisposing genes.[63 92 93]

Two conference abstracts and one observational study found improved clinical outcomes using validated tools with the use of PGx in depression and/or anxiety. A Canadian group in collaboration with the Center of Addiction and Mental Health presented findings that patients genetically tested had clinically significant reductions in medication-related side effects, as measured using the Clinical Global Impression scale.[94] The full results of this research are yet to be published, however in this conference abstract the authors indicated other "positive clinical outcomes" were found. Another recent conference presentation reported improved PHQ-9 (Patient Health Questionnaire-9) and GAD-7 (General Anxiety Disorder-7) scores in depression and anxiety, respectively, with pharmacogenetic testing.[95] While limited analysis can be done on these conference proceedings, these preliminary reports are promising. The observational study, conducted in a German hospital treating patients with major depressive disorder (MDD), found that while overall Beck Depression Inventory-II (BDI-II) scores were not different between tested and untested cohorts, the tested group saw more rapid improvement in symptoms per day (corrected).[65] A reduction in time to reach clinical outcomes is meaningful to patients, and this goal is also supported by this group's findings that mean length-of-stay (corrected) was reduced in the genetic-tested group compared to controls (36.3 ± 19.3 days vs 46.6 ± 19.1 days, respectively; $p = 0.003$). These results, however, must be interpreted in the context of the time correction applied. With limited capacity, the mean test turnaround time (TAT) was 17.8 days. Due to this delay, all time-based results were actually worse in the pharmacogenetic-tested group prior to

correction. This highlights that prompt TAT is not only necessary for feasibility, but that it is also imperative in avoiding unintended adverse effects to the intervention itself.

Other psychiatric-specific studies reported on surrogate findings that in theory may lead to improved outcomes. These were recognized as enhancing pharmacists' ability to find drug-therapy problems (DTPs),[63] reducing the number of DGIs present after pharmacogenetic-guided interventions,[91] high prescriber and patient acceptance, [49 96 97] and identifying patients at risk of adverse effects to cannabis.[98] This last study also revealed that a patient population that primarily used cannabis for anxiety and/or depression (70% of patients, all patients had at least one mental health diagnosis) found genetic testing and tailored pharmacy education about cannabis use valuable. Testing pediatric populations was generally well accepted by patients, with 97-100% of approached guardians consenting to buccal testing.[49 97] Pharmacists' recommendations were also well received by prescribers, with one group reporting that 63% of patients had all recommendations approved, and 22% had some of their recommendations approved.[96] Another study saw 100% prescriber acceptance of SSRI recommendations as a result of pre-emptive testing and case-conferences.[97] Other research on polypharmacy patients found antidepressants to be the most common indication for genetic testing,[59 99] and one of the most actionable classes of drugs.[66 86 87 99 100] Given the frequency, cost, actionability, and acceptance of PGx testing for antidepressants and other psychotropics in studies within this review, this is a reasonable target to consider in pharmacy-based services.

2.4.2.3 Pain management and palliative medicine

While studies on the pharmacogenomics of chemotherapy in this review were excluded, it was prudent to include studies evaluating non-chemotherapy medications in the cancer and palliative population. Patients with end-stage diseases may be on medications for pain

management, other symptoms, and chronic disease, all referred to as "supportive" therapies in most literature.

2.4.2.3.1 Opioids

Programs such as pre-emptive testing of *CYP2D6* for potential codeine use in children with ALL, as described earlier in this review,[46] can improve patient safety by identifying those more likely to experience toxicity. Improvements in efficacy may also be seen with PGx-guided pain therapy for cancer patients. One manuscript detailing two cohort studies had evaluated pain control with pharmacogenetic testing plus pharmacist assessment in one protocol, and pharmacy assessment alone in the other.[101] While they did not see a significant difference in proportion of patients with pre-defined clinically significant pain improvement between tested and untested cohorts, they did see potential pain improvement in two other comparisons: pharmacist vs. no pharmacist, and DGI vs. no DGI. Pharmacist-assessed patients in both cohorts had more patients experience pain improvement than in the historical control cohort of patients without pharmacist intervention (53% vs 30%, $p<0.001$). Within the PGx tested cohort, there was a trend towards statistically significant improvement in those with DGIs compared to those without (73% vs 46%, $p = 0.12$). Significance was likely not reached due the lack of power of a secondary analysis. Despite some negative findings, these studies confirm the value of the pharmacist in providing pain management services in oncology. It also indicates that there may be a specific subgroup of patients more likely to benefit from pharmacogenetic testing for pain therapy.

Cicali et al.[97] further describes three other studies in opioid prescribing, two of which have some, or all of their data currently published for further analysis.[102 103] In one protocol, patients prescribed opioids for chronic non-cancer pain were evaluated.[103] Similar to Patel et al., but reaching statistical significance, they found that IMs and PMs in the PGx-guided group on tramadol

or codeine at baseline had greater improvement in pain scores compared to patients without testing (-1.01 ± 1.59 vs. -0.40 ± 1.20, p = 0.016). A greater proportion of these patients in the PGx arm also experienced clinically significant pain relief (24% vs 0%). The other protocol, treating cancer patients, demonstrated that most of those tested were not changed to pain medications congruent with their genotype by the patient's prescriber, and thus these early findings appear negative.[102] However, this only serves to prove that genetic testing protocols enable utilization at the point of prescribing. Taken in the context of other studies in this review, this also demonstrates the important role of the pharmacist in ensuring that pharmacogenetic test results are followed up on and used in patient care.[51]

2.4.2.3.2 Other pain therapies

While opioids are the most researched pharmacogenomics literature, other analgesics and adjuvant pain treatments are also susceptible to genetic polymorphisms, and these medications are considered imperative to the management of chronic non-cancer pain.[104] An early report found in a conference abstract in 2012 describes the use of panel testing in the community pharmacy setting to assist in pain management for a patient with fibromyalgia. CYP1A2 metabolism status was used to support an increase in duloxetine from 60mg to 120mg per day, and the patient subsequently reported a decrease in pain frequency.[58] Duloxetine is considered one of the first-line options for chronic pain, especially neuropathic pain,[105] and it can be susceptible to polymorphisms in both *CYP1A2* and *CYP2D6*.[73] Non-steroidal anti-inflammatory drugs (NSAIDs) are also important in pain management, especially acute or nociceptive pain,[106] and these have recently updated clinical guidelines published by CPIC for *CYP2C9* polymorphisms.[107] While current pain management research using PGx focusses on opioids, assessing PGx with these adjunct treatments can potentially add to the benefit seen thus far.

2.4.2.3.3 Other supportive medications in palliative care

The feasibility of pharmacist-led pharmacogenetic testing in patients diagnosed with cancer or other palliative diagnoses, many of whom are cared for in the community,[108] is confirmed by other studies in this review. Kasi and colleagues had pharmacists interpret pharmacogenetic test results and provide applicable medication recommendations, at times enacting the recommendations themselves.[62] Through this, it was observed that there are opportunities to optimize medication therapy with PGx testing, as patients had an average of 4.4 DGIs each. This high actionability in the palliative population is confirmed by a conference abstract wherein pharmacist assessment of panel PGx testing to hospice patients with unspecified diagnoses is reported. They found these patients to be on a significant number of drugs (mean of 16 medications), with 73% of patients requiring medication changes based on testing.[86] Though these studies do not evaluate the clinical outcomes related with the medication recommendations made, a case study by another institution highlights the outcomes of testing as well as the individualized assessment required. This patient, a 73-year-old male with advanced urothelial cancer, had genetic polymorphisms indicating rapid metabolism of omeprazole and sertraline, however only the former was inefficacious. Therefore, the pharmacist advised a change to omeprazole, congruent with guidelines, and the patient reported gastroesophageal reflux disease (GERD) symptom resolution.[64] Similar to other forms of therapeutic drug monitoring, the inaction on this patient's specific serotonin reuptake inhibitor (SSRI) demonstrates the need to take the genetic test result in the context of the patient's clinical picture, especially in cancer and other palliative patients where often symptom control is a priority.

2.4.2.3.4 Surgical settings

A recent study had a research pharmacist assess patients within a peri-operative clinic for 12 genes that had implications for analgesia, post-operative nausea, and anesthesia medications.[109] Within all patients tested, 1% were found to have higher susceptibility for malignant hyperthermia with neuromuscular blockade, as predicted by *RYR1* polymorphisms. *CACNA1S* is also an important pharmacogene in this assessment, though no patients in this study tested positive for known polymorphisms. Of medications specific to the operative setting, analgesics demonstrated the most actionability among patients with current prescriptions. However, as testing was pre-emptive and the prescribing decisions informed by genetics were not reported, the impact of pharmacogenomics in these patients cannot be determined by the available literature.

2.4.2.4 Other therapeutics

There are other medications identified in included studies for pharmacy-based pharmacogenomic intervention that do not fall in the above categories. These are: carbamazepine, azathioprine, and proton pump inhibitors (PPIs). Furthermore, there are medications with clinical guidelines available that are not evaluated in pharmacy-based pharmacogenomics literature. These can be found at https://www.pharmgkb.org/guidelineAnnotations, and should be considered for evaluation in future implementation research.

2.4.2.4.1 Carbamazepine

Two studies[68 110] evaluate genomics for carbamazepine, a drug used for epilepsy, bipolar-disorder, and neuropathic pain conditions, among others.[73] It is commonly dispensed in the community pharmacy and carries the risk of severe immune-mediated reactions such as Steven Johnson's syndrome (SJS) or toxic epidermal necrolysis (TEN). These are extremely grave adverse

drug reactions with a mortality rate ranging from 1% to 5% for SJS, and up to 35% for TEN.[111] Pre-emptive *HLA-B*1502* testing can predict patients at risk of these reactions, thus avoiding morbidity and mortality by ensuring an alternative drug is used in this high-risk population.[112] While not explicitly studied in pharmacy-based PGx literature, phenytoin is also susceptible to this immune-mediated reaction and thus therapy with this medication can also be guided by PGx testing. The CPIC provides phenytoin dosing recommendations for both *HLA-B* and *CYP2C9* in recently updated guidelines.[113] While therapeutic drug monitoring can aid in preventing adverse outcomes related to CYP-mediated metabolism in this medication, PGx testing can inform the initial dosing by following guidelines, as well as the frequency of this monitoring or the sensitivity the practitioner should have to borderline results.

2.4.2.4.2 Azathioprine

Azathioprine is an immune-suppressant used to treat autoimmune diseases such as inflammatory bowel and rheumatoid arthritis.[73] It is inactivated by thiopurine S-methyltransferase (*TPMT*), a protein with polymorphisms that can decrease its function, thus increasing adverse effects in patients who carry these alleles. Toxicity to azathioprine can be severe and involve bone marrow suppression that can lead to bleeding secondary to thrombocytopenia, infection secondary to neutropenia, and anemia from a reduction of red blood cell production. These severe reactions can also be prevented by pre-emptive pharmacogenetic testing for *TPMT* as done by a few studies within this review **(Table 2.3)**. One of these studies focused on the use of PGx testing in a non-oncologic setting, using a clinical decision support tool developed in a pharmacist-managed program. This program found that congruent prescribing was utilized for all actionable *TPMT* results, indicating an effective system.

2.4.2.4.3 Proton pump inhibitors

Protein pump inhibitor (PPIs) indications are identified as another use for pharmacogenetic testing. PPIs are used to treat gastrointestinal disorders such as GERD, H. pylori infection, and gastric ulcers.[73] Both the CPIC[114] and the DPWG[80] provide clinical guidelines for the dosing of PPIs based on pharmacokinetic data predicting an increased risk of treatment failure in ultra-rapid metabolizers. One study found to be a feasible implementation by pharmacists[97] saw a significant reduction in symptoms of GERD in children with PGx-guided PPI therapy.[115] Several other studies identify PPIs as one of the most genetically-actionable medications, based on the frequency of DGIs observed.[59 63 66 87 99 100] Therefore, the actionability, availability of guidelines, and the evidence of clinical outcomes makes PPI therapy a reasonable target for pharmacy-based pharmacogenetic services.

2.4.2.5 Polypharmacy and complex patients

As alluded throughout this review, there has been an emergence of panel-based PGx testing in the more medically complex within pharmacy practice over the last five years. This shift can be explained by the increase in pharmacist knowledge through curricula and continuing education, and resources available due to technology advancements such as panel PGx tests that can evaluate multiple genes simultaneously.[32-35] These practices make use of the pharmacist's ability to integrate knowledge of organ function, patient clinical signs and symptoms, and interactions other than drug-gene (e.g. drug-drug, drug-disease) into their assessment of pharmacogenetic test results.[11]

2.4.2.5.1 Phenoconversions and Drug-Drug-Gene Interactions (DDGIs)

One of the most significant factors in the assessment of PGx test results that is within the pharmacist's scope is the phenomenon of phenoconversion, by which the genetically determined

metabolism status is altered by an interaction with a medication that either inhibits or induces the enzyme.[116] The manuscript published by Cicali et al. in 2019 identified that it was only in cases of direct pharmacist intervention that phenoconversion was identified.[97] Arwood and colleagues highlighted the significance of phenoconversion in the pharmacogenetic assessment with 24% of all patients tested for *CYP2D6* experiencing phenoconversion from drug-drug interactions (DDIs). This is also seen in a convenience sample of 100 patients from Bain et al.'s original study wherein 1.3 of the average 1.7 DGIs had a concomitant DDI affecting metabolism. This effect was most observed in the P450 enzymes CYP3A4 and CYP2D6.[117] Another study found that 7.2% of all DTPs were mixed drug-drug-gene interactions in patients with pharmacogenetic testing.[85] Eight other papers in this review mention or discuss the clinical importance of phenoconversion or drug-drug-gene interactions.[52 63 64 100 101 118-120] Within these, the ability of the pharmacist to capture these complex interactions is identified, especially when aided with clinical decision support software.

2.4.2.5.2 PGx Testing in the Elderly Polypharmacy Population

PGx testing polypharmacy patients has demonstrated improvements in meaningful outcomes, which are identified in **Table 2.2**. A randomized-controlled trial comparing home-health patients PGx tested and assessed using clinical decision software to those untested and assessed with standard drug resources found a significant decrease in readmissions and emergency room visits in the PGx-tested group by 52% and 42%, respectively ($p = 0.007$ and 0.045, respectively).[120] This confirmed results from an earlier prospective observational study comparing tested patients to historical controls with no PGx and presumably no pharmacist intervention.[118] This group had also found benefit in hospitalizations (9.8% vs. 16.1%; RR = 0.61, 95% CI: 0.39-0.95; $p = 0.027$) and emergency room visits (4.4% vs. 15.4%; RR = 0.29, 95% CI: 0.15-0.55; $p = 0.0002$). Albeit confirmatory studies on such meaningful outcomes in the community pharmacy setting would be

prudent to solidify such applications, given the current evidence it is reasonable to assert that elderly polypharmacy patients would likely benefit from PGx testing in the community pharmacy.

2.4.3 Key features of successful practice models

Within this review, practice model success was evaluated based on the frequency of DGIs found (either per patient for multiple gene panels, or the proportion of patients with actionable results for single-gene analyses), and the uptake of PGx-based recommendations by prescribers. DGI frequency is of particular use in comparing the therapeutic classes, as discussed above. The approval of recommendations by prescribers implies the efficacy of pharmacist communication. It is reasonable to consider in defining overall program success particularly for early feasibility studies, as the impact of PGx testing is facilitated or limited by whether therapy changes are made utilizing results. Studies supporting feasibility consistently share qualities in the provision of pharmacist education, effective collaboration, and the use of clinical decision software. Thus, as studies conclude feasibility with these in place, further research should focus on primary objectives encompassing meaningful outcomes.

2.4.3.1 Pharmacist education

Pharmacist knowledge and confidence within the field of pharmacogenomics is still lacking. A recent survey of pharmacists in Alberta, Canada found that only 25% felt confident in their ability to interpret and use PGx test results in patient care.[121] Similarly, 38% of institutional pharmacists in Minnesota, USA felt confident in PGx test interpretation.[122] Within this review, while not all studies identified whether pre-implementation training took place for pharmacists, studies which describe this step indicate or imply that it is critical to feasibility.[46 48 49 51 52 64 98 109 123 124] On the other hand, some studies without specified pharmacogenetics education plans had

limited outcomes that may be related to insufficient communication with patients or providers on the rationale behind testing and congruent prescribing,[53 55 100] or misinterpretation of genetic test results.[53] Some of these studies lacking education saw patient recruitment as low as 27% of approached patients,[55] while others describe limited action on genetic test results, with prescriber agreement on less than 30% of all recommendations.[53 85 100] While these low numbers of prescriber agreement only occur in studies not identifying pharmacist education, it is difficult to prove that this is a causal relationship. Nevertheless, much of the body of evidence indicates that not all healthcare providers have sufficient knowledge in pharmacogenomics, and that education of pharmacists and other healthcare professionals is important to clinical implementation.

2.4.3.2 Collaboration and provider relationships

Another explanation for differences in prescriber uptake of pharmacist recommendations is the professional relationship that exists between these two groups. One study, with success defined by an 87% acceptance rate of pharmacist recommendations, was implemented in a practice that had already fostered a relationship with the local prescribers through an anticoagulation practice.[59] Ferreri and colleagues also saw a high 83% acceptance rate for pharmacogenetic recommendations after providing pre-implementation education to prescribers.[50] This relationship between prescriber education and success is seen in other studies.[46 87 97] Multidisciplinary team models are also observed in this review,[45 65 91 96 125] and in addition to collaboration, these have the distinct advantage of including a provider that is able to bill for services under local legislation[45] where such a right for pharmacists is lacking. They are also able to implement changes to therapy immediately in places without pharmacist prescribing. Other studies, likely through collaborative practice agreements, have pharmacists able to directly act on genetic test results,[76] eliminating the delay caused by the requirement of a response to

genetic-based medication recommendations. Therefore, scenarios in which a pharmacist may directly prescribe or otherwise enact recommendations in direct collaboration with a practitioner with prescribing rights are the most feasible and efficacious models of pharmacogenomic implementation.

2.4.3.3 Clinical decision software

Eighteen studies used some form of electronic support to identify drug-gene interactions, and occasionally drug-drug interactions and phenoconversion. This is brought forth by several studies as an important facilitator to implementation,[46 51 53 63 64 66 85 87] with one study acknowledging that negative results may have been avoided with the use of such software.[53] Weitzel and colleagues point out, however, that clinical software alone was insufficient at ensuring congruent prescribing at point-of-care. They highlight that the pharmacist was necessary to follow-up on actionable results, ensuring patients are placed on genetically congruent treatment.[51]

2.4.4 Impact on patient outcomes

Pharmacogenetics in the pharmacist's assessment has been proven to reduce hospitalizations, or duration of hospitalizations, in warfarin use,[78] antidepressant therapy,[65] antiplatelets,[24] and polypharmacy patients[118 120] as highlighted in **Table 2.2**. However, this benefit appears contingent on both prompt test turn-around and subsequent action on test results.[65 120] Symptomatic benefit has also been observed in pain management,[101 103] GERD,[115] and depression.[95] Other studies, while not following up directly on clinical outcomes, have findings that can lead to better outcomes should they be analyzed. One study noted that the use of PGx testing with CDSS in MTM services found more serious DTPs than either of the two other arms consisting of MTM alone and MTM with CDSS.[85] Another study saw that physicians were more accepting of

genetically-based recommendations compared to non-genetic medication advice in MTM care-plans.[99] This increase in the identification and action on serious DGIs and DTPs can lead to decreased emergency room visits, hospitalizations, and length of hospitalizations. These changes not only impact patient quality of life, but both patient and system costs.

No studies reported real patient or healthcare system costs sufficiently for analysis, though some reported estimated savings from reductions in hospitalizations or medication optimization. One group calculated that patients may have saved an average of $788 USD each within the four-month study period based on observed decreases in hospitalizations with PGx testing and the calculated mean hospital costs in the region. The authors noted that this nearly offset the cost of testing, which is a considerable gain in such a short time.[118] Another conference abstract, in its brevity, did not identify the timeframe which patients saved an average of $317 USD each.[86] Other publications reported information regarding pharmacogenetic test coverage by third parties, finding 88%[51] to 100%[126] of third parties accepted claims for these services, and patients had co-payments under $500 USD[126]. One study reported cost-modelling results from a convenience sample of their original study population.[87 127] Based on DGI rates and average physician acceptance of recommendations, they determined savings of $810 USD per patient, or $378 USD per DGI, assumed to be per year but this was unclear. The study previously mentioned by Elliott et al. on home health patients saw that the reduction in emergency room visits and readmissions saved patients an estimated $4382 USD within the 60-day study period.[120] Overall, pharmacogenomics is purported to extend its cost effectiveness over years from reductions in morbidity and mortality by reducing serious drug reactions or treatment failures.[51] The preliminary evidence presented in this review appears to support the improvement in these clinical and humanistic outcomes. However, more longitudinal data on actual patient or health system

expenditures is needed to quantify the cost-benefit relationship for patients receiving pharmacogenomic testing in the pharmacy setting.

2.4.5 Limitations

As noted in the discussion, the studies described in this review varied greatly in design, patient demographics, genes, medications studied, and practice setting. While this makes a different review method such as a meta-analysis not feasible as there were many variations in outcome measures, a scoping design allowed a broad look at this diverse body of evidence. Studies throughout this review are predominantly exploratory in nature. Most of these had primary outcome measures of identifying or quantifying drug-gene interactions and actionable genotypes found by pharmacists. A few are even more pragmatic, simply aiming to discuss policies and processes in the implementation of testing. As pharmacogenomics is still in the early stages of adoption into practice, these trials are necessary. However, with established feasibility, investigations should begin to shift from exploratory to more rigorous experimental protocols.

While articles in this review were included regardless of language, untranslated keywords, or regional terminology may cause some articles to be missed by indexing. However, in utilizing the bibliographies of included articles in the search strategy, the impact of the search language is minimized. This supports the finding that most of the literature in clinical pharmacy implementation to date takes place in the United States, and this is an important consideration if using this evidence in countries with a different scope of practice. Additionally, in excluding articles without sufficient identification of a pharmacist in the patient care process, studies that did involve pharmacists but did not explicitly state this were excluded. These studies, as well as studies without pharmacists, may have valuable information on the use of pharmacogenomics in

patient care. Indeed, some of these excluded studies could be linked to included articles, and thus utilized in the discussion. However, none of the studies excluded for lack of pharmacist had addressed a therapeutic class or medication not found in the included literature. Therefore, the inclusion criteria were appropriate to address all the research questions identified.

Another limitation within included literature is a minimal evaluation of potential harms. This is not an issue unique to pharmacogenomics studies, but rather a problem common among pharmacy practice research.[128] Within the included literature, some potential harms are understated, such as longer hospitalizations with slow test turnaround time[65] or erosion of the patient-physician relationship.[53] Another risk is that of incidental or secondary disease findings.[31] Despite the growing list of genes included in pharmacogenetic panels, and more research into disease-allele correlations,[20 129] only one study evaluated the incidence of secondary disease findings.[109] These occurred in 7% of patients, and included alleles for genes commonly tested in this review such as those for *DYPD*, *F2*, and *F5*. This study described a patient and provider education process, followed by referral to a genetic counsellor for these cases. Two other studies describe processes to manage disease findings. One center developed a procedure in that incidental findings that do not have recommended actions before the age of 18 are not released until the patient reaches that age and can choose to provide informed consent to receive these results.[49] Another site has processes at intake to obtain consent if a patient wishes to be informed of secondary disease findings that become apparent with further research.[51] The identification of these risks and processes to manage them are crucial in the planning stages of any pharmacogenomics project, especially with our knowledge of these genes growing by the day. Having a plan will also inspire confidence in these services within patients. Concerns about genetic discrimination with these findings, such as in obtaining insurance, are mitigated in some nations

by legislation (examples include the Genetic Non-Discrimination Acts of Canada and the USA) but not in others. Additionally, disease risk knowledge may complicate family planning or lead to health-related anxiety.[130] Future studies should evaluate these risks in light of any new evidence or current legislation prior to testing, ensure proper education of patients regarding risks identified, and have adequate knowledge, policies, and resources to manage the occurrence of incidental disease findings. While delays in therapy, erosion of physician trust, and incidental findings all can be mitigated with pharmacist education and robust policies, there is a need to ensure quantification of actual risks and harms in any clinical practice study, including PGx, in order to provide a balanced body of evidence.

Lastly, all pharmacogenomics research, including this review, is limited by the infancy of this field of study. The information known today has advanced significantly over the last 20 years as the impact genetics play on drug response, and how pharmacists can manage this information, becomes better understood over time and research. The growth in collective understanding is exemplified in the CPIC guidelines on clopidogrel use,[23 131] which after an update in 2013 two years after the initial publication, will be rewritten again to include findings from the recent TAILOR-PCI trial.[132 133] This is also seen in the Pharmacogenomics Competencies Statement,[31] which is in the process of being updated in the near future. As it stands, this is the most comprehensive information available on the applications of pharmacogenomics in pharmacy practice today.

2.5 Conclusions

There has been significant and exponential growth in research applying pharmacogenetic testing to MTM and clinical services provided by pharmacists through the last decade. Research occurs in a variety of practice settings, with almost a quarter of studies to date in the community

pharmacy. There are a wide variety of medications with evidence in pharmacy-based pharmacogenomics literature including those used in cardiology, psychiatry, pain, neurology, and gastrointestinal disorders. *CYP2C19* testing in antiplatelet selection was one of the most studied and was shown to improve cardiovascular outcomes. Single-gene tests such as this are particularly suitable in pilot programs and settings with less time or compensation compared to multi-gene analyses. Panel tests, however, can identify more drug-gene interactions with more genes tested. Additionally, when used in the older polypharmacy population, panel tests may have a greater clinical impact demonstrated by a reduction in hospitalizations. There may be a benefit to genetic testing in niche practices such as pain management and anticoagulation, though the ideal populations and protocols have yet to be defined.

It was also evident in all settings that certain pharmacist roles facilitate implementation. These key functions included interpretation of pharmacogenetic test results, and provision of medication therapy recommendations. Often, these recommendations were based not only on the genes identified, but also the patient's signs, symptoms, adherence, other laboratory tests, and other interacting medications. This integration of pharmacogenomics into medication therapy management occurs regardless of where pharmacists practiced. Rather, the feasibility and clinical relevance of any one model is heavily dependant on testing logistics, patient populations tested, and individual pharmacist ability. Key supports identified in the implementation of pharmacogenomics in pharmacy practice are effective pharmacist training, interprofessional collaboration, and the use of clinical decision support technology. One of the largest barriers to clinical implementation found in this review were delays in test return and provider response to pharmacist recommendations. Rapid point-of-care tests, interdisciplinary teams, and pharmacist prescribing all have the potential to overcome these issues and improve patient outcomes. There

are currently few studies that test clinical, economic, and humanistic outcomes in the clinical implementation of pharmacogenomics in pharmacy practice, and so further research should now be directed towards these measures.

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2.8 Declarations of interest

None

2.9 CRediT author statement

MH: Methodology, Funding acquisition, Data Curation, Writing - Original Draft, Writing-Reviewing and Editing; **DAH**: Conceptualization, Methodology, Funding acquisition, Writing-Reviewing and Editing; **SHM**: Conceptualization, Methodology, Funding acquisition, Writing-Reviewing and Editing.

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Chapter 3: Pharmacist Education in Pharmacogenomics

The efficacy of a didactic and case-based pharmacogenomics education program on improving the knowledge and confidence of Alberta pharmacists

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The efficacy of a didactic and case-based pharmacogenomics education program on improving the knowledge and confidence of Alberta pharmacists

Abstract

Background: Pharmacogenomics (PGx) is the study of how genetic variations for functional proteins such as metabolizing enzymes and drug receptors, impact drug pharmacokinetics and pharmacodynamics. In theory, pharmacists are well-suited to utilize PGx in tailoring medications to patient genetics when providing medication therapy management services. However, PGx education needs to reach pharmacists prior to implementation. The aim of this study is to develop and evaluate a PGx course for pharmacists.

Methods: A PGx education program was created and offered synchronously (virtual) and asynchronously (self-study) to pharmacists in Alberta, Canada. Lectures were delivered by experts live (virtual) with a question-and-answer period for synchronous sessions. These sessions were recorded for asynchronous delivery. Six case studies were discussed in large and small groups ("breakout rooms") in synchronous sessions, and provided for self-study in the asynchronous subgroup. Topics included genetic and PGx concepts; therapeutic applications; ethical, legal, and social considerations; and practical implementation. Pre- and post-course surveys measured self-rated knowledge using a 5-point Likert Scales and tested objective knowledge with a graded quiz.

Results: Thirty-six pharmacists completed the course and both surveys. Participants reported backgrounds in community (88.9%) and hospital (38.9%) practice. Prior education in PGx was reported by 44.4% from degree programs and 27.8% from continuing education. Overall responses to statements about confidence in PGx moved from a median of "Disagree" at baseline to "Agree" after receiving PGx education (2-point difference [1,2] on 5-point Likert Scale; $p<0.001$), indicating

an increase in self-assessed competency in PGx. Likewise, mean participant grades on the knowledge quiz improved (20.8 ± 21.9% pre-course vs. 70.2 ± 19.1% post-course, $p<0.001$). There was no difference in these results between synchronous and asynchronous groups.

Conclusion: A didactic and case-based PGx education program was effective at increasing pharmacist knowledge and confidence in PGx in both synchronous and asynchronous environments. Knowledge gained can be utilized in delivery of patient-centered, personalized medication therapy management in the pharmacy setting.

3.1 Introduction

Pharmacogenomics (PGx) is a field of medicine and pharmacy that stands to reduce hospitalizations,[1,2] improve drug efficacy and safety,[3-5] and through these measures ultimately reduce patient morbidity and mortality. PGx accomplishes this by tailoring drug therapy to individual patient DNA sequences encoding for drug metabolizing enzymes, transporters, receptors, and other functional proteins.[6,7] Published guidelines are available through the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network of Pharmacogenetics (RNPGx). A compilation of these guidelines, along with dosing labels by the United States Food and Drug Administration (FDA) website, are available through the Pharmacogenomics Knowledge Base (PharmGKB) for the interpretation and application of PGx information.[8,9] Furthermore, PGx information is now incorporated into the drug information available within commonly used online medication resources, such as Lexicomp and Micromedex[10]. PGx reports typically provide phenotype interpretation from genotype, occasionally aided by the healthcare provider's assessment for phenoconversion. When used in conjunction with other factors such as organ function, laboratory test results, clinical symptoms, concomitant medications, and environment/lifestyle factors,[11] healthcare providers are able to tailor a drug therapy plan for the patient in what is known as precision medicine.[12,13] While pharmacists are nominated and acknowledged to be the best-suited healthcare provider to interpret PGx test results, and subsequently recommend appropriate drug therapy,[14,15] few pharmacists have the training, knowledge, or confidence to do so currently **(Table 3.1)**. Within the results of a recent scoping review on the implementation of pharmacogenomics in pharmacy practice,[16] it was identified that settings with well-described pharmacist PGx education programs

prior to providing such services saw greater prescriber acceptance of recommendations, compared to studies without pharmacist education. This demonstrates the improved ability of PGx-educated pharmacists to assess drug-gene interactions (DGIs) and communicate the appropriate management of these interactions to other health care providers. Therefore, it is critical pharmacists are equipped with sufficient knowledge and understanding of pharmacogenomics in order to safely, effectively, and confidently assess medications with pharmacogenetic implications. Albeit the gap in pharmacogenomics education has improved in the last decade,[17-19] currently practicing pharmacists and recent graduates alike will need to be provided with updated information in this rapidly evolving field through continuing education programs. By supplementing pharmacists' established competencies in medication therapy management (MTM) and patient education,[11,20] we can ensure the effective implementation of PGx within the pharmacy patient care process, to the betterment of patient drug therapy outcomes.

There are important considerations in developing a PGx program for practicing pharmacists. One is that effectively studied and validated teaching methods should be utilized. Case-based learning has been shown to be highly effective in the education of pharmacists[21-23] and pharmacy students[24,25] in pharmacogenomics, and has demonstrated its utility in other therapeutic topics as well.[26] While there are a few PGx education programs available for continuing education in Canada, only one of these has been evaluated to date.[21] Teaching methods from these studies and other research in pharmacy education[26-29] can be adopted, there is a need to develop and validate a new program for Alberta pharmacists specifically. In this province, practice is wider in scope compared to other Canadian provinces and to other countries, as it includes the additional authorization to independantly prescribe.[30] Other research in Alberta

supports the benefit to patients that can be realized with pharmacist prescribing in chronic disease management. In another Alberta-based study, patients with hypertension managed directly by pharmacists (utilizing prescribing when required to titrate or change medications) experienced a 18.3 ± 1.2mmHg reduction in systolic blood pressure, compared to the reduction of 11.8 ± 1.9mmHg observed in a control group receiving standard education without pharmacist prescribing.[31] This ability to ensure patients receive optimal pharmacotherapy can potentially extend into PGx services, as pharmacists can incorporate PGx test results into their medication therapy plan.

The aims of this study were to 1) establish an up-to-date, validated PGx webinar course that covered the competencies established by Roederer et al. **(Figure 3.1)**,[32] key therapeutics identified in scoping the literature available on PGx in pharmacy practice,[16] and insights shared by international PGx experts; 2) evaluate the impact of this course on the knowledge and confidence of Alberta pharmacists in PGx; 3) explore the baseline understanding of PGx among study participants; 4) develop a validated continuing education and course curriculum that can be shared with other Alberta pharmacists asynchronously for wider future implementation of PGx in Alberta.[33]

Figure 3.1. Pharmacogenomic competency domains, adapted from Roederer et al.[32]

Table 3.1. Recent survey assessments of pharmacist knowledge, confidence, and training in pharmacogenomics. While there have been very few studies in Canada analyzing this data, studies globally reflect the current landscape of pharmacist competence in pharmacogenomics.

Reference	Country	Pharmacist Population	Mean Knowledge Score	Self-rated confidence/ understanding moderate to high	Prior training or exposure in PGx	Desiring more PGx education[d]	Other Findings
Brown et al. (2021)[53]	USA	Pediatric institutional pharmacists at mostly urban academic settings	N/A	N/A	78.6%	50%	Low-use sites cited more barriers in knowledge, support, and ELSI; both high-use and low-use indicate cost and technology barriers
Tsuji et al. (2021)[48]	Japan	Pharmacists in mostly hospital settings (81.3%)	43%	12.5%	25.7%	72.4%	93.6% felt PGx was/could be useful for care, 30.8% could identify 5 or more drugs with PGx indications.
Jarrar et al. (2021)[54]	Palestine (West Bank)	Pharmacists in mostly community or outpatient settings (75%)	N/A	30%	16.8%	N/A	Most pharmacists agree they should know more about (94%) and use (~80%) PGx in patient care.
Edris et al. (2021)[55]	Belgium	Pharmacists (community and hospital)	37%	23%	42%	N/A	Most pharmacists (and physicians) surveyed were unfamiliar with PGx resources (89% of pharmacists were unfamiliar with PharmGKB, 92% with CPIC, 80% with DPWG, and 70% with FDA PGx labels.
Rahma et al. (2020)[56]	United Arab Emirates	Registered pharmacists	56.7%	29.7%	41.5%	57.8%	91.9% of all survey respondents (HCPs including RPhs) support PGx testing. Other barriers identified include cost (62%) and insurance coverage (57.2%). Only 9% of all respondents agree that pharmacists should perform PGx services.
McMurdo et al. (2020)[57]	Canada (Alberta)	Registered pharmacists	N/A	25%	52%	N/A	80% of pharmacists agreed that PGx testing is beneficial and it is important to comprehend test results.
Petit et al. (2020)[47]	Canada (Quebec)	Pharmacists (community, hospital, and other settings)	63.2%	37.7%	72.6%	90.3%	While the proportion of participants with prior training in PGx is high, 66.7% identify this training cumulates to less than 5h of exposure total.
Crown et al. (2020)[21]	Canada (Ontario)	Community and primary care clinic pharmacists	56%[a]	Low[b]	57%	High[c]	
Nagy et al. (2020)[44]	Egypt	Pharmacists at the Children's Cancer Hospital	41.7%	13%	9.6%	64%	An 80% survey response rate and overall, mostly agree/strongly agree responses in the opinion surveys of PGx indicate positive opinions on PGx testing among pharmacists and physicians.
Hundertmark et al. (2020)[47]	USA	Hospital pharmacists	N/A	37.4%	24%	88%	58% of pharmacists agree that pharmacists are the best provider to implement PGx testing. Those with residency training are more likely to rate their knowledge higher than those without (p = 0.03).
Karuna et al. (2020)[58]	Thailand	Hospital pharmacists	43%	N/A	18.7%	13%	Barriers identified include test reimbursement and ELSI concerns
Algahani (2020)[44]	Saudi Arabia	Hospital pharmacists	59.8%	32.5%	30%	83%	76% agreed pharmacogenomics should be used in practice.
Meloche et al. (2020)[59]	Canada (Quebec)	Pharmacists (community and hospital)	N/A	14%	31%	91%	100% of pharmacists agree PGx testing will be able to support medication selection and dosing to some degree. 94% of pharmacists have at least some concerns about genetic discrimination.

Notes: [a] Pre-course scores in an education study. [b] Mean pre-program rated confidence in using PGx 1.6 on a 5-point Likert Scale. [c]143 applicants for 25 seats in the program; color coding: red = poorly rated, orange = moderately rated, yellow = highly rated, [d]reverse coding used. **Abbreviations:** CPIC: Clinical Pharmacogenomics Implementation Consortium; DPWG: Dutch Pharmacogenetic Working Group; ELSI: ethical, legal, and social implications; FDA: [United States] Food and Drug Administration; HCP: healthcare provider; PGx: pharmacogenomics; RPh: pharmacist

3.2 Methods

3.2.1General Design

This was a longitudinal survey-based observational study measuring the impact of a training program on pharmacists' knowledge, confidence, and opinions of PGx delivered as either a live two-day webinar, or as a self-study course derived from recordings and written materials included in the live sessions. Participants served as their own control, answering the same survey prior to and after the education program. Instructors were invited from Canada, USA, Egypt and Qatar to facilitate incorporation of global perspectives in PGx.

3.2.2 Participants

3.2.2.1 Recruitment

Practicing pharmacists in the province of Alberta, Canada, were recruited through email correspondence with pharmacy managers, general social media posts, and word-of-mouth referrals for either synchronous, asynchronous, or mixed attendance. After expressing interest from a potential participant, a formal recruitment email was sent to the potential participant with details regarding both the research study and PGx course. The recruitment email contained a link to the implied consent form and pre-course survey. Recruitment commenced March 2021. Synchronous and mixed participants were accepted until the night before course commencement on June 12, 2021, and asynchronous participants were eligible for inclusion in primary outcome data analysis if pre-course and post-course surveys were completed prior to 23:59 September 20, 2021.

3.2.2.2 Inclusion Criteria

Any pharmacist with an active pharmacy practice Alberta license was eligible for inclusion, and there was no specific exclusion criteria. Pre-course surveys without a matched post-course survey were still eligible for inclusion in the secondary outcome analysis of baseline knowledge and confidence among practicing pharmacists.

3.2.3 Outcomes

The primary outcome of this research study was the change in median Likert Scale scores for opinion/confidence questions, as well as the change in mean knowledge quiz scores, in paired data analyses of pre-course and post-course surveys. The secondary outcomes of interest were the baseline demographic, individual opinion/confidence answers, and knowledge quiz scores in the pre-course survey only. The secondary outcomes were compared among subgroups of pharmacists based on prior training in pharmacy, years of practice, age, gender, and prior exposure to pharmacogenomics.

3.2.4 Survey Design

A survey was created to collect demographic and pharmacy education/experience pre-course and measure subjective and objective competency in pharmacogenomics both pre- and post-course. Education and experience questions focused on practice environment as well as prior exposure to PGx information. There were 11 questions on pharmacist opinions and confidence on pharmacogenomics, each to be rated on a Likert Scale, with possible answers consisting of “Strongly Agree,” “Agree,” “Neutral,” Disagree,” and “Strongly Disagree.” The survey closed with 7 exam-style questions testing pharmacogenomics knowledge, with varied question types that included single choice and multiple checkbox answers to total a maximum potential mark out of

14. Questions for both Likert Scale and knowledge quiz were created utilizing a review of similar research and consultation with experts. The topics addressed in these were considered of high importance for pharmacist PGx competencies according to the American Association of Colleges of Pharmacy.[32] Survey questions underwent face validation by pharmacy educators and practicing pharmacists to ensure clarity of questions. The surveys took approximately 10 minutes for participants to complete. The full survey is available in **Appendix C.**

3.2.5 Pharmacogenomics Education Course Content

The training program consisted of 11 lectures **(Appendix C, Table S3.2.1)** by various experts covering the competences and therapeutics identified in **Figure 3.1**[32] and the scoping review,[16] respectively, and 6 case studies developed by the research team **(Appendix C, Table S3.2.2)**. Speakers were invited by the research team based on their expertise in the field of PGx in pharmacy, with an aim to recruit experts from different countries to incorporate an international PGx approach. The therapeutic areas of focus for this course were selected based on a scoping review on the use of pharmacogenomics in pharmacy practices.[16,28] Particularly, the applications of PGx in cardiovascular, psychiatric, and pain indications, which all have guidelines available from organizations such as the CPIC, were found in the literature to be feasible and clinically useful in the pharmacy setting.[16] The AACP PGx Competency statement[32] also informed the education sessions on basic genetic and pharmacogenetic knowledge, as well as the ethical, legal, social, and practical implications of use of PGx in pharmacy practice. The pharmacist patient care process[11,34] was utilized within a dedicated session as well as throughout course and case-study design to emphasize the role of PGx information in concert with other patient characteristics and the larger clinical picture.

The preliminary design of this research study and course was a completely synchronous program to take place over two days, ideally in a live conference setting. However, due to the circumstances of the COVID-19 pandemic, the decision was made to utilize virtual venues in concordance with public health guidelines at the time. Participants were provided with the option to attend both days live (synchronous, virtually), self-study (asynchronous, online), or a combination of these options suitable to their schedule and commitments (mixed).

3.2.5.1 Synchronous Course

For participants able to attend some or all the content live, a virtual course was held over Zoom (Zoom Video Communications, Inc., San Jose, California) on June 12-13, 2021, for 5 hours each day. Handouts were provided the night prior to each day, containing lecture slides and case studies without answer keys. Within each major topic, case studies would be provided for participants to work through with the facilitators in between didactic sessions. Breakout rooms were included in half of the cases to allow participants to interact with one another and solve problems posed within the cases together with a course facilitator (a research team member and the invited speaker). Each didactic lecture included a question-and-answer period with the speaker, with questions from the chat-box read out by a moderator. The use of a chat-box was to ensure participant confidentiality in recordings of sessions in alignment with research ethics, as these recordings were used in the asynchronous course described below. The breakout rooms where discussions occurred between facilitators and speakers were not recorded. Live didactic sessions ran for 15-45 minutes per session (including the Q&A), and 15-30 minutes were spent on each of the case studies.

3.2.5.2 Asynchronous Course

For participants requiring self-study for some or all the course content, the live sessions were recorded and organized into individual modules. Case studies were provided with answer keys and instructions on the suggested timing to complete the case within the order of the video content. Mixed participants unable to attend the first day live were provided the session recordings, handouts, and case studies by email, with sufficient time to complete these before the second day sessions. Completely asynchronous participants were given access as "viewers" of a Google Drive folder (Google LLC, Mountain View, California) after completing the pre-course survey. The course folder contained instructions for completing the course, each individual session video with slide handout, case studies with answer keys, and supplementary materials such as additional readings and resources referenced in the course. Asynchronous participants were advised of a deadline of September 13, 2021, to complete the post-course survey.

3.2.6 Data Collection

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Alberta.[35,36] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Pharmacists who expressed interest in participating were sent a pre-course survey from REDCap prior to attending the live course or receiving access to the course materials depending on synchronous or asynchronous participation, respectively. After participants completed either synchronous or asynchronous learning, they received the post-course survey by email. Synchronous participants were given time before closing remarks to complete the post-course survey, and asynchronous participants were provided direction to complete the post-course survey as soon as reasonably

possible after viewing all videos and completing all case studies. Participants were not provided with their answers to either survey after completion.

3.2.7 Statistical Analysis

Participant demographic data was summarized as mean ± standard deviation (SD), or n (%) for normally distributed numerical variables and categorical variables, respectively. The Central Limit Theorem (CLT) was applied to non-normal data with an $n \geq 30$, while non-normal data with an $n < 30$ was summarized as median (interquartile range; IQR). Likert scale responses were coded as follows: Strongly Disagree (1), Disagree (2), Neutral (3), Agree (4), and Strongly Agree (5), with a higher number reflecting more positive opinions/greater self-confidence. Answers to these questions were analyzed for the primary outcome by paired Wilcoxon Rank Sum analysis for the Likert scales used, and the knowledge-based quiz was graded by the research team and compared pre- and post- education as mean ± SD in a paired Student's t-test if distribution was normal or CLT could be applied. If these assumptions were not met, Wilcoxon Rank Sum was used for analysis. In the secondary analysis, individual responses to Likert scale and knowledge test questions were summarized as n(%). Subgroup comparisons of Likert scale responses and non-normal knowledge test data were compared using Wilcoxon Rank Sum or Kruskal-Wallis test depending on the number of groups. If significance was found with Kruskal-Wallis, the Dunn test was used for multiple comparisons and adjusted p-values were manually calculated for the number of comparisons. A forward selection linear regression was built for knowledge test scores for all pre-course surveys received using demographic and education history data and mean value of confidence rated on the Likert-scale questions. A similar regression was built for mean confidence scores using demographic and education history data and knowledge test scores pre-course. The mean values were used in the linear regression on confidence scoring rather than median for

higher sensitivity. Lastly, to validate the subjective survey administered, mean Likert responses were compared to mean test grades for participants in a linear analysis for all pre-course surveys, all post-course surveys, and the calculated difference in these values from pre-course to post-course. All statistical analyses were performed using STATA version 17 (StataCorp, College Station, Texas, USA), and a $p < 0.05$ was considered statistically significant.

3.2.8 Ethics Approval

Informed implied consent form was included on the cover page of both the pre-course and post-course surveys. Electronic Consent was implied by completion of the surveys, documented in the de-identified participant record by the completed status on the REDCap database. Written (wet ink) consent was not sought out due to the virtual nature of participation for live course participants from a broad geographical region, and due to the asynchronous nature of participation for self-study course participants. Within this study design, participants never met in person with the research team. However, the study procedures were explained to each participant through the invitation email approved through ethics, with a member of the research team responding to any potential participant queries in a timely manner. The study team's contact information was provided to all participants within the implied consent form, which participants were advised to print for their records. This study and consent procedure was approved by the University of Alberta Research Ethics Board (Pro 0108818).

3.3 Results

3.3.1 Participants

At least 2000 pharmacists were reached through social media, email, and word of mouth referrals (**Figure 3.2**). While there is no method to determine the true number of potential

participants reached by social media, interested pharmacists reached out through email and social media for more information, and were subsequently sent an email invitation to participate in the study. There were 69 Alberta pharmacists invited to complete the initial pre-course survey. A total of 36 pharmacists were included in the primary outcome analysis: 10 attended all live Zoom sessions synchronously, 9 participated through a combination of synchronous and asynchronous methods, and 17 completed the course asynchronously only. An additional 23 pre-course surveys without a matched post-course survey were included in the secondary analyses. Pharmacist demographics are summarized in **Table 3.2**. Most pharmacists who completed both surveys for primary analysis had community experience (88.9%) and over a third had worked in hospital settings. In the primary analysis, only 11 (30.6%) had no prior education or exposure to pharmacogenomics.

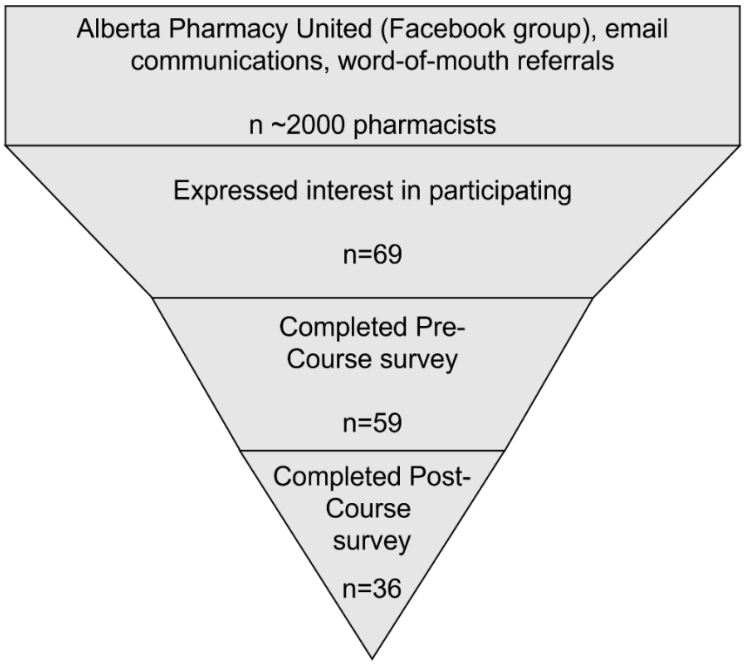

Figure 3.2. Pharmacists were recruited to participate through a variety of measures that resulted in 69 official study invitations. Of these, 85.5% completed the initial survey, and 52.2% completed both surveys.

Table 3.2. Demographics, education, and pharmacogenomics exposure for participating pharmacists.

Characteristic	Completed course (n = 36) Mean ± SD or n (%)	Pre-course survey only (n = 23) Mean ± SD or n (%)
Gender		
Male	13 [a] (36.1)	8 (34.8)
Female	22 [a] (61.1)	15 (65.2)
Age (years)	37.3 ± 8.3 [a]	39.3 ± 9.0
Years of Practice		
Less than 2 years	4 (11.1)	5 (21.7)
2-5 years	4 (11.1)	-- --
6-10 years	11 (30.6)	3 (13.0)
More than 10 years	17 (47.2)	15 (65.2)
Country of Entry-to-Practice Degree [a]		
Canada	25 (69.4)	18 (78.3)
Egypt	4 (11.1)	1 (4.4)
India	2 (5.6)	1 (4.4)
Other	4 [b] (11.1)	3 [f] (13.0)
Highest Degree Obtained		
Bachelor's	27 (75.0)	13 (56.5)
Pharm D	5 (13.9)	4 (17.4)
Master's	1 (2.8)	2 (8.7)
PhD	3 (8.3)	2 (8.7)
Additional Training or Certifications [c]		
Additional Prescribing Authorization	22 (61.1)	17 (73.9)
Certification to Administer Injections	31 (86.1)	18 (78.3)
Certified Diabetes Educator	3 (8.3)	2 (8.7)
Accredited Canadian Pharmacy Resident	4 (11.1)	2 (8.7)
Other	6 [d] (16.7)	-- --
Settings of Pharmacy Practice in Career [c]		
Community Pharmacy	32 (88.9)	21 (91.3)
Hospital	14 (38.9)	7 (30.4)
Primary Care Network	-- --	1 (4.4)
Research / Academics	3 (8.3)	1 (4.4)
Industry	2 (5.6)	-- --
Other	3 [e] (8.3)	2 [g] (8.7)
Prior Pharmacogenomics Exposure [‡]		
Education on PGx in Degree Program	16 (44.4)	7 (30.4)
Education on PGx in Post-Graduate or Continuing Education	10 (27.8)	4 (17.4)
Prior Experience with PGx Testing	1 (2.8)	4 (17.4)

Notes: [a]denotes one missing value; [b]n = 1 each of Nigeria, Philippines, South Africa, and United Kingdom; [c]Participants could select more than one choice; [d]n = 1 each of Board Certified Ambulatory Care Pharmacist, Board Certified Psychiatric Pharmacist, Certified Respiratory Educator, Hepatitis C Prescriber, Certified Tobacco Educator; [e]n = 1 each of Government Drug Program, Military, and Corporate. [f]n = 1 each of Libya, Nepal, and United Kingdom; [g]n = 1 each of Military and Corporate. **Abbreviations:** PGx: Pharmacogenomics; SD: Standard Deviation.

3.3.2 Knowledge, Confidence, and Opinions

3.3.2.1 Survey Validation

In addition to face validation, simple linear regression analyses were performed to determine correlation between subjectively rated knowledge (mean Likert scale responses) and objectively tested knowledge (mean scoring on quiz portion of survey). Moderate, statistically significant relationships between subjective and objective knowledge was observed (pre-course $r = 0.476$, $p<0.001$; post-course $r = 0.401$; $p = 0.015$). This indicated that a participant's subjectively rated knowledge was proportional to their objectively tested knowledge, with this relationship slightly stronger prior to education.

3.3.2.2 Subjective Self-Rated Confidence

3.3.2.2.1 Impact of Pharmacogenomics Course on Confidence

As noted in the statistical analysis, Likert Scale responses were coded 1 = "Strongly Disagree" to 5 = "Strongly Agree". Pharmacist responses to Likert-Scale statements changed from a median of "Disagree" (2 [2,3]) to "Agree" (4 [4,4]) after pharmacogenomics education ($p<0.001$) in the 36 participants included in the primary analysis, indicating an overall improvement in participant self-rated knowledge. The improvement in mean subjectively rated knowledge (Likert scales) was determined to have a positive linear relationship with improvements in objective knowledge test grades with pharmacogenomics education (**Figure 3.3**), meaning those who experienced greater improvement in their own self-assessed competency, had also experienced greater improvement in their objectively tested knowledge. Statistically significant improvements in subjective responses were observed consistently among each individual question (**Figure 3.4**), showing global improvement among all PGx domains. There was no significant difference in the change in subjective knowledge or the final subjective knowledge as rated on the Likert scales based on course participation method, all methods demonstrated improvement in PGx subjective and objective knowledge. Furthermore, there were no

identified participant characteristics such as experience, years of practice, or prior use of PGx that indicated a difference in final post-course confidence.

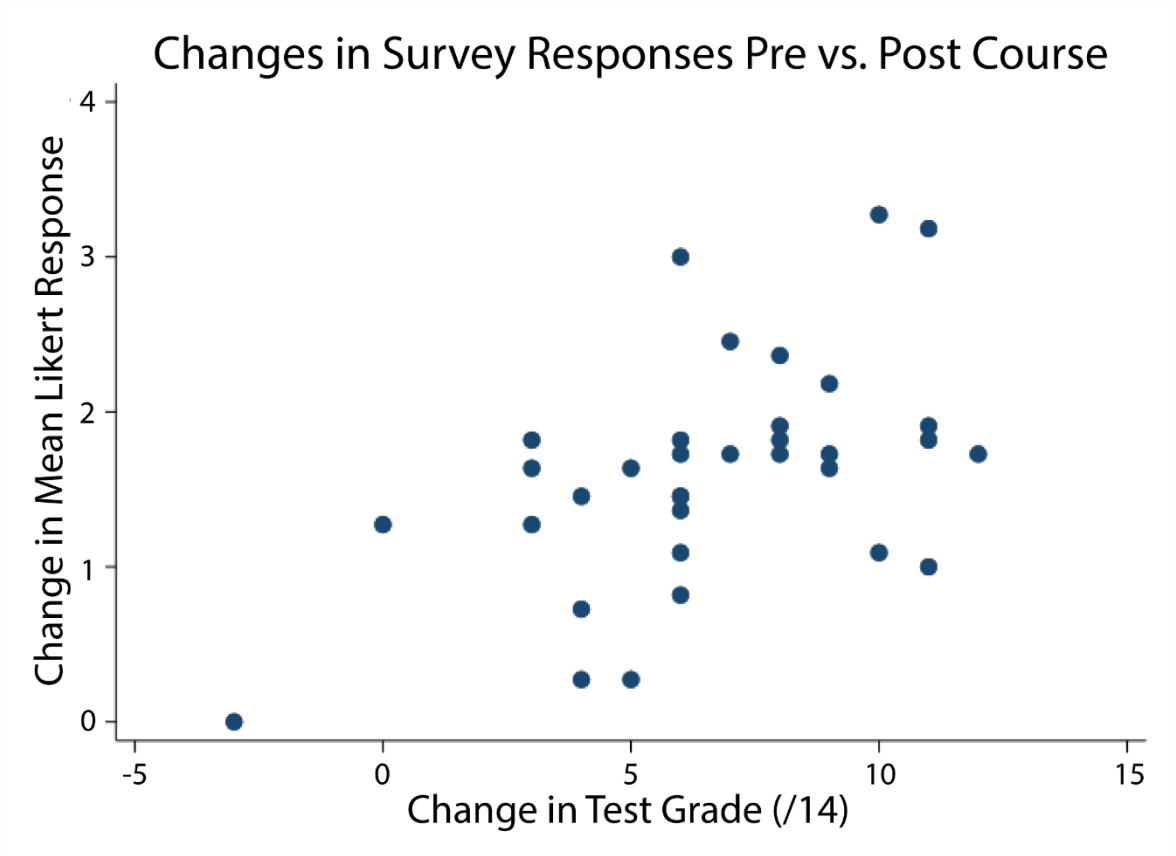

Figure 3.3: Mean Likert responses in agreeance with confidence in pharmacogenomics increased by 0.12 ± 0.20 points for every correct answer gained on the knowledge test after education (r = 0.516; p = 0.002; n = 34).

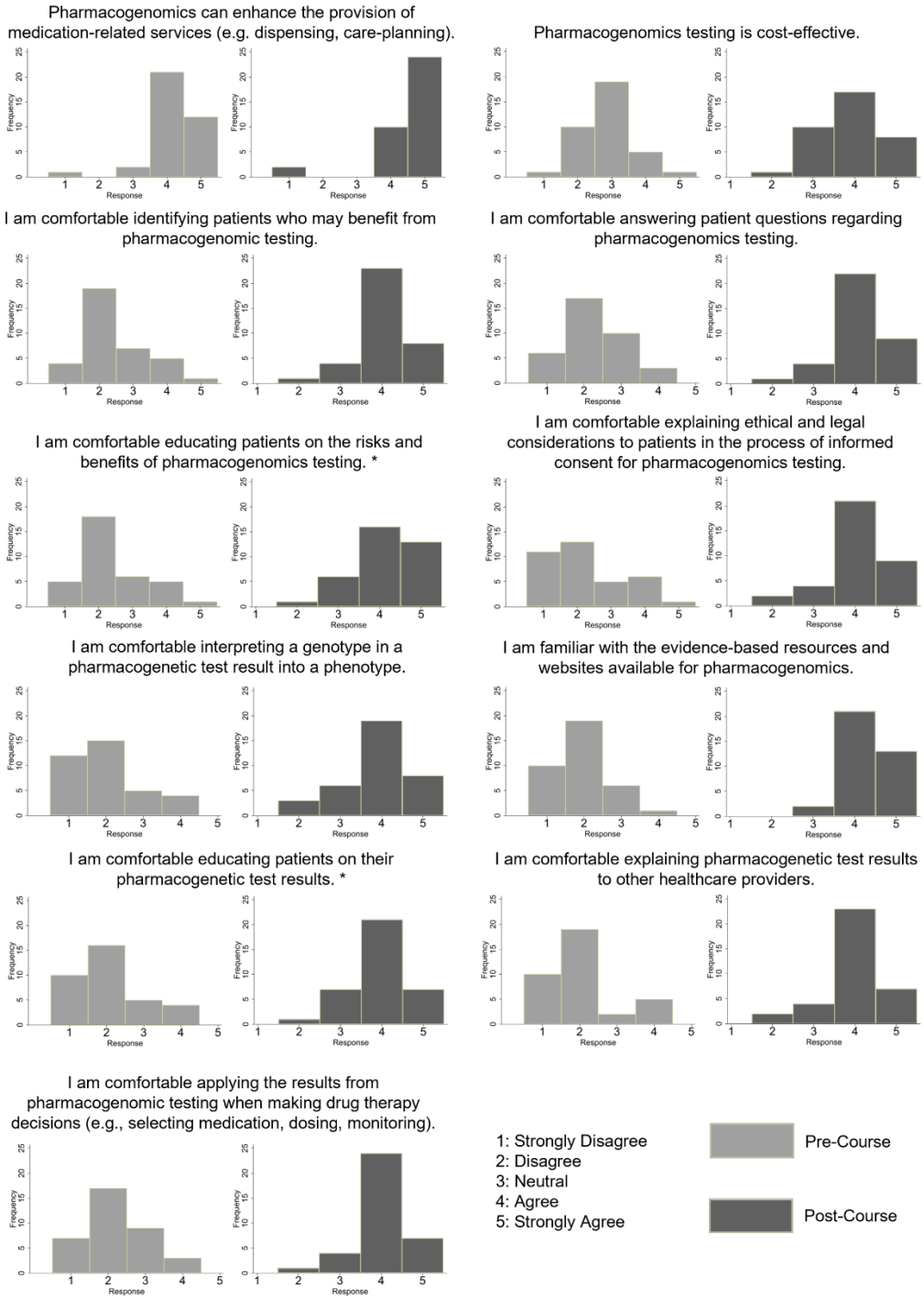

Figure 3.4. Frequencies of responses to 11 Likert scale (1-5) questions by participants (n = 36) before and after pharmacogenomics education. * One missing value in pre-course survey.

3.3.2.2.2 Baseline Confidence Assessment

Among the 59 pre-course surveys received, median responses for nearly all questions were "Disagree" (2) at baseline. Only the two opinion-based statements, "Pharmacogenomics can enhance the provision of medication-related services (e.g. dispensing, care-planning)" and "Pharmacogenomics testing is cost-effective" received median responses greater than 2 (these were 4 and 3, respectively). There was a significant difference in baseline median confidence/opinions between pharmacists with prior PGx training in their degree program vs. those without (2 [2,3] vs. 2 [1.5,2]; p = 0.003); and in internationally educated pharmacists vs. Canadian graduates (3 [2,4] vs. 2 [2,2]; p = 0.005).

When a forward selection linear regression was built with the mean Likert responses, higher objective knowledge test scores (p = 0.001), international education (p = 0.006), prior experience with PGx testing (p = 0.137, included due to plausible effect), and prior PGx education in degree program (p = 0.002) and in continuing education (p = 0.021) were all found to fit a model that explained 53.1% of the variation in mean Likert responses agreeing with positive opinions and subjective knowledge in PGx pre-course (p<0.001). Objective knowledge test scores alone appeared to account for 22.6% of the variation in Likert responses on its own in pre- course analysis. This relationship was slightly less strong post-course, with only 16.1% of variation in Likert responses explained by objective knowledge.

3.3.2.3 Objective Tested Knowledge

3.3.2.3.1 Impact of Pharmacogenomics Course on Knowledge

Mean participant grades in the knowledge test portion of the survey improved significantly pre-course vs. post-course (20.8 ± 21.9% vs. 70.2 ± 19.1%, p<0.001; **Figure 3.5**). Each question saw significant improvement in correct responses post-course **(Table 3.3)**. There was no difference between course participation methods and the quantitative test grade improvement of participants (synchronous, asynchronous, mixed; 64.3% [42.9, 78.6], 42.9% [42.9,57.1], 42.9% [35.7, 50.0]; p =

0.199), albeit synchronous participation had numerically greater test grade improvement than asynchronous and mixed methods. In comparing standalone post-course grades, there was only a significant difference in median grades between the synchronous and mixed groups (78.6% [78.6, 92.9] vs. 64.3% [42.9, 78.6]; adj-p = 0.014), while the difference in synchronous vs. asynchronous (78.6 [57.1, 78.6]) approached significance (adj-p = 0.091). The only demographic/exposure factor found to impact post-course grades was that hospital experience resulted in better post course grades (64.0 ± 21.3% without hospital experience vs. 80.1 ± 8.5% with hospital experience; p = 0.003).

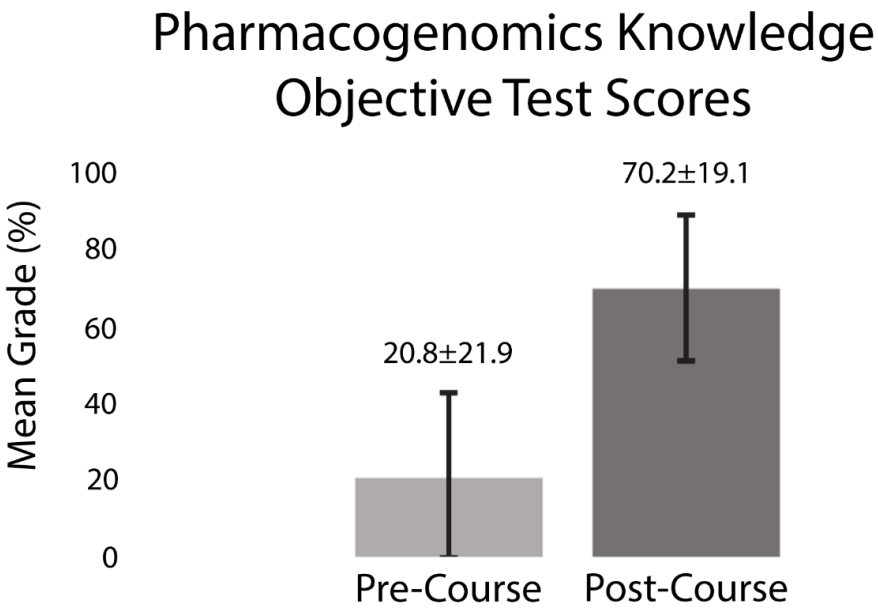

Figure 3.5. Pharmacists (n = 36) completed a knowledge test before and after pharmacogenomics education.

Table 3.3. Breakdown of participant (n = 36) responses to knowledge test questions (in bold text) pre vs. post course.

Which pharmacogene is most relevant to antiplatelet selection?

Response	Pre-Course n(%)		Post-Course n(%)	
CYP1A2	--	--	--	--
CYP2C9	3	(8.3)	5	(13.9)
CYP2C19 *	14	(38.9)	30	(83.3)
CYP2D6	2	(5.6)	0	--
COMT	1	(2.8)	0	--
I don't know	16	(44.4)	1	(2.8)

If a patient provides you with a result for a *CYP2D6* test, and is asking you to provide their physician with a recommendation for treatment of depression, which online resource would you find most useful in interpreting their phenotype (metabolism status)?

Response	Pre-Course n(%)		Pre-Course n(%)	
Lexicomp	3	(8.3)	1	(2.8)
eCPS	1	(2.8)	--	--
PharmGKB.org *	3	(8.3)	32	(88.9)
PharmacyGenes.org	2	(5.6)	1	(2.8)
I don't know	27	(75.0)	2	(5.6)

Which of the following would be considered the MOST correct definition of incidental findings in the context of pharmacogenomic testing?

Response	Pre-Course n(%)		Pre-Course n(%)	
Coincidental identification of a drug-gene interaction that was not the focus of the test ordered (e.g. *CYP2C19* testing for antiplatelet selection that also shows patient is at higher risk of side effects from their current antidepressant)	8	(22.2)	14	(38.9)
Identification of polymorphisms that indicate a different risk of an inheritable disease (e.g. CACNA1S testing to determine the risk of malignant hyperthermia with volatile anesthetics and succinylcholine that also reveals genetic risk for the development of hypokalemic periodic paralysis, an inheritable and sometimes debilitating disease) *	1	(2.8)	18	(50.0)
Finding a drug-gene interaction for which there is no current drug-related problem (e.g. panel testing shows ultrarapid metabolism of PPIs via CYP2C19, however the patient feels GERD is well controlled at current low dosage)	6	(16.7)	1	(2.8)
I don't know	21	(58.3)	3	(8.3)

Pharmacogenetic testing for *VKORC1* looks at a change in drug effect at the level of:

Response	Pre-Course n(%)		Pre-Course n(%)	
Pharmacokinetics	3	(8.3)	10	(27.8)
Pharmacodynamics*	3	(8.3)	22	(61.1)
Off-Target effect	1	(2.8)	2	(5.6)
I don't know	29	(80.6)	2	(5.6)

HLA-B genotyping in patients with Chinese ancestry is suggested in the FDA guidelines for which antiepileptic drugs? (check all that apply)

Response	Pre-Course n(%)		Pre-Course n(%)	
Phenytoin *	7	(19.4)	17	(47.2)
Valproic acid	2	(5.6)	2	(5.6)
Lamotrigine	5	(13.9)	5	(13.9)
Carbamazepine *	9	(25.0)	30	(83.3)
I don't know	22	(61.1)	3	(8.3)

Which medications have known drug-gene interactions, with therapy modification recommendations available through a clinical guideline? (check all that apply)

Response	Pre-Course n(%)		Pre-Course n(%)	
Sertraline *	7	(19.4)	32	(88.9)
Bupropion *	3	(8.3)	12	(33.3)
Hydromorphone	7	(19.4)	13	(36.1)
Metoprolol *	3	(8.3)	23	(63.9)
Pravastatin	7	(19.4)	6	(16.7)
I don't know	21	(58.3)	1	(2.8)

Which of the following cannot be done <u>without</u> the patient's consent regarding the sharing of pharmacogenetic test results?
i) Sharing results with a patient's physician
ii) Sharing results with an insurance company
iii) Sharing results with a related patient who may carry the same gene
iv) Documenting results on the patients' pharmacy care record

Response	Pre-Course n(%)		Pre-Course n(%)	
i, ii, and iv	--	--	--	--
i and iv	1	(2.8)	1	(2.8)
only i	1	(2.8)	1	(2.8)
only iv	2	(5.6)	3	(8.3)
i, ii, iii, and iv *	18	(50.0)	29	(80.6)
I don't know	14	(38.9)	2	(5.6)

Notes: Correct answers are shaded in yellow and indicated by *.

3.3.2.3.2 Baseline Knowledge Assessment

In a forward selection linear regression analysis, practice experience less than 10 years ($p = 0.034$), hospital practice ($p = 0.005$), foreign pharmacy education ($p = 0.209$), and higher subjective self-assessments ($p = 0.012$) all predicted higher pre-course tested knowledge, accounting for 38.2% of variation in pre-course knowledge test scores ($p<0.001$). While country of pharmacy education was not significant, it was included in the multivariate model due to its effect on other covariates (without interaction), and impact on r^2. As noted in the subjective Likert response results, higher post-course subjective confidence/opinions predicted better post-test grades.

3.4 Discussion

Pharmacogenomics in clinical practice involves testing genes for certain metabolizing enzymes, receptors, and other functional proteins that are involved in drug disposition and/or effect. [6,7] This information is used alongside other patient factors such as signs, symptoms, lab values, and preferences, to select optimal drug therapy. [12,13] Other components of PGx include the education the HCP must provide the patient before and after testing, and the communication of PGx information with other healthcare providers. Such clinical PGx use in pharmacy practice has increased dramatically over the last decade.[16] This study resulted in the development of a two-day webinar-style course in PGx for practicing pharmacists to support future clinical implementation. This course was further adapted as a self-study program, and both methods of learning showed significant improvement in self-rated (subjective) knowledge as well as proportional improvement in tested (objective) knowledge. Interest in this course was relatively high considering the COVID-19 pandemic, wherein pharmacists' priorities were already stretched in delivering vaccinations, asymptomatic testing, managing drug shortages exacerbated by the crisis, and patient education, all in addition to pre-existing clinical and distributive roles.[37] For context, typical online sessions by the Alberta Pharmacists' Association saw between 30-100 participants for brief one-hour sessions (internal sources), compared to the 19 pharmacists that were

able to commit to at least one full five-hour day of learning within the presented study. In social-media and email communications, there were 69 pharmacists that reached out with interest in this research study, and of these, 85.5% completed the initial survey and 52.2% completed both pre- and post-course surveys. Anecdotally, many potential participants indicated that the flexibility provided by the self-study option suited their current practice and educational needs as they could complete the material between these competing priorities. While online learning has been present for much of the history of the internet, the recent COVID-19 pandemic has appeared to enhance learners' ability to utilize this platform for education,[38] and this benefit lends itself to this course in many ways. Due to the online nature, speakers were able to be recruited worldwide and as far away as USA, Egypt and Qatar. This allowed the facilitation of a global perspective on the emerging field of PGx, which truly has been an international effort over the last decade. It also brought in a diverse population of Alberta pharmacists within both the synchronous and asynchronous platforms. Participants varied in practice experience, education, and prior knowledge in PGx. Despite these differences, only hospital practice experience appeared to lead to the greatest retained PGx knowledge indicated by testing, and no participant characteristics affected the level of confidence experienced post-course.

The results of this study suggest a positive effect of this pharmacogenomics course on both subjective and objective knowledge of pharmacists in pharmacogenomics immediately following education. Pharmacists transitioned from a median of "Disagree" with competency statements pre-course, to a median "Agree" post-course, indicating positive opinions of their own abilities to manage, interpret, and communicate pharmacogenomic information after receiving education, i.e., a greater level of confidence. Tested knowledge also improved by more than 3-fold, with participants answering on average 6.9 ± 3.2 more questions correct (out of a total possible score of 14) in post-course surveys compared to pre-course. Furthermore, there is strong correlation ($r = 0.516$; $p = 0.002$) between improvements in pharmacists' tested and self-rated knowledge assessments. This observation indicates

two things: 1) improved knowledge was observed by participants themselves, therefore supporting pharmacists confidently applying PGx in practice; and 2) that high self-rated confidence after learning was not simply hubris. This correlation, in addition to moderately strong linear relationships between pre and post course subjective and objective knowledge measures validates pharmacists' ability to recognize and accurately rate their own knowledge in pharmacogenomics using the survey in this study. Thus, they felt more confident in their knowledge and appear able to actualize this potential with the correct use of knowledge gained.

The course provided to study participants included a blend of didactic and case-based learning similar to those used by Zembles et al.,[23] Kisor et al.[39] and Crown et al.[21] The results of this research were congruent with the latter two studies in both subjective and objective measures.[21,39] While Zembles did not report knowledge results, their study did reveal high satisfaction with this method of training congruent with findings of Crown.[21,23] The mixture of learning methods in the presented study had also supported learning by providing the immediate opportunity within case studies to practice knowledge and skills gained in the lectures. Another study by Kisor et al. indicated the critical need for experiential education in PGx training.[40] While Kisor and colleagues did see pharmacist knowledge improve in all domains of the AACP pharmacogenomics competencies without case-based learning,[32,40] other research, including the results of this study, supports the use of case studies in long-term retention of knowledge gained. One study on pharmacist education in weight management saw the best subjective and objective knowledge four weeks after learning in the small-group discussions, closely followed by large-group discussions, compared to lecture-only groups, indicating better knowledge retention with peer-based learning.[28] The size of the group discussions in the presented study was of similar size to the small-groups in Sarayani et al.,[28] with even smaller groups in the three break-out room portions of the live course. Other studies have proved the merits of peer discussion in pharmacist and pharmacy student education in pharmacogenomics,[41] with particular interest in the "flipped classroom"

concept, wherein lectures are delivered asynchronously while classroom time is entirely devoted to utilize critical thinking and application of knowledge gained from lectures.[42] One such study on pharmacy students found that specific pharmacogenomic items with flipped content had significant improvement in correct responses on test questions compared to traditional didactic methods.[43] Such a method could be adopted for future pharmacogenomics courses such as this, to allow more time for participant interaction, questions, and practice within cases while shortening the overall time required for live attendance. While asynchronous participants did not receive the benefit of a formal group discussion, the case studies were presented in a scripted format, allowing the participant to read the questions as if they were being asked by a facilitator. They would be asked to solve the question posed before turning to the answer key, then proceed with the next question, thus accomplishing the experiential component. One case study is provided, for example, in **Appendix C**. This design of asynchronous case study appears to be effective in providing similar quality of education to live group discussion, as post-course knowledge and confidence did not appear to differ between synchronous and asynchronous participation methods. The difference in post-course grades seen between synchronous and mixed methods (78.6% [78.6, 92.9] vs. 64.3% [42.9, 78.6]; adj-p = 0.014), may be explained by the gap that many participants had between day 1 of live participation, and final course completion indicated by the date of the post-course survey (approximately 3 months). This suggests that future iterations of this course forgo the blended live/self-study route, opting for either a full synchronous or full asynchronous learning only.

Among the subgroup analyses, an interesting finding of this study was the high level of agreement among pharmacists with the statements “Pharmacogenomics can enhance the provision of medication-related services (eg dispensing, care-planning)” and “Pharmacogenomics testing is cost-effective.” Many studies before this also show a high degree of support by pharmacists in the clinical utility and feasibility of pharmacogenomics even with low rated or tested knowledge.[44-48] Speculatively,

this may be related to the increased exposure to PGx information in degree programs over the last decade.[17-19] As with this study, other research has shown that subjective (self-rated) knowledge is greater in those with prior PGx training.[49] However, this study conflicts with other findings that objective (tested) knowledge is also higher in those with prior PGx training,[47] as this study did not find a difference in pre-course test scores between those with PGx education in degree, in continuing education, or prior use of PGx, compared to those with no prior exposure. Some potential explanations for this observation include the rapid changes occurring and quickly advancing technology in PGx, and/or possibly due to knowledge decay in unused information. Other medical skills, such as resuscitation, follow a trend wherein the skills learned in a course are lost after 12 months if not frequently used, whereas knowledge is retained better when it is utilized more frequently in practice.[50]

In 2015, the United States Accreditation Council for Pharmacy Education addressed the knowledge gap in pharmacists by adding pharmacogenomics to the required curricula of entry-level Doctor of Pharmacy programs.[17] Although Canada has no formal requirement for PGx education in pharmacy schools at present, adoption of PGx has occurred across most of the country's University pharmacy degree curricula. Therefore, incoming pharmacy graduates within North America are likely to have an acceptable base-level of knowledge of PGx applications.[18,19] It should be noted however that pharmacogenomics is still a relatively new field, and as such, guidelines have been known to change as new evidence becomes available. One example of such is the CPIC guidelines for clopidogrel dosing in percutaneous coronary intervention (PCI) patients, which did not provide a phenotype for *CYP2C19* *2/*17 in 2011, and therefore recommended clopidogrel therapy in these patients.[51] In 2013, these guidelines were updated to interpret an "intermediate metabolizer" phenotype from this particular genotype based on more current evidence, thus changing the medication selection advice in these patients to an alternative antiplatelet therapy such as ticagrelor or prasugrel.[52] It is due to frequent

changes in evidence, such as this example, that even those with prior education in PGx will need ongoing updates to their knowledge through courses such as this.

While pharmacy curriculums are teaching pharmacogenomics to incoming pharmacists,[19] Alberta currently has a limited ability to utilize this in practice. Green Shield, a Canadian pharmacy benefit manager, has only recently added PGx testing to their services while Alberta's largest benefit manager, Alberta Blue Cross, has yet to provide these services to its beneficiaries. In part, this is due to the limited evidence available to support cost-efficacy to date, as one review found that within pharmacy practice, no research to date has followed real-world economic outcomes.[16] With most patients required to pay for this out of pocket ($200-$1000), the demand for pharmacogenomics testing is currently limited. Furthermore, it is reasonable to assume that if the pharmacist population, as shown in this study, is not confident in their ability to manage, interpret, and educate patients and providers on PGx information, they likely will not recommend PGx testing in the first place. Therefore, in addition to recurring education to manage knowledge decay and the changes in information available, pharmacists must also have the opportunity to utilize learned PGx skills in practice, to the benefit of both their ability to provide care, and importantly, to the benefit that PGx can have on patient outcomes.

3.4.1 Limitations & Strengths

While this study demonstrates the effectiveness of a PGx course on pharmacist competency in this subject, the study and the course itself are not without limitations. A previously validated survey measuring the specific competencies identified by AACP[32] and the therapeutics supported in the literature[16] was not available, and thus had to be created for this study. In addition to undergoing face validation, the observation of congruency between self-reported competence (Likert Scales) and objective knowledge (quiz grades) in baseline, final, and changes between assessments indicates construct validity of the tool used in this study. Further to assessment of survey results, although

instructions indicated these were to be completed to the best of the participant's ability, there is no way to confirm that participants did not check resources or notes while completing the quiz. However, a strength of the quiz portion was the inclusion of an option for "I don't know" with each question to minimize correct guesses that falsely overestimate knowledge. Another noted limitation of this study was its inability to measure long-term knowledge retention post-course. Given the pilot nature of this course and study, longitudinal evaluation was not the focus of the research presented. With short-term efficacy now established, research should be directed towards changes in knowledge with time post-course.

Another strength of this study was the utilization of current guidelines and resources in the generation of course content. These guidelines are subject to frequent updates and changes given the growing body of evidence in this relatively new field. Additionally, the AACP competencies[32] themselves are likely to be updated in the near future. Thus, it is imperative that these clinical and competency updates reach all pharmacists in an accessible format to ensure that PGx practices remain current. This applies to all pharmacists regardless of prior education in pharmacogenomics, as evident by the lack of difference in pre-course objectively measured knowledge between pharmacists with prior PGx education and those without. Therefore, this study highlights the need for recurring PGx education for pharmacists regardless of PGx knowledge background. Another strength of this paper is the comparison between synchronous and asynchronous learning, something that has not been evaluated to date in the available literature of pharmacogenomics education in pharmacists. This study showed no difference in these different learning methods, which may support more accessible PGx education in the future. Due to the limitations of the COVID-19 pandemic, a live in-person course could not be evaluated, and therefore another future research opportunity could be to compare virtual vs. in-person methods when public health measures allow.

3.5 Conclusions

A PGx course for pharmacists was developed using evidence-based resources and collaboration with field experts, utilizing a blend of didactic lectures with case studies for experiential education. This course was delivered to Alberta pharmacists in live and self-study formats and was found to significantly improve subjectively rated and objectively tested knowledge in PGx regardless of participation format among pharmacists with varying practice experience, education, and prior exposure to PGx information. Knowledge gained can be utilized in delivery of patient-centered, personalized medication therapy management in the pharmacy setting, and this course can be adopted for broader education of pharmacists regardless of current practice in both synchronous and asynchronous learning environments.

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3.8 Disclosure

The authors reports no conflicts of interest in this work.

3.9 Author Contributions

MH: MSc. student, methodology, data acquisition, statistical analysis, writing – original draft, writing- reviewing and revising; SHM: grant co-PI, conceptualization, methodology and study design, funding acquisition, statistical analysis, writing- reviewing and revising; DAH: grant PI and setting research study idea and design, conceptualization, main curricula setting and nominating speakers, methodology and study design, funding acquisition, writing- reviewing and revising. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work All authors have reviewed and agreed on all versions of the manuscript submitted and take responsibility for the contents within.

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Chapter 4: Pharmacogenomics Implementation Alberta Community Pharmacies

Implementation of pharmacogenomics within community pharmacies in Alberta, Canada: An observational study

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Abstract

Introduction: Pharmacogenomics (PGx) use in the Canadian community pharmacy is a new practice and currently has limited uptake, in part due to lack of standard policies and funding. Implementing and observing PGx testing in Alberta pharmacies may aid decision-makers in developing policies and funding models for PGx in pharmacy practice. This study sought to implement PGx testing in community pharmacies in Alberta, Canada, and had the primary aim of quantifying the frequency of drug-gene interactions (DGIs) identified by pharmacists as a measure of implementation.

Methods: Selected community pharmacies across Alberta, Canada were recruited as implementation study sites for PGx testing and patient education as part of standard care. Inclusion criteria for patient participant recruitment included those who were: age 18 years or older, able to provide informed consent, with a new, current, or planned prescription for an antidepressant, antipsychotic, atomoxetine, protein pump inhibitor, tramadol, codeine, simvastatin ≥40mg/day, or atorvastatin ≥40mg/day; any clopidogrel prescription; or any planned warfarin prescription. Collected data included participants' demographics, medication history, genotype/phenotype, DGIs, drug therapy problems (DTPs), test turnaround, and pharmacist time required. Data was summarized with descriptive statistics and a logistic regression analysis was performed for DGI predictors.

Results: To date, 8 pharmacies have provided PGx testing to 46 patients across Alberta. Twenty-four results have been returned with a mean of 1.1 DGIs per patient. Fifteen care-plans have been completed with 26 DTPs identified. DTPs were managed through monitoring without changes in 11 DTPs, and recommendations for changes made to the patient's primary care provider in 11 DTPs. Recommendations were to change medication (27.3% of recommendations), increase dose (27.3%), decrease dose (18.2%), start new medication (18.2%), and stop medication (9.1%). PGx services took

78.3 ± 12.2 minutes per patient (n = 9), with test turnaround at 60 (30,65) days (n = 19). This study aims to recruit up to 300 patient participants among 15 pharmacies in the next two years.

Conclusion: Pharmacogenomic testing has been implemented in the community pharmacy setting across Alberta, Canada. Pharmacists have demonstrated an ability to identify DGIs and DTPs with relevant PGx information and can formulate resulting care-plans in collaboration with patients.

4.1 Introduction

Pharmacogenomics (PGx) strives to improve patient medication-related outcomes through tailored pharmacotherapy based on an individual's genetic makeup, thus maximizing drug efficacy while reducing or avoiding toxicity.[1] This occurs at both the pharmacokinetic (PK) and pharmacodynamic (PD) levels, in which the transcription and/or translation of proteins involved in drug disposition and effect vary among members of the population due to differences in genetic sequences.[1,2] PK proteins include drug metabolizing enzymes, such as the cytochrome P450 (CYP) family that are responsible for the metabolism of approximately 30-50% of all medications.[1,3] Other disposition targets are transporters involved in absorption and elimination, such as the organic anion transporting polypeptide 1B1 (OATP1B1, coded for by the gene *SLCO1B1*) in which PGx has been demonstrated to predict myopathy in statins that utilize this transporter for uptake in to the liver for subsequent metabolism.[4] Based on CYP enzyme activity predicted by genotype, patient phenotype can be categorized as poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), rapid metabolizer (RM), or ultrarapid metabolizer (UM) for each CYP enzyme.[1,5] PD-PGx can be observed in receptors and drug targets, for example: the β2 -adrenoreceptor,[2] mu-opioid receptor,[6] the serotonin transporter,[2] and vitamin K epoxide reductase.[7] There is also PGx guidance for proteins contributing to off-target effects such as hypersensitivity reactions secondary to drug exposure combined with certain alleles for the human leukocyte antigen (HLA) protein.[2]

Commercial PGx tests approved by health regulatory authorities are available for the general public to purchase. Some are available through pharmacies or clinics registered with the laboratory, while others may be used by the patient without health professional consultation.[8] The latter group may experience difficulty in understanding the test results, requiring assistance from a healthcare provider to

interpret results and provide medication advice using available PGx prescribing guidelines. To bridge this gap in the utilization of PGx test results, pharmacists are often acknowledged as one of the best-suited healthcare practitioners to facilitate implementation.[9-11] Use of PGx testing by pharmacists has increased consistently over the last two decades. A scoping review identified 43 publications on the use of PGx testing specifically by pharmacists between the years of 2007-2020. Of these, 77% of research occurred in outpatient settings, with 30% of outpatient use of PGx occurring in the community pharmacy (**Table 4.1**).[12] While PGx utilization by pharmacists has been growing throughout Canada, with some pilot projects occurring in other provinces,[13] there have been no studies published to date evaluating the use of PGx within Alberta specifically. This study was an implementation pilot of pharmacogenomic testing in community pharmacies across Alberta, Canada. The aim of this study was to quantify the frequency of drug-gene interactions (DGIs) identified by pharmacists in community pharmacies using panel testing in addition to standard medication therapy management (MTM). Additionally, this study aimed to describe frequency and types of drug therapy problems (DTPs) identified by pharmacists, and the types of recommendations or prescribing decisions taken to manage these DTPs, describe time requirements for pharmacist assessment and test turnaround time (TAT), and summarize acceptance of pharmacist recommendations by prescribers. Lastly, this study aimed to summarize the frequencies of alleles and phenotypes in tested genes. By implementing and subsequently quantifying the use of pharmacogenomic testing in community pharmacies, results can be directed to determine feasibility, identify patient populations, and aid regulatory authorities in forming policy decisions.

Table 4.1. *Studies evaluating the use of pharmacogenomics in the community pharmacy setting identified between 2007 to November 7, 2020.[12] Studies included selective genes tested for specific medications, and larger panel (multi-gene) tests to assess for any interacting medications in a typically polypharmacy population. ADR: adverse drug reaction; DGI: drug-gene interaction; MTM: medication therapy management; PGx: pharmacogenomics; PPI: proton pump inhibitor; RPh: pharmacist; SBP: systolic blood pressure.*

Author (Year)	Country	PGx-based service implemented	Key Findings
Papastergiou et al. (2020)[18]	Canada	*CYP2C9*, *AKT1*, and *COMT* tested for cannabis users to inform RPh cannabis education.	Greater than half of patients (60%) had genotypes revealing risk of ADR to cannabis, 75% of patients felt the consult was valuable, with 65% reporting improved comfort in selecting cannabis strain after PGx and RPh education.
Bank et al. (2019)[65]	Netherlands	PGx panel testing for patients on certain statins and antidepressants, with results forwarded to prescribers for management of DGIs	Most patients (90%) had at least 1 actionable phenotype, with 9.5% identified with 4 or more polymorphisms affecting medication response. There were DGIs in 31% of incident medications. Physicians were very accepting of medication changes suggested by report, with an approval rate of 89%.
Crown et al. (2018)[66]	Canada	PGx testing for patients with inefficacy, side effects, or starting an antidepressant or antipsychotic to inform medication recommendations and follow-up by RPh.	Most patients had medication recommendations suggested by RPh after testing (80%), with 68% of these accepted by the prescriber. A clinically significant decrease in side-effects were observed in 46% of patients attending all study visits.
Bain et al. (2018)[67]	United States	PGx panel testing for patients enrolled in Programs of All-Inclusive Care for the Elderly (PACE) on a broad range of medications with PGx implications, to inform medication therapy recommendations by RPh after MTM service.	Almost all patients (99.7%) had at least 1 actionable phenotype, 35.8% had 4 or more polymorphisms affecting medication response. An average 1.5 DGIs per patient were observed, and 89% of RPh recommendations were accepted by prescribers. Clopidogrel, warfarin, antidepressants, PPIs, opioids, and beta-blockers were among the most affected medications.
Papastergiou et al. (2017)[8]	Canada	PGx panel testing for patients on a broad range of medications with PGx implications to inform medication therapy recommendations by RPh after MTM service.	A mean of 1.2 DGIs per patient were observed. PGx-based RPh recommendations were more accepted by physicians than non-PGx recommendations (63.2% vs. 51.4%). Clopidogrel, opioids, warfarin, statins, and antidepressants were among the most actionable medications.
Bright et al. (2015)[68]	United States	*CYP2C19* testing for patients on clopidogrel for percutaneous intervention, to inform antiplatelet therapy recommendations by RPh.	There were 27.9% of patients who had a DGI with *CYP2C19* and clopidogrel, indicating alternative antiplatelet, and 40% of physicians agreed to this recommendation. One patient was found to be on clopidogrel unnecessarily and was discontinued.
Moaddeb et al. (2015)[14]	United States	*CYP2C19* and/or *SLCO1B1* testing for patients on clopidogrel or simvastatin to inform recommendations for these medications by RPh.	Without training, RPhs interpreted 94% of *CYP2C19* and 88.7% of *SLCO1B1* results correctly. There were 34% of patients with actionable genotypes, however no medication therapy changes were made at time of publication.
Ferreri et al. (2014)[12]	United States	*CYP2C19* testing for patients on clopidogrel to inform antiplatelet therapy recommendations by RPh in an MTM service.	There was a DGI between *CYP2C19* and clopidogrel in 38.9% of patients, with recommendations accepted by physicians 83% of the time.
Rodriguez-Arcas et al. (2013)[69]	Spain	*CYP3A4* and *CYP2C9* testing in conjunction with MTM in patients on antihypertensives.	There was an average of 1.1 medication recommendations made by RPh per patient, half of these PGx-based, and 64% of these accepted by prescribers. Adherence was improved with PGx and MTM from 54.8% to 83.9% ($p = 0.015$) and had resultant improvements in SBP from 145.6 ± 21.8 mmHg to 135.7 ± 19.5 mm Hg ($p = 0.043$).
Condinho et al. (2012)[70]	Portugal	PGx panel testing for a patient with depression and fibromyalgia to inform medication therapy recommendations by RPh. (Case report).	Panel testing revealed 10 actionable genotypes and at least 4 DGIs. The patient had DGIs to duloxetine, escitalopram, alprazolam, and omeprazole. Authors observed a subjective decrease in pain symptoms after duloxetine increased based on PGx results.

4.2 Methods

4.2.1 Study Design

This study was a prospective, multi-site, non-controlled observational study on the use of PGx testing in community pharmacies in Alberta, Canada. The nature of this study was descriptive and exploratory to inform future research, practice, and policy within Alberta and Canada. Although this research funded pharmacogenomic testing for included participants, the research team had no influence on the medication therapy or other healthcare decisions (such as medication therapy recommendations, care plans, or prescribing) made by pharmacists in collaboration with the patient and other healthcare providers (such as physicians) at study sites. All drug therapy and other decisions were made without the research team's involvement, with this information only being conveyed to the research team in the data collection process.

4.2.2 Study Site Selection

Community pharmacies were selected as study sites if they fit the following criteria: 1) location in Alberta, Canada; 2) registration with the pharmacogenomic test company used in this study (MyDNA; Melbourne, Australia); and 3) at least one pharmacist with at least 8 hours of accredited or unaccredited learning in PGx, in addition to the online training provided by MyDNA required for registration. All study site pharmacies were given access to further PGx education developed by the research team. Pharmacies were selected in geographically diverse locations across the province. The requirement of significant training in PGx was decided based on the findings of a study in the United States determining that a lack of specific training in PGx limited the ability of the pharmacists to interpret results or communicate DGIs sufficiently to promote change to congruent medication therapy.[8 14] Study site pharmacists participated in an on-boarding discussion and review of the study procedures with the

research team to ensure study site practices were in concordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2018).

4.2.3 Participants

4.2.3.1 Inclusion Criteria

Potential participants were eligible for this study if they were 1) at least 18 years of age; 2) able to provide informed consent as deemed by the recruiting pharmacist; and 3) with either a) any active clopidogrel prescription; b) an anticipated new warfarin prescription; c) a new prescription for any medication in **Table 4.2** started within the last 28 days from the time of recruitment; or d) potential inefficacy or side-effects to a **Table 4.2** medication, regardless of current prescription status or start date. After consultation with study site pharmacists the decision was made to also include patients not experiencing any active drug therapy problems due to the potential for the DGI to manifest with changes in other patient parameters. Potential participants were excluded if they had any of the following: kidney disease defined as an eGFR less than 30 ml/min, liver disease defined as a Child-Pugh classification of B or C, an active respiratory infection, inability to provide a buccal sample, or otherwise deemed inappropriate for PGx testing or participation in research as per the study site pharmacist. The medications for inclusion specified were those within therapy classes with either established clinical benefit, such as clopidogrel,[15] or an apparent higher number of drug-gene interactions observed in a recent scoping study.[16] The inclusion criteria is summarized in **Figure 4.1.**

Table 4.2. *Medications for consideration of inclusion within the research study.*

▪ Any antidepressant ▪ Any antipsychotic ▪ Atomoxetine ▪ Any proton pump inhibitor	▪ Tramadol ▪ Codeine ▪ Simvastatin (≥40mg/day) ▪ Atorvastatin (≥40mg/day)

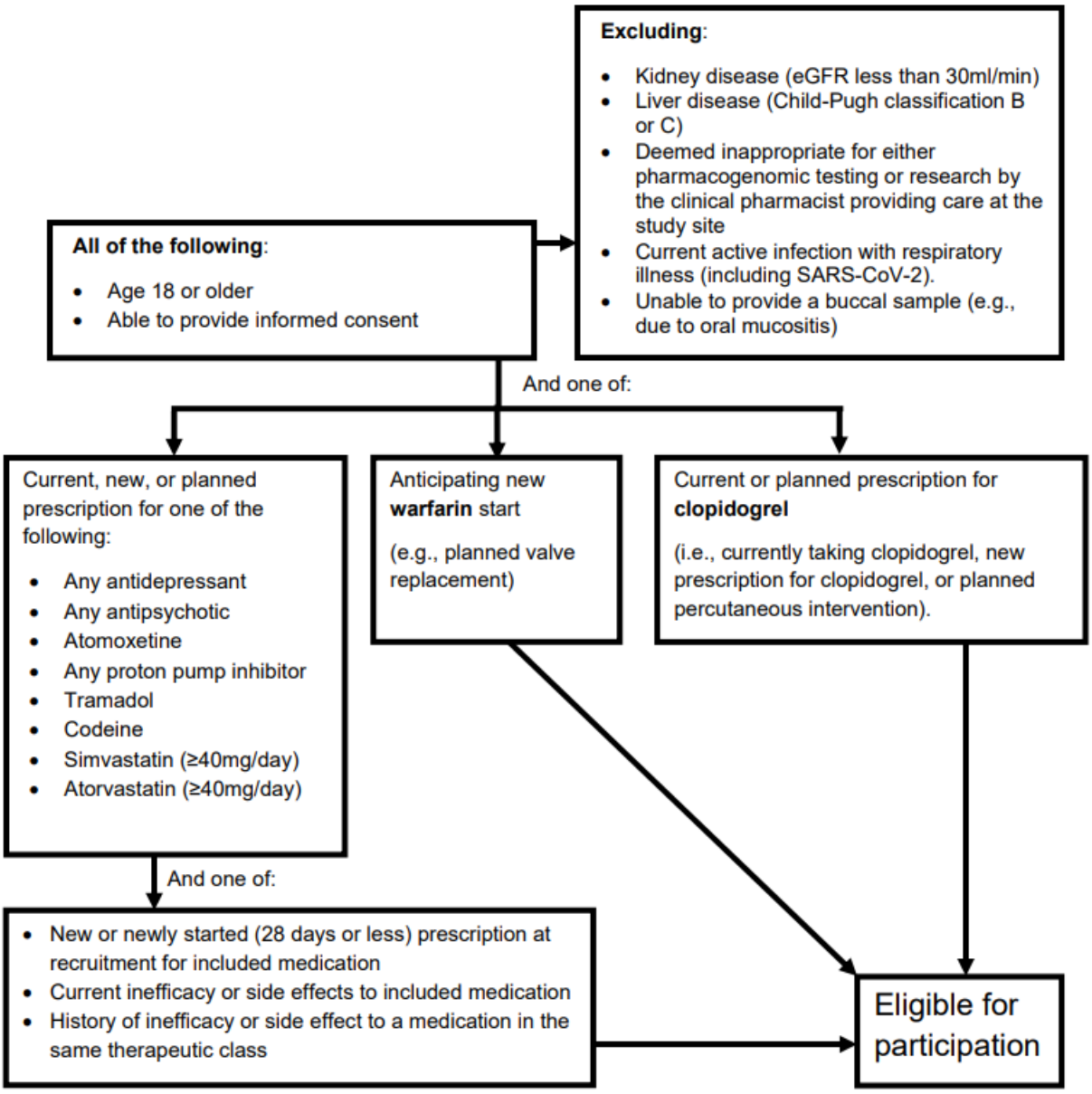


Figure 4.1. Inclusion/exclusion criteria flowchart used in this study.

4.2.3.2 Recruitment and Consent

Pharmacists at study sites offered pharmacogenomic testing as part of standard care. "Standard care" is defined as utilizing available patient-specific factors such as organ function, current signs and symptoms, concomitant medications, and other clinical data to assess the indication, efficacy, safety, and adherence of medication therapy through assessment of new or repeat prescriptions, or medication

therapy management services referred to in Alberta as Comprehensive Annual Care Plans (CACPs) and Standard Medication Management Assessments (SMMAs).

Potential participants fitting the inclusion criteria were informed by the study site pharmacist of the opportunity to participate in research, and upon expression of interest, provided with information about the research study and the contact information for the research team. Study site pharmacists were directed to use a script approved by the Research Ethics Board (REB) to provide the study site and research team information. If the potential participant is still interested in the research, they were provided with the research and MyDNA consent forms (both found in **Appendix D**), time to review the forms, and the opportunity to contact a member of the research team if more information was required. If the potential participant understood and was satisfied with the information, written informed consent for research and PGx testing was provided, and the participant received PGx testing at no cost. Standard of care was maintained regardless of agreement to participate; pharmacy patients were provided the option for PGx testing outside of the research study, or standard care without any PGx testing. Participants could withdraw from the study at any time and request their information be removed from the data collection tool. Recruitment commenced on December 8, 2021 and is ongoing, with a planned target of 300 patient participants to be recruited.

4.2.4 PGx Testing Procedures

Embedded in the consent procedure was pre-test PGx patient education performed by the pharmacist, including the indications and rationale for testing, the risks and benefits of testing, and how the results will be used to inform medication therapy. Following consent, pharmacists obtained a saliva sample using a buccal swab sent to GenSeq Labs (Melbourne, Australia; a subsidiary of MyDNA), a National Association of Testing Authorities, Australia, accredited laboratory. DNA was extracted at the testing facility with EDTA from saliva samples and open array technology (Life Technologies QuantStudio

12K; Thermo Fisher Scientific, Waltham, MA USA) was used to detect single nucleotide polymorphisms (SNPs) for *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *SLCO1B1*, *VKORC1*, and *OPRM1*. *CYP2D6* copy number variants were detected by real-time PCR (QuantStudio 6; Thermo Fisher Scientific, Waltham, MA USA) allowing for quantification of up to 4 copies. 3D PCR (QuantStudio 3D; Thermo Fisher Scientific, Waltham, MA USA) is used to determine which allele is duplicated. A full list of alleles tested can be found in **Appendix D.**

Following genotyping, patient reports were generated using MyDNA's software, uploaded to a secure password protected website for pharmacist access. MyDNA's software links phenotypes and medications to PGx prescribing guidelines, with preference for the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines over the Dutch Pharmacogenetics Working Group (DPWG) Guidelines. United States Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) labelling may also be referenced as additional sources. A sample report is provided in **Appendix D.** Following report review, the pharmacist would book an in-person follow-up post-test education appointment with the patient. The agenda of these appointments was typically to review the genotype and phenotype results, discuss the implications for current medications, as well as for future medications, and perform a comprehensive medication care-plan with this information. After consult, the results were released to the participant and with consent uploaded to the patient pharmacy record and/or sent to the patient's primary care provider along with any care-plan medication therapy recommendations. Education that the patient's results should be shared by the patient with future prescribers was highlighted. The research team had no influence on MyDNA policies or procedures, and no influence on day-to-day pharmacy operations, clinical interventions, medication recommendations, or site policies and procedures.

4.2.5 Data Collection

All data was entered by a study site pharmacist onto a REDCap electronic data capture tool hosted at the University of Alberta.[37,38] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Data collection in this study occurred at 5 timepoints after informed consent: 1) prior to or at the time of PGx sample collection (demographics and health history, some care-plan data at the pharmacists' discretion); 2) at the availability of PGx test results (PGx test results, pharmacist phenotyping/phenoconversion assessment, and test TAT); 3) at medication care-plan (can occur before and after, or only after PGx testing; data included DGIs identified, DTPs, and pharmacist recommendations); 4) if a response was received from the patient's primary care provider (PCP); and 5) at conclusion of participation (a participant survey). Pharmacist time required to provide PGx testing was collected at intervals 1, 2, and 3. A copy of the data collection tool is found in **Appendix D**.

4.2.6 Outcomes

4.2.6.1 Primary Outcome

The primary outcome was the frequency of DGIs identified by pharmacists using PGx testing. A DGI was defined for this study as the occurrence of a genotype that may alter pharmacokinetics or pharmacodynamics of a medication the patient is taking (e.g., *CYP2C19 *2/*1* leading to predicted intermediate metabolism in a patient on clopidogrel) compared to an individual carrying two wild-type alleles, regardless of action taken or the availability of clinical guidelines on the interaction. It was possible for one gene to have more than one interacting medication, and one medication to have more than one interacting gene, and these were all counted as individual DGIs. DGIs were quantified as a total, and as individual drug/gene pairs. Additionally, while it is possible the patient may have more DGIs than those identified by the pharmacist, this study only measured the DGIs specifically found by the study site pharmacist, to observe actual practice.

4.2.6.2 Secondary Outcomes

The secondary outcomes of this study included: the frequencies and types of DTPs (PGx and non-PGx based), pharmacist prescribing, medication therapy recommendations sent to PCP, medication therapy changes, PCP responses to recommendations; and actionable phenotype occurrence in PGx test results; total time required by pharmacists and for test TAT; and subgroup analysis of demographic and medication factors predicting the frequency of DGI occurrence. This study also looked to summarize the frequencies of alleles and phenotypes of tested genes in the study population.

4.2.7 Statistical Analysis

Due to the exploratory nature of this study a sample size was not statistically calculated and a convenience sample of 300 participants was targeted due to available funding. Data were summarized as mean ± standard deviation (SD), or n (%) for normally distributed numerical variables and categorical variables, respectively. Nonnormal numerical data were described as median (interquartile range; IQR). The number of DGIs were summarized as mean ± standard deviation per participant. The frequency of pharmacist prescribing, DTPs, medication therapy recommendations made, the types of medication interventions, and phenotypes were summarized in a similar fashion. Genotype was presented as raw data. Exploratory subgroup analysis on demographic and medication predictors for DGIs were performed by Student's t-test or Wilcoxon rank-sum for normal and non-normal data as applicable. All analyses were carried out using STATA version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TX: StataCorp LLC.) and a $p < 0.05$ was considered statistically significant.

4.2.8 Ethics Approval

Informed written consent was provided by the participant on the form approved by the REB following receipt of information from the study site pharmacist, the opportunity to contact the research team, and the time the participant required to read and understand the consent form (**Appendix D**).

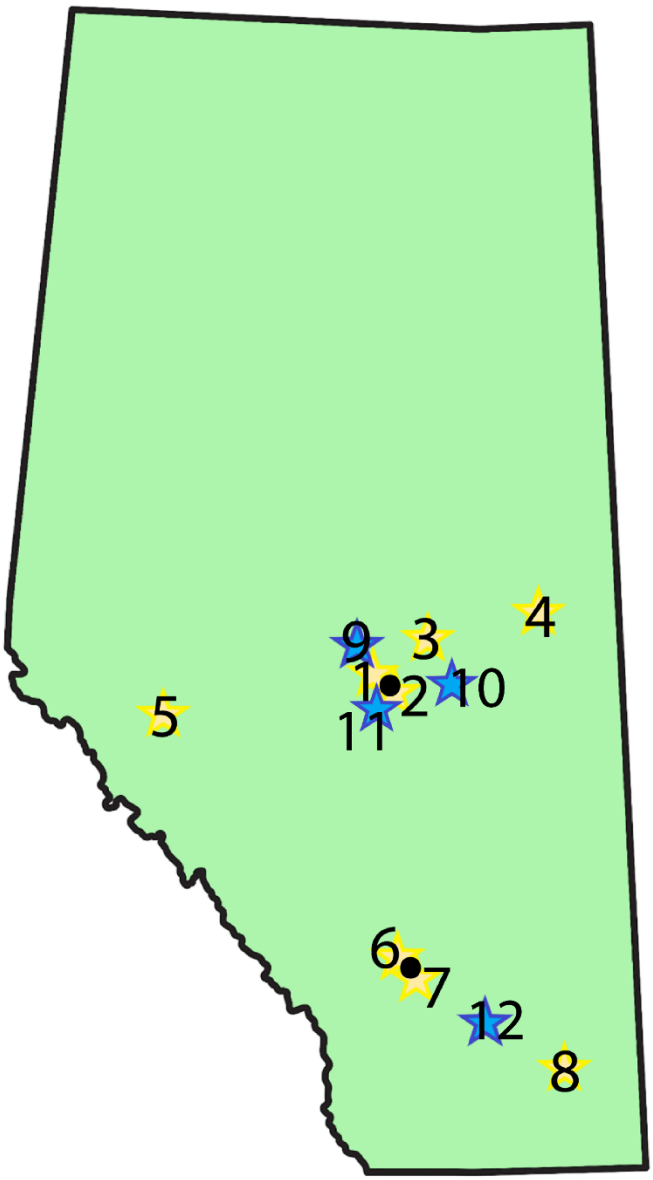
This study was approved by the University of Alberta REB (PRO 00112442). An additional implied consent page precedes the patient survey, accessed by the participant through the REDCap tool. Written consent was provided for the survey at onset of participation as well.

4.3 Results

4.3.1 Participants

Community pharmacies were selected across Alberta to implement PGx broadly in different geographical regions (**Figure 4.2**). There were initially 10 pharmacies onboarded as study sites in the winter of 2021, however 2 had withdrawn prior to any participant recruitment due to increased workload in the COVID-19 pandemic as well as reduced staffing. Of the 8 initial pharmacies, 4 were in rural or suburban communities (St. Paul, Hinton, Redcliff, and Fort Saskatchewan), and 4 were in urban centres (2 each in Calgary and Edmonton). An additional 4 pharmacies have since been recruited in the summer of 2022 in the areas of Vulcan, Edmonton, St. Albert, and Beaumont.

To date, 8 pharmacies have recruited 46 participants across Alberta, with the demographics described in **Table 4.3**. Individual pharmacy data is not presented to avoid participant unmasking. Distributions of gender and residence of urban vs. rural was near equal: 58.7% were female and 52.2% from rural settings. A total of 88 medications among all participants fit the inclusion criteria for testing in this study (mean 1.9 medications per participant). Any antidepressant was the most common medication indicating testing and accounted for half of the 88 medications selected for inclusion: twenty six participants (56.5%) were on at least one antidepressant, and 5 were taking 3 or more antidepressants (10.9%). Other medications identified for inclusion were proton pump inhibitors (PPIS; 43.5% of participants, 22.7% of medications), tramadol (n = 10), any antipsychotic (12 medications among 9 participants), clopidogrel (n = 7), atorvastatin (n = 6), codeine (n = 6), simvastatin (n = 2), and atomoxetine (n = 1). No participants were identified for potential warfarin initiation.



Number (on map)	Pharmacy Name	City / Town
1	Medi-Drugs Millcreek	Edmonton
2	Pharmasave #344	Edmonton
3	AbEx Pharmacy	Fort Saskatchewan
4	Catalyst Pharmacy	St. Paul
5	King Drug	Hinton
6	Discovery Ridge Pharmacy	Calgary
7	Richmond Square Pharmacy	Calgary
8	Pharmasave #304	Redcliff
9	People's Pharmacy	St. Albert
10	AbEx Beaumont	Beaumont
11	Co-Op Chappelle	Edmonton
12	Lifemed Pharmacy	Vulcan

Figure 4.2. Distribution of study sites for pharmacogenomic testing implementation in community pharmacies in Alberta, Canada. Original study sites recruited in 2021 are indicated by yellow stars, additional study sites recruited in 2022 are indicated by blue stars. Black circles indicate the major urban centres of Alberta: Edmonton (North) and Calgary (South).

Table 4.3. Demographic information of participants (n = 46). *more than one option could be selected therefore total percent is greater than 100%; IQR: interquartile range; SD: standard deviation.

Characteristic	Mean ± SD, median (IQR), or n (%)
Gender	
Male	19 (41.3)
Female	27 (58.7)
Age (years)	49.2 ± 15.8
Number of chronic medications	5 (4,7)
Location	
Rural (Population <20,000)	24 (52.2)
Sub-Urban (population 20,000-100,000)	13 (28.3)
Urban (population >100,000)	9 (19.6)
Ethnicity	
Caucasian	37 (80.4)
Aboriginal	3 (6.5)
South Asian	3 (6.5)
Black	2 (4.4)
Latin American	1 (2.2)
Medications identified for inclusion in study *	
Any antidepressant	27 (58.7)
Any proton pump inhibitor	20 (43.5)
Tramadol or codeine	16 (34.8)
Any antipsychotic	9 (19.6)
Atorvastatin or simvastatin (≥ 40mg daily)	8 (17.4)
Clopidogrel	7 (15.2)
Atomoxetine	1 (2.2)
Reasons identified for inclusion in study * (n = 88 medications)	
Inefficacy	49 (46.3)
Side effects	29 (33.0)
History of inefficacy or side effects to a medication in the same class	29 (33.0)
Assess stable therapy (monitoring)	22 (25.0)
Planning to start medication	6 (6.8)
New prescription (within 28 days)	5 (5.7)

Among 88 medications identified for study participation, the most common reason for inclusion was therapeutic inefficacy (46.3% of medications), followed by side effects (33.0% of medications) and the history of either inefficacy or side effects to a medication in the same class as one identified (33.0%). Other reasons included a new (n = 5 medications) or planned (n = 6 medications) prescription, or to monitor clopidogrel (n = 7) or another medication in the inclusion criteria without active drug therapy problems (n = 15).

Only 5 final participant surveys have been completed at time of writing, and therefore these results are not presented in this manuscript to avoid unmasking and due to the limited conclusions that can be drawn from a small sample.

4.3.2 Pharmacogenomic test results

At time of writing, 24 participants had received pharmacogenomic test results. The phenotype assignments of included participants within the MyDNA test reports provided to pharmacists are summarized in **Table 4.4** and **Table 4.5**. Genotype data for all participants to date is presented in **Table 4.6**.

Table 4.4. Phenotype assignments of CYP enzyme genes within the study population (n = 24).

	Phenotype Assignment [n (%)]				
Gene	Poor Metabolizer	Intermediate Metabolizer	Normal Metabolizer	Rapid Metabolizer	Ultrarapid Metabolizer
CYP1A2	n/a	n/a	13 (54.2)	n/a	11 (45.8)
CYP2C9	0 (0)	8 (33.3)	16 (66.7)	n/a	n/a
CYP2C19	1 (4.2)	5 (20.8)	11 (45.8)	6 (25.0)	1 (4.2)
CYP2D6	1 (4.2)	5 (20.8)	18 (75.0)	0 (0)	0 (0)
CYP3A4	0 (0)	3 (12.5)	21 (87.5)	n/a	n/a
CYP3A5	18 (75.0)	5 (20.8)	1 (4.2)	n/a	n/a

Table 4.5. Phenotype assignments of non-metabolism genes within the study population (n = 24).

	Phenotype Assignment (n, %)		
Gene	Low Function	Intermediate Function	Normal/High Function
VKORC1	2 (8.3)	10 (41.7)	12 (50.0)
OPRM1	0	5 (20.8)	19 (79.2)
SLCO1B1	3 (12.5)	6 (25.0)	15 (62.5)

Table 4.6. Genotypes in participants with results returned (n = 24).

Demographics			Genotypes								
Age	Sex	Ethnicity	*CYP1A2*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*OPRM1*	*VKORC1*	*SLCO1B1*
61	Male	Caucasian	*1F/*1F	*1/*1	*2/*17	*1/*2	*1/*1	*3/*3	A/A	G/G	T/T
74	Male	Caucasian	*1F/*1F	*1/*1	*2/*17	*1/*2	*1/*1	*3/*3	A/G	G/G	T/C
59	Male	Black	*1F/*1F	*1/*2	*1/*1	*1/*1	*1/*1	*3/*3	A/A	A/G	T/C
82	Male	Caucasian	*1A/*1F	*1/*1	*1/*17	*2/*4	*1/*1	*3/*3	A/A	A/G	T/T
27	Male	Caucasian	*1A/*1F	*1/*1	*1/*17	*2/*5	*1/*22	*3/*3	A/A	A/G	C/C
53	Male	Caucasian	*1A/*1F	*1/*1	*1/*17	*2/*2	*1/*1	*3/*3	A/A	G/G	C/C
44	Female	Caucasian	*1A/*1F	*1/*1	*1/*17	*1/*2	*1/*1	*3/*2	A/A	A/G	T/T
31	Male	Caucasian	*1F/*1F	*1/*2	*1/*1	*2/*41	*1/*1	*1/*3	A/A	G/G	T/C
22	Female	Caucasian	*1A/*1F	*1/*2	*1/*17	*1/*2	*1/*1	*3/*3	A/A	G/G	T/T
29	Female	Caucasian	*1A/*1F	*1/*2	*1/*17	*1/*2	*1/*1	*3/*3	A/A	A/G	T/C
57	Female	Caucasian	*1A/*1F	*1/*1	*1/*1	*1/*4	*1/*1	*3/*3	A/G	G/G	T/T
75	Male	Caucasian	*1F/*1F	*1/*2	*1/*1	*1/*41	*1/*1	*1/*3	A/A	G/G	T/T
37	Male	Caucasian	*1A/*1F	*1/*12	*1/*1	*2/*2	*1/*1	*3/*3	A/A	A/G	C/C
33	Female	Caucasian	*1A/*1F	*1/*2	*1/*1	*2/*41	*1/*1	*3/*3	A/A	A/A	T/T
50	Male	Black	*1F/*1F	*1/*1	*2/*2	*1/*1	*1/*1	*1/*1	A/A	A/G	T/T
41	Female	Caucasian	*1F/*1F	*1/*1	*1/*1	*2/*2	*1/*1	*3/*3	A/G	G/G	T/T
39	Male	Caucasian	*1A/*1F	*1/*1	*17/*17	*1/*41	*1/*1	*3/*3	A/A	G/G	T/C
44	Female	Caucasian	*1F/*1F	*1/*1	*1/*1	*4/*4	*1/*1	*3/*3	A/A	A/G	C/C
68	Female	Caucasian	*1F/*1F	*1/*1	*1/*1	*1/*2	*1/*22	*3/*3	A/A	G/G	T/T
27	Female	Caucasian	*1A/*1A	*1/*1	*1/*2	*2/*2	*1/*1	*1/*3	A/G	A/A	T/T
37	Female	Caucasian	*1F/*1F	*1/*2	*1/*1	*1/*4	*1/*1	*1/*3	A/A	A/G	T/T
61	Female	Caucasian	*1A/*1F	*1/*1	*1/*1	*2/*4	*1/*1	*1/*3	A/G	A/G	T/T
44	Male	Caucasian	*1F/*1F	*1/*1	*1/*2	*1/*1	*1/*22	*3/*3	A/A	G/G	T/T
58	Female	Caucasian	*1A/*1F	*1/*2	*1/*1	*2/*41	*1/*1	*3/*3	A/A	A/A	T/T

Pharmacogenomic testing revealed 26 DGIs among the 24 participants with test results available, presenting a mean of 1.1 ± 1.1 DGI per patient in the primary outcome, with 66.7% of participants identified with at least 1 DGI, and 25.0% with 2 or more DGIs. The drug-gene pairs most frequently implicated in DGIs were PPIs with *CYP2C19* (n = 8), followed by codeine/tramadol with *CYP2D6* (n = 4), and antidepressants with *CYP2C19* (n = 3) (**Figure 4.3**). Many cases of PPI inefficacy were found to occur in CYP2C19 rapid metabolizers, with one case detailed in **Appendix D**. An important DGI was found in one patient who was a poor metabolizer for CYP2C19 on clopidogrel therapy (detailed in **Appendix D**). There were an additional 44 medications identified with relevant pharmacogenomic test results not expected to affect medication disposition or effect, leading to a total of 70 drug therapies (mean 2.9 per participant) with pharmacogenetic testing implications.

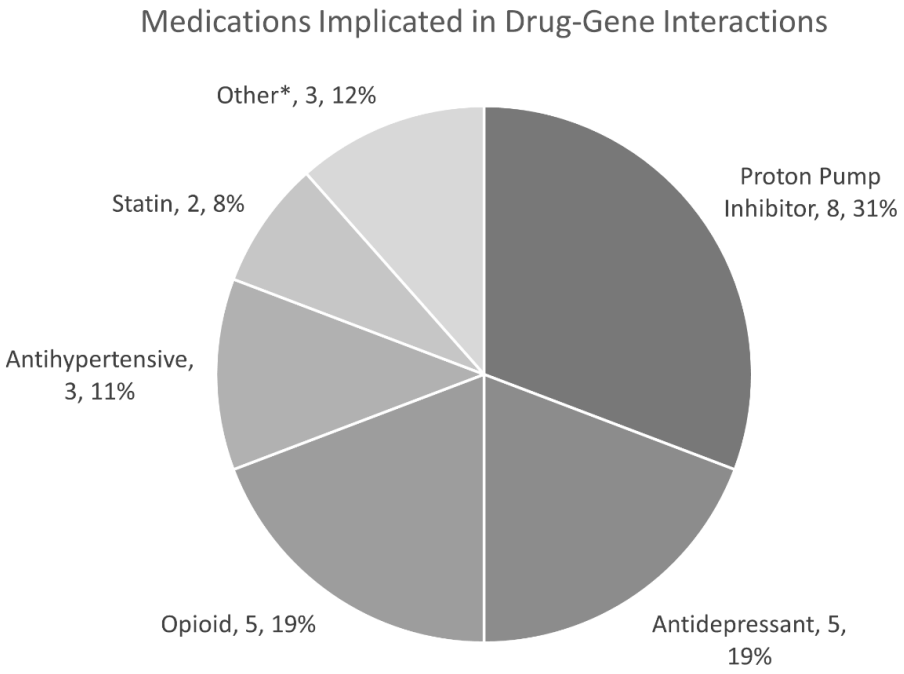


Figure 4.3. Distribution of medications identified in drug-gene interactions (DGIs; n = 26). Other: clopidogrel n = 1, diazepam n = 1, clarithromycin n = 1.

In exploratory analysis patients with more than 6 chronic medications had a greater median number of DGIs than those with 6 or fewer medications (1.5 [0.5, 2] vs. 1 [0, 1]; p = 0.043), as did those included in the study for PPI use compared to those not on PPIs (1 [1, 2] vs. 0 [0, 1]; p = 0.008), and those on statins compared to no statin use (3 [2, 4] vs. 1 [0, 1]; p = 0.002). There was no significant difference in DGIs for any other included medication, or for age, sex, or ethnicity.

Pharmacist translation of genotype to phenotype deviated from the myDNA (Melbourne, Australia) generated analysis (example report provided in **Appendix D**) in three reported results wherein the presence of bupropion phenoconverted normal metabolizers to poor metabolizers secondary to strong CYP2D6 inhibition by bupropion, in one case affecting patient's duloxetine therapy, another case of bupropion/CYP2D6 inhibition, and a case of fluoxetine/CYP2D6 inhibition. Ultimately, due to unpredictable drug metabolism from both this interaction and inducible CYP1A2 with current smoking status, the pharmacist recommended alternative drug therapy informed by the knowledge of PGx results in one case of bupropion/CYP2D6 inhibition. In the other case of this interaction, no active drug therapy problems were identified with current affected therapies and therefore monitoring plans were made with no changes. Fluoxetine CYP2D6 inhibition may have contributed to side effects seen with aripiprazole in a third case. Two of these cases are further detailed in **Appendix D**. Other instances of the presence of inhibitors or inducers were not identified in data collection due to limited reporting of pharmacists' individual assessment of phenotype. Pharmacists most frequently utilized the PharmGKB website for genotype assessments (n = 89 gene-patient combinations [GPC]) for test interpretation. Other resources included the CPIC guidelines (n = 44 GPCs), Lexicomp (n = 33 GPCs), other databases (n = 14 GPCs), smoking in CYP1A2 interactions (n = 12 GPCs), the DPWG or drug-drug interactions (n = 2 GPCs each), and primary literature or the electronic Compendium of Pharmaceuticals and Specialties (n = 1 GPCs each).

4.3.3 Pharmacist care planning

Pharmacists identified 26 drug-therapy problems (DTPs) among 15 participants, at a mean of 1.7 DTPs per participant. Of these, 25 (96.2%) DTPs involved the use of PGx test results in evaluation and management; 7 of these used a "normal" phenotype to inform medication therapy plan. A case of the latter circumstance with atomoxetine use in ADHD is described in **Appendix D**. Pharmacists provided 11 recommendations to other care providers (e.g. physicians), created 11 monitoring plans with patients, and did not take any further action on 4 identified DTPs (**Figure 4.4A**). Of the recommendations made 3 were for dose increase, 3 were to change to an alternative medication, 2 were for dose decrease, 2 were for initiation of new drug therapy, and 1 was to discontinue drug therapy (**Figure 4.4B**). At time of writing, no care-plan recommendation responses from other care providers had been collected.

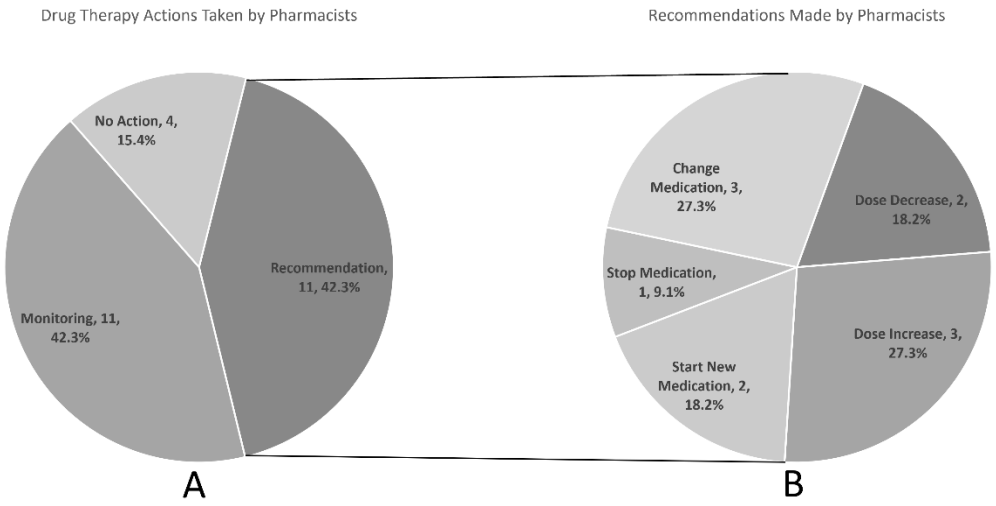


Figure 4.4. A: Actions taken by pharmacists in response to identified drug therapy problems (DTPs; n = 26). **B**: Recommendations made to other healthcare providers regarding identified DTPs (n = 11).

4.3.4 PGx testing logistics

Pharmacists took a mean time of 28.3 ± 12.1 minutes to collect patient information, discuss testing, obtain informed consent, and provide necessary pre-test patient education (n = 46). The median test TAT from collection to report available to pharmacist was 60 (30,65) days (n = 19). Pharmacists then took a mean of 32.8 ± 16.3 minutes and 32.3 ± 13.5 minutes to interpret the results and provide post-test counselling while performing a medication therapy care-plan in n = 20 and n = 13, respectively. Pharmacists took a total of 78.3 ± 12.2 minutes to implement PGx services among the 9 participants to date with complete data from pre-test to final care-plan. Four interpretations and 2 care plans did not have time reported at time of writing.

4.4 Discussion

In the presented study, participants have been provided with PGx testing to inform medication therapy care plans performed by pharmacists in community pharmacies across Alberta, Canada. To date 46 patients attending 8 pharmacies have received PGx testing within this implementation effort, with an average of 1.1 DGIs and 1.7 DTPs identified per patient. Most often pharmacists managed DTPs with either drug therapy recommendations (n = 11) or recommendations to prescribers (n = 11). No instances of pharmacist prescribing were identified. To date, no data has been collected regarding physician response to recommendations. The entire implementation process took pharmacists an average of 78 minutes per patient, with the most time spent in the test interpretation (33 minutes), followed by care plan formation (32 minutes) and the initial pre-test consultation (28 minutes). The phenotypes of CYP metabolizing enzymes found in Alberta follow normal distribution and were similar to what has previously been reported in the literature for Caucasians,[17] of which this study population identified as predominantly (80.4%).

4.4.1 Pharmacist Identification of DGIs

This is the first published PGx implementation pilot within Alberta, Canada in any setting. Elsewhere in Canada, PGx has been studied in community pharmacies in British Columbia (BC)[13] and Ontario,[8 11 18 19] and has been piloted in institutional practices in Ontario long-term care[20] and pediatric tertiary care.[21] Similar to the BC project,[13] geographically diverse pharmacies were selected to support widespread implementation that facilitates adoption of PGx in both urban centres, where the majority of PGx research already exists, as well as more under-served rural communities where there is typically less access to healthcare.[22 23] The BC study had identified an average of 0.73 DGIs per participant,[13] whereas the research presented in this manuscript identified 1.1 DGIs per participant. This discrepancy may be due to differences in inclusion criteria. While the BC project's[13] inclusion criteria focused only on mental health medications, the ICANPIC study in Ontario by Papastergiou et al. in 2017[8] included a broader range of medications with PGx implications for participant identification and inclusion, thus finding a mean of 1.3 DGIs per patient, which bears closer alignment the findings presented in this manuscript. The inclusion criteria utilized by both the ICANPIC project and this study appear to aid pharmacists in identifying patients most likely to benefit from PGx services. PGx interaction probability (PIP) algorithms may also serve to better identify patients best-suited for PGx testing, especially in a publicly-funded healthcare setting where it may not be feasible to test every patient.[24] PIP scores take into consideration the number of medications with PGx prescribing implications, DGIs, and known proportions of alleles in a population.[24] While this study did not have the ability to generate PIP scores, the inclusion criteria used did target patient populations found to have a larger likelihood of DGIs or clinical benefit as found in a recent scoping review,[16] and thus in the absence of PIP scores this criteria could be considered in future implementation models and funding decisions in a public payer health system such as that found in Canada. Of important consideration for patients with benefit for testing, exploratory analysis revealed that those with more chronic medications, as expected, had more DGIs.

This is consistent with the findings of a recent scoping review in which studies with a greater mean number of medications had more DGIs.[16] Patients that should also be considered for funding or policies for PGx testing may include those on medication classes in this study found to have a greater number of DGIs. Preliminary data in this analysis points to PPIs and statins. This is likely because these are commonly prescribed medications[25] with relatively common variations in phenotype occurring in the population in previous research[17 26] and in this sample. Likely for these reasons, the ICANPIC study similarly saw statins as common DGI offenders,[8] however unlike this study had many more patients with clopidogrel DGIs. Recruitment rates for participants on clopidogrel were comparable between studies, and therefore there is no reason outside of geography that can explain this difference at this time. While ICANPIC did not have as many DGIs with PPIs as this study did (likely due to a fewer proportion of patients recruited on PPIs), other pharmacist-led PGx pilots have shown PPIs to be common offenders as this study has.[27] As noted, due to the small sample size, these results are hypothesis-generating only and more rigorous analysis will be performed once target recruitment of a sample size of 300 participants is reached, and all PGx test results are returned.

4.4.2 Testing Logistics

Numerous studies conducted within the United States (U.S.), a predominantly private-payer health system, have supported outpatient PGx implementation by pharmacists. Arwood et al. developed a PGx consult clinic wherein patients were referred by internal medicine for pharmacist assessment. If determined to be appropriate by the pharmacist, patients were tested for variants in *CYP2C19* and/or *CYP2D6* to enhance MTM services provided. The collaboration with physicians appeared to greatly benefit this model, as 87% of pharmacists' recommendations were accepted by prescribers.[27] The study described in this manuscript is currently collecting data on prescriber acceptance of pharmacist recommendations, however there is not sufficient data at this time to present. Arwood et al., which took place in the ambulatory care setting, as well as two other U.S. projects in the community pharmacy

by Haga et al. in 2015[28] and Ferreri et al in 2014[12] demonstrated similar time requirements as this study of 60-80 minutes for the implementation of pharmacogenomic testing services with medication therapy management services provided by pharmacists. Thus, it is imperative that funding decisions incorporate not only the costs of the test, but the time required for pharmacists to assess the PGx information in each individual patient context. Limited time may have contributed to missed drug-drug-gene interactions as the report provided by laboratory used in this study did not incorporate these into phenotype identification. In future research, use of decision support software such as Sequence 2 Script[30] would aid pharmacists in identifying cases of phenoconversion as observed in several other studies.[16]

4.4.3 PGx Implications on Medication Therapy

4.4.3.1 CYP1A2

Nearly half of all participants in this study were found to have inducible CYP1A2 metabolism as identified by homozygous *1F/*1F allele carriage. This was most frequently found to impact duloxetine therapy. There is currently no PGx prescribing information for duloxetine with either of its two major metabolism pathways of CYP1A2 or CYP2D6,[31] and thus one patient described in results and **Appendix D** with inducible CYP1A2 and concomitant CYP2D6 inhibitor was considered for change to an alternative therapy due to the unpredictable nature of these metabolic pathways in the presence of drug inefficacy. Currently there are no recommendations for any medication therapy changes in any medications with *CYP1A2 *1F* carriage and thus more research is required to determine if duloxetine and other CYP1A2 metabolized therapies such as olanzapine should be modified in these patients.

4.4.3.2 CYP2C9

CYP2C9 genotype has medication therapy recommendations to non-steroidal anti-inflammatory (NSAID) or COX-2 therapies, and warfarin initiation by guideline groups such as the CPIC that would

impact 33.3% of all participants in this sample as identified CYP2C9 intermediate metabolizers. Neither of these medications were identified in this patient population unlike other studies which have utilized *CYP2C9* genotype in analgesia[32 33] and warfarin management,[7] thus establishing its role in future implementation. Within pharmacy practice, where pharmacists often assist patients with selecting over-the-counter therapies, there is also a place for knowledge of *CYP2C9* genotype, given the availability of NSAIDS without prescription. With regards to other therapeutic implications of *CYP2C9*, there were three CYP2C9 intermediate metabolizers in this study on irbesartan therapy. While no current guidelines are available to manage irbesartan therapy in reduced metabolism phenotypes, there is evidence that reduced-function alleles do impact its antihypertensive effect.[34 35] No drug therapy problems were identified from these interactions, likely due to the titratable nature of antihypertensive drugs.

4.4.3.3 CYP2C19

CYP2C19 was the most relevant gene tested for medication therapy within this study, involved in 13 out of 26 identified DGIs. These were mostly with proton pump inhibitors, which have guidelines to inform medication therapy dosing by both the CPIC and the DPWG.[36 37] Some of these participants had therapeutic inefficacy potentially attributable to rapid metabolism of the active parent compound, and thus genotype knowledge aided the pharmacist in providing the recommendation to increase dose. A small study in children supports this practice,[38] however more research is required in adults to further establish *CYP2C19* genotyping in PPI therapy. *CYP2C19* genotype also was relevant in recommendations to adjust dosing or change therapy in patients on antidepressants regardless of phenotype, as pharmacists at study sites identified that a normal metabolism status was equally useful in deciding next pharmacological steps in cases of inefficacy. With the availability of extensively reviewed guidelines by the CPIC,[39] genotype-guided antidepressant therapy has been demonstrated to improve patient response to medication in both depression and anxiety in a recent randomized controlled trial,[19] and thus this gene is clinically useful in future implementation strategies. This is likely due to the extensive

CYP-mediated metabolism of the first-line therapies in both diagnoses: selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Given that a recent survey found that one in four Canadians aged 18 had symptoms of depression, anxiety, or post-traumatic stress disorder,[40] the impact PGx testing can have on patient mental health outcomes in Alberta could be very large and warrants further research in the form of a randomized controlled trial on genotype-guided prescribing compared to standard care.

In addition to gastrointestinal and psychiatric indications, there is considerable evidence of the benefit of *CYP2C19* genotyping in antiplatelet selection to prevent major cardiac and cerebrovascular events after percutaneous coronary intervention/acute coronary syndromes (PCI/ACS) and ischemic stroke.[41,42] The single CYP2C19 poor metabolizer within this study was on clopidogrel for the secondary prevention of stroke. Clopidogrel is a P2Y12-inhibitor drug that is bioactivated by CYP2C19 metabolism in order to exert its antiplatelet effects, and thus reduced metabolism has been shown in the CHANCE2 trial to increase risk of recurrent major cardiovascular or cerebrovascular event (MACCE) after stroke in IMs and PMs on clopidogrel compared to NMs, and use of an alternative (active-parent compound) P2Y12 agent such as ticagrelor reduces MACCE in IM and PM patients after stroke.[42] In Canada, clopidogrel is the current guideline-recommended drug-of-choice when a P2Y12 inhibitor is indicated, despite the proportion of patients that may not sufficiently activate this medication due to reduced CYP2C19 metabolism. Similar impact of *CYP2C19* genotype has also been demonstrated in PCI/ACS: IMs and PMs are consistently shown to have more MACCE on clopidogrel than alternatives, while NMs, RMs, and UMs on clopidogrel have equivalent efficacy outcomes to those on alternatives, with less minor bleeding.[41] Within Alberta, where this study takes place, clopidogrel is not the current drug of choice for P2Y12 inhibitor in dual antiplatelet therapy regimens after PCI/ACS due to the availability of ticagrelor. However, as some analyses have demonstrated a cost-benefit with genotype-guided prescribing,[43] broad-scale PGx testing may be able to produce cost savings in a public-payer health system, as 75% of

the participants in this study could effectively receive clopidogrel therapy if a P2Y12 were indicated for them, and PM patients such as the one identified in this study, are placed on alternatives to clopidogrel before experiencing a debilitating MACCE event.

4.4.3.4 CYP2D6

As with *CYP2C19*, *CYP2D6* is also relevant to some antidepressant therapies such as paroxetine and fluvoxamine,[39] however no participants in this study were on either of these medications with *CYP2D6*-based guideline advice. Some participants were on either duloxetine, as discussed above, or fluoxetine, which like duloxetine has multiple metabolic pathways and thus no clear guidance on the management of aberrant CYP2D6 metabolism.[39] Within this study sample, CYP2D6 metabolism status was relevant to the assessment of tramadol and codeine. CPIC guidance on the management of these medications with *CYP2D6* DGIs is available[6] and primarily informed by research confirming that IMs and PMs to CYP2D6 experience greater pain improvement with genotype-guided therapy after initial tramadol or codeine prescription pre-genotype, compared to normal metabolizers.[44] This is mostly explained by the bioactivation required for these two medications by CYP2D6. These are the only medications available in Canada in the WHO guidance for management of moderately rated pain,[45] despite the identification that 25% of patients tested in this study may not experience sufficient analgesia with these agents due to IM or PM status. Poorly managed pain is one of many risk factors identified in the development of substance use disorders in Canada,[46] and thus PGx may serve to not only improve individual patient outcomes, but potentially has societal implications on a complex public health issue.

4.4.3.5 CYP3A4

CYP3A4 is involved in the metabolism of more than 50% of hepatically cleared medications[47] however there are very few guidelines available from CPIC or DPWG on management of DGIs with this gene. Its genotype is relevant for quetiapine therapy,[37] of which patients in this study were identified to

be taking. However, no DGIs with this gene were found among participants in this study. One participant with results identified as relevant to their quetiapine therapy was NM, while an IM on quetiapine did not have this medication noted as a potential interaction. The report from the laboratory used in this research provides medication therapy recommendations from the CPIC primarily, and thus it is possible that the DPWG advice on this DGI was missed. However, it should be acknowledged in this context that DPWG do not advise modification based on IM phenotype, recommending dose reduction or alternative therapy in PM phenotypes only.[37] No participants in this study were CYP3A4 PM. One DGI in this study was identified with clarithromycin in an intermediate metabolizer, however at the time of test result return, therapy was complete and thus no DTP was identified. Clarithromycin does not currently have any guideline advice in *CYP3A4* genotype however is both a substrate and inhibitor of this enzyme[48] and therefore may need further PGx-based research to determine the role of genotyping in its use.

4.4.3.6 CYP3A5

In Caucasians, the predominant CYP3A5 phenotype is PM, and NM status is considered different than the reference population. For the 25% of participants in this study with a phenotype other than PM (20.8% IM, 4.2% NM), this is relevant to tacrolimus therapy in organ transplant indications.[49] While this is a condition that would likely be managed outside of the community pharmacy setting, it is important that patients understand to communicate their genotypes to their entire healthcare team. Such understanding is one of the most important components of the post-PGx consultation provided by pharmacists, as this information is not readily available on current electronic healthcare records in Alberta. Until this technological barrier is overcome, it is the pharmacist's responsibility to ensure the patient is aware of the future implications of their PGx test results and the need to share them with all care providers.[50]

4.4.3.7 OPRM1

The PGx test used in this study included genotyping the *OPRM1* gene coding for the mu-opioid receptor. Data regarding the impact of *OPRM1* genotype on opioid therapy is conflicting, and therefore there is no current prescribing advice based on *OPRM1* genotype in the most current CPIC guidelines for opioid therapies.[6] This highlights the importance of pharmacist use of evidence-informed guidelines in PGx-guided therapy and taking into consideration the entire context of the patient in front of them with respect to current signs and symptoms of inefficacy or side effects rather than relying on genotype alone, particularly in the absence of prescribing guidelines.

4.4.3.8 VKORC1

There were no patients in this study that were planning on initiating warfarin. Genotype is relevant in initial dosing regardless of the presence or absence of variant alleles as algorithms exist to aid dose selection for the first week of therapy, after which all patients transition to INR-based dose changes in previous studies.[7] Warfarindosing.org provides personalized initiation advice based on *VKORC1* and *CYP2C9* genotypes, as well as other patient factors such as weight and interacting medications, based on numerous studies cited on their website.[51] There is no current PGx-based maintenance dosing guidance or algorithms, as previous studies have transitioned to standard algorithms after the initiation week.[7] As such, a recent scoping review identified that long-term patient outcomes (i.e. 90 days) were no different in genotype-guided vs. standard algorithm groups.[16]

4.4.3.9 SLCO1B1

The *SLCO1B1* genotype currently only has guidance for selection and dosing of statin pharmacotherapy, of which two patients were identified to have a relevant DGI. The CPIC recently updated their clinical guidelines on PGx-guided statin therapy to expand the relevance of this genotype to all statin therapies.[52] At the time of protocol development, previous guidance had only indicated a role in atorvastatin[37] and simvastatin[37 53] therapy, and thus these were the only medications identified in

the inclusion criteria in this study. Some participants included for other indications were identified on rosuvastatin therapy, with one of these accounting for a DGI identified by this study. This participant did not have a care-plan reported at time of writing. The other *SLCO1B1* intermediate-function patient was provided a recommendation to potentially reduce dosage to prevent statin-related adverse musculoskeletal symptoms (SAMS). While no outcomes research to date demonstrates PGx-guided statin therapy is effective at avoiding SAMS, current research does indicate that it does not reduce therapeutic efficacy,[54] thus providing a reasonable risk-benefit ratio of dosage reduction in those with reduced transporter function and a role of genotyping in statin therapy.

4.4.3.10 Longevity of PGx Information

PGx information is not only useful for a patient's current medications and DTPs, but has applications for a patient's future therapies as well, as the genotypes identified do not change over time. A community pharmacy pilot in the Netherlands found that 97% of patients previously genotyped were subsequently prescribed another medication with PGx implications within 2.5 years following the initial PGx test.[55] Another study by the the Implementing GeNomics in PracTice (IGNITE) Network Pharmacogenetics Working Group identified that in the setting of *CYP2C19* genotype use in antiplatelet selection after PCI, 92.5% of patients were prescribed at least one medication with *CYP2C19* implications, and 51% at least two medications (including antiplatelet drugs) within one year following the PGx test.[56] These results imply that the benefit of reusability can be seen almost immediately (within 1-2 years), and can inform future medication therapies. This also highlights the importance of the post-test counselling performed by pharmacists, as patients must be aware of these implications and share their results with future prescribers. The PGx test report provided to patients by MyDNA (Melbourne, Australia), aids patients in this understanding and future communication, as it lists all noted medications with current PGx-based prescribing advice curated from the CPIC and DPWG guidelines by pharmacists (**Appendix D**).

4.4.4 Strengths and Limitations

This study was able to implement PGx testing in predominantly rural populations, which serves to increase the reach of PGx awareness across the province for both patients and healthcare professionals alike and improves the gaps identified in research in this population.[22 23] Furthermore, while this population was predominantly Caucasian, there is still improved representation of ethnic minorities compared to most other PGx research. Ethnicity has been largely acknowledged to contribute to predicted phenotypes, however in an admixed population such as Canada, it is also important to acknowledge the large amount of intra-ethnicity diversity in genetics that begins to negate the ability to presume genotypes based on ethnicity.[57]

This study was also pragmatic in observing the real-world implementation of PGx testing in the community pharmacy setting and thus provides informative data on time requirements, barriers, and which patients' pharmacists are best able to provide PGx services to. The observational nature of this study, however, limits its ability to determine how great an impact PGx has on pharmacist DTP identification as there is no comparison to standard practice. Other research fills this gap in demonstrating greater DTP identification with PGx testing and concomitant use of CDSS.[58-60] The lack of CDSS was also identified as a limitation of this study, as pharmacists in this study likely lacked the time to individually assess PGx data outside of the report already provided by the laboratory. There are currently no funding models in Alberta for PGx testing to account for total time of more than an hour required to provide this service. The lack of CDSS in this study, however, was compensated for by the extensive education pharmacists received prior to implementation. All pharmacists at implementation sites were given access to the asynchronous course materials of a previous Alberta-based study that validated the course's efficacy on pharmacist knowledge and confidence in PGx.[61]

Other limitations pertain to the choice of testing laboratory. While the PGx testing company used in this study had an accredited laboratory and had been used and further validated in other Canadian PGx research,[13] its remote location (Australia) significantly delayed test TAT to months. It is difficult to compare this to other research, however, as TAT for multi-gene panels ranges greatly. Future research should endeavor to utilize local laboratories to avoid delays in turnaround. Such delays have been shown in other studies to reduce the positive impact PGx testing can have on patient outcomes.[16] While this study did not investigate outcomes, it has established that pharmacists in the community pharmacy setting in Alberta are able to begin implementing PGx testing services, thus increasing the availability of this service which has been established in other studies to reduce emergency visits and hospitalizations.[58 59] The laboratory selected did not have the option of customizing genes and alleles tested. Within pre-emptive testing strategies, *HLA* genotyping has important implications in preventing debilitating and potentially fatal hypersensitivity reactions with drugs such as carbamazepine, phenytoin, and allopurinol,[62-64] and thus should be considered in future Canadian implementation projects as these results would be reusable for the patient's lifetime.

4.5 Conclusion

Pharmacogenomic testing has been implemented in the community pharmacy setting in both urban and rural areas within Alberta, Canada. Pharmacists have demonstrated an ability to select patients suitable for testing, identify DGIs and DTPs with relevant PGx information, and can formulate resulting care-plans in collaboration with patients. Overall, this research will inform future PGx implementation policy in the Canadian community pharmacy setting by identifying suitable patients for testing and the time requirements for pharmacists. Future results of this research will identify the collaboration with other healthcare providers with information on responses to drug therapy recommendations made with genotype information.

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Chapter 5: Summary

5.1 General Discussion

This thesis endeavored to facilitate the adoption of pharmacogenomics (PGx) into routine clinical pharmacy practice within Alberta, Canada using evidence-based practice and research. Pharmacists have frequently been acknowledged in the literature as well-suited to handle, interpret, and communicate PGx information.[1] [2] This is due to their extensive knowledge of medication pharmacokinetics and pharmacodynamics affected by genetics,[3] their knowledge in other factors impacting medication response such as drug levels, organ function, and drug interactions,[3] [4] as well as their accessibility and communication skills.[5] PGx has been identified as an additional component of medication therapy assessment within the concept of precision medicine that strives to provide healthcare based on individual patient needs.[6] The benefit of PGx has been demonstrated in areas such as cardiovascular medicine, with *CYP2C19* genotyping in particular showing that antiplatelet therapy optimized with PGx testing can have benefits on patient-important outcomes such as cardiac events and bleeding,[7] and healthcare system outcomes like cost savings.[8] When incorporated into the process of medication therapy selection and titration, PGx has also been shown to improve validated measures of depression and anxiety,[9] and pain management.[10] [11] Since all of these indications for PGx testing have implications in the Alberta population, the overarching aim of this thesis was to support the adoption of PGx in community pharmacy practice in this province. This aim was addressed through deliberate steps to first evaluate the evidence to date through a scoping literature review, deliver an education program on PGx for practicing pharmacists, and finally support implementation in community pharmacies by PGx-educated pharmacists using the principles defined in the scoping review along with the American Association of Colleges of Pharmacy (AACP) PGx competencies.[12] Through evidence-informed implementation policy, PGx adoption in Alberta can potentially improve the health of the population through personalized prescribing in a precision-medicine framework facilitated by pharmacists.

5.1.1 Scoping review: an overview of PGx in pharmacy

The scoping literature review identified 43 publications detailing prior implementation of PGx in pharmacy practices from database inception to November 2020, with 10 studies occurring in community pharmacies, 4 in Canada, and only one study in a community pharmacy in Canada, revealing the gap that occurs in PGx implementation in this country. Since this review, implementation pilots have been completed in British Columbia[13] and Ontario,[4] which along with the study described in this thesis, add to the literature supporting that PGx testing in the community pharmacy in Canada is feasible. The scoping study performed also identified that it is meaningful for Canada to adopt PGx testing into pharmacy practice, particularly in the therapeutic areas of cardiovascular, pain, and psychiatric therapies, and in patients with complex polypharmacy regimens. These populations may benefit from PGx testing through greater drug-gene interaction (DGI) identification and a resultant reduction in major cardiovascular adverse events, improved control of pain and depression, and fewer emergency room visits, and hospitalizations. The literature also supported the use of education pre-implementation, as well as collaboration with physicians and other healthcare providers in successful pharmacist-led PGx implementation models. No research had previously evaluated the literature for PGx applications specifically in the pharmacy setting, and thus this study is important in shaping future research in pharmacist-led PGx initiatives.

5.2.2 PGx knowledge mobilization

Limited knowledge of PGx is frequently cited as a barrier to implementation. [2 14 15] To bridge this gap, a PGx course was created for pharmacists. Knowledge generated from the review was combined with the AACP PGx competencies described in Roederer et al., which highlights four key areas of competency for pharmacists in the application of PGx. These competencies are knowledge in: basic genetic concepts, genetics and disease, pharmacogenetics/pharmacogenomics, and the ethical, legal, and social considerations (**Figure 3.1**).[12] A two-day virtual course was held to deliver live education to 10 pharmacists, and the materials of the course were made available for asynchronous learning by a further 17 pharmacists. Nine pharmacists participated through a combination of synchronous and asynchronous

learning. In all groups, the course was found to have a positive impact on pharmacist knowledge measured on subjective Likert scales and in objective knowledge tests applied before and after learning, with increases in these measures proportional to one another. Thus, this course successfully supported these pharmacists' future adoption of PGx in practice by improving their practical knowledge of this subject. A few of these pharmacists went on to support a prospective observational study in the application of PGx in practice as study personnel, as described in **Chapter 4** and below. Implementation is considered to be the final step in continuing medical education (CME), as described in Moore's Framework, wherein learners "… do what the CME activity intended them to be able to do in their practices,"[16] and therefore implementation is a critical component in the evaluation of knowledge.

Of important consideration around PGx education are frequent changes in the body of knowledge as evidence is uncovered, leading to updated guidelines and a subsequent need to update practitioner knowledge. Even the priorities of *what* pharmacists need to know about PGx has changed dramatically in the last decade, with an update from AACP in their PGx competencies published since the education program described in this thesis was launched (Gammal et al., 2022, in press). The primary focus within these guidelines has shifted from a basic understanding of genetic and pharmacogenetic concepts identified in **Figure 3.1**, to more specific knowledge such as "translating genotype to phenotype to drug therapy recommendation" and "distinguish[ing] between actionable and non-actionable pharmacogenomic test results using high-quality, evidence-based PGx databases and guidelines." As competencies are updated, pharmacists' knowledge will also require maintenance, updates, and refreshers. The course created within this thesis created a model that can be adapted, updated, and upscaled. The course also identified that it was suitable for self-directed learning, as these participants improved similarly to their live-course counterparts. Therefore, an evidence-based framework for supporting the common PGx implementation barrier of limited knowledge is overcome through a comprehensive education program.

5.2.3 Implementation of PGx in community pharmacy practice

While PGx implementation in the United States has increased steadily over the last decade, Canada has lagged in research and adoption of PGx. This study adds to both the body of implementation literature supporting the feasibility of PGx in community pharmacy and to real-world clinical practice in Canada in supporting PGx adoption at study sites. It should also be noted that no study previously had utilized this specific inclusion criteria, which leveraged the literature available to target patients with clinically important and actionable PGx test results. This resulted in an average of 1.1 DGIs identified per patient, among 24 participants with PGx test results returned at time of writing. A total of 46 patients among 8 pharmacies have received pharmacogenomic testing to date in this pilot. This impacts not only these patients, but also their entire healthcare team through exposure to PGx knowledge and information, as to date 15 of these participants have had care-plans with PGx information communicated to their primary care physician (with patient consent). For pharmacists, this also had a positive impact in the feasibility of the provision of PGx testing ongoing, as anecdotally study site pharmacists have indicated in team meetings that they find the process more seamless and easier with each case. This research is ongoing and is expected to provide further information regarding the patient populations most likely to benefit from PGx services in Alberta based on subgroup analyses, as well as physician acceptance of recommendations.

While both education and implementation have been studied in other jurisdictions, no prior research had occurred to date in Alberta wherein pharmacists carry one of the widest scopes of practice in the world, which includes the ability to independently prescribe. Pharmacist prescribing could be considered useful in acting on PGx test results at the point of care, as the scoping review had identified that a delay in therapy changes by prescribers following pharmacist recommendation limited the impact of PGx testing on short-term patient outcomes. No instances of pharmacist prescribing have been identified in the limited care-plan data collected to date. It is anticipated by study completion that some pharmacists will prescribe in response to PGx results in collaboration with the patient and primary care provider, and these

results will provide information towards the circumstances in which pharmacist prescribing in PGx implementation is beneficial.

Lastly, this research occurred in a largely rural population, wherein there is limited PGx based research to date. Overall, implementation in these areas serves to ensure equivalent access to advancements in healthcare such as PGx testing, improves patient, pharmacist, and other healthcare provider awareness of the availability of PGx testing, and advances the use of PGx within Canada.

5.2 Limitations

While this thesis makes breakthroughs in PGx implementation, it carries limitations which can be considered in conducting future PGx research in Canada. First, while the literature review identified use of PGx in pharmacy practice, there are examples of PGx implementation that while they do not explicitly leverage the unique knowledge and strengths of pharmacists, could still provide valuable information regarding potential patient populations to target. Therefore, it is possible to execute a more thorough search specifically for clinically meaningful outcomes to patients regardless of care provider in the context of PGx utilization. This knowledge can also add to pharmacists' understanding of PGx as the course provided in the context of this study will need continual updates with new PGx knowledge to stay current. Even since the presentation of the information to course participants in the Summer of 2021, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has updated their guidelines on a number of DGIs including those for clopidogrel[17] and statins.[18] The evaluation of the course described was also limited in that it did not re-evaluate participant knowledge directly months after course participation, thus providing no information on long-term knowledge retention. However, it could be considered that the course was indirectly assessed by the pharmacists who later took the next step towards learning in implementation. However even this assessment of knowledge within the implementation pilot is limited. While it is assumed that the pharmacists applying PGx understood the concepts demonstrated by their implementation in practice, we were not provided ethics approval to survey the pharmacists in addition to the other study

aims. Such gaps could be accomplished in the future with a specific research study recruiting community pharmacists implementing PGx to measure their current understanding of PGx concepts. Lastly, a limitation of the education study design is it did not have a control group comparator (i.e. a group that did not receive any education). A control group would enhance robustness of the comparison between synchronous and asynchronous subgroups and give greater strength to the finding that there was no difference in change in knowledge between these.

This research also took place at an interesting time in which the world was in a pandemic caused by a coronavirus disease (COVID-19). This limited the ability of our team to recruit pharmacies as study sites due to stated workload concerns and prevented the education course from being held live. However, the latter case became a strength as the course was adapted for delivery live online and asynchronously. This allowed those who would have had to travel for attendance attend from their home, and those who could not attend due to scheduling to still complete the course and participate in the research in their own time. It also gave our project the ability to assess the comparative efficacy of these two different learning methods and ultimately find that asynchronous learning was equally effective to live for this course.

5.3 Future directions

This research forms a foundation for further studies on pharmacogenomics implementation in pharmacy practices and in Alberta. First the scoping review search and data collection strategy can be replicated as more literature becomes available. This research will continue to provide a foundation for PGx research in identifying populations with the most DGI and clinical benefit in PGx to inform implementation strategies and study designs. Such implementation studies can also be enhanced with PGx education programs similar to that created and used in this thesis. These education programs can be scaled up and used both to provide education to a greater number of pharmacists, adapted to other health professions, and evaluated more rigorously with control groups and long-term knowledge data collection. This would not only benefit implementation by improving healthcare provider knowledge, but it would benefit

continuing medical education understandings as well in providing more data on synchronous vs. asynchronous learning. Lastly, as the implementation pilot is still in progress, research directions with this project will be more directed towards policy and procedural requirements including the perspectives of pharmacists, policy-makers, stakeholders, and most importantly, patients, in where and how pharmacogenomics would be best implemented. Furthermore, as this research does not collect outcomes data such as patient adverse events or costs, these would need to be evaluated, preferably in a randomized-controlled trial design, to provide further information on feasibility and clinical utility of PGx in the community pharmacy.

5.4 Conclusion

PGx implementation by pharmacists in Canada is limited to date. To fill this gap, a scoping review was conducted and identified feasible and clinically useful opportunities for PGx implementation in cardiology, psychiatry, pain, and polypharmacy patients. It also provided a framework to facilitate adoption that includes pharmacist education and collaboration with other healthcare providers. This knowledge was leveraged in creating a course for practicing pharmacists that improved subjectively rated and objectively tested knowledge of pharmacists regarding PGx concepts. Some of these pharmacists proceeded to implement PGx into their community pharmacy practices. They were able to identify patients suitable for testing, provide testing, interpret results, and communicate results with patients and primary care providers in formulating care-plans using PGx information. Thus, the foundation for future PGx adoption into mainstream clinical pharmacy practice is laid through evidence review, education, and piloted implementation.

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Appendices

Appendix A: University of Alberta Ethics Approval (Education Study)

[redacted]

Ethics Application has been Approved

ID:	Pro00108818
Title:	Training Community Pharmacists on Pharmacogenomics
Study Investigator:	Dalia El Sayed
	This is to inform you that the above study has been approved.
Description:	Click on the link(s) above to navigate to the workspace.
	Please do not reply to this message. This is a system-generated email that cannot receive replies.

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Appendix B: University of Alberta Ethics Approval (Implementation Pilot)

[redacted]

Ethics Application has been Approved

ID:	Pro00112442
Title:	Pharmacogenomics in the Community Pharmacy Setting
Study Investigator:	Dalia El Sayed
	This is to inform you that the above study has been approved.
Description:	Click on the link(s) above to navigate to the workspace.
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Appendix C: Supplementary Materials for Chapter 3 (Education Study)

The efficacy of a didactic and case- based pharmacogenomics education program on improving the knowledge and confidence of Alberta pharmacists

Supplementary Materials

Contents

Supplementary Materials 3.1

Survey

Education of Pharmacists in Pharmacogenomics: Pre- and Post-Education Evaluation

Survey Information/Implied Consent

Study Title: Evaluation of the Effectiveness of a Didactic and Case-Based Education Program on Pharmacist Knowledge and Comfort in Pharmacogenomics

Principle Investigator (PI):

Dalia A. Hamdy, RPh (ACP), PhD, MBA

Clinical Assistant Professor, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

[contact information masked]

Co-PI:

Dr. Sherif Hanafy Mahmoud

Clinical Associate Professor, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

[contact information masked]

Co-Investigators:

Mrs. Meagan Hayashi

MSc. Student, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

[contact information masked]

Invitation to Participate: You are invited to participate in a web-based online survey regarding your knowledge in pharmacogenomics and its application in community practice. You will be asked to complete 2 surveys: one before and one after the educational program.

Pharmacogenomics is defined as the utilization of individual genetic variation in DNA to predict drug safety and response. Pharmacists are medication experts who routinely examine patient medication profiles for drug interactions, therapeutic duplications, dose adjustments, appropriateness of therapy management. Personalization of therapy based on the patient's genetic profile utilizing pharmacogenetic testing is a future mechanism that may help increase medication effectiveness, and reduce time and money wasted for patients and the health care system.
Despite how the idea of the pharmacogenomics sound applicable and feasible, there remains few challenges that healthcare system needs to tackle in order to be able to implement such practice into action. They include: a. knowledge barriers such as healthcare professionals' education and patient education, b. insurance and payer coverage and c. access to testing. Community pharmacists are in a position to facilitate access to testing and patient education as well as assist other health care professionals.

Purpose of the study: Our proposed research aims to educate pharmacists on the principles of pharmacogenomics, and evaluate

the effectiveness of this education program on pharmacist knowledge and comfort in pharmacogenomic principles

Participation: Your participation in this survey is voluntary, however, it is going to help us assess the learning outcomes of the educational course you are attending. You may refuse to take part in the research or exit the survey at any time without penalty. You are free to decline to answer any question you do not wish to answer for any reason. If you want to participate in the study, please complete the survey. It should take approximately 15 minutes to complete the survey.

Once you have completed the survey, please click the "submit" button

Benefits: You will receive no direct benefits from participating in this research study other than the exposure to new PGX knowledge and practice in addition to increasing your confidence during PGX patient counselling. However, the results from this study will be shared with you following data analysis, via the platform from which you were recruited.

Risks: There are no foreseeable risks involved in participating in this study other than those encountered in day-to-day life.

Confidentiality and Anonymity: Your survey answers data will be stored in REDCap, a secure password protected database hosted at the University of Alberta. The survey will not collect identifying information such as your name, email address, or IP address. Therefore, your responses will remain anonymous. No one will be able to identify you or your answers, and no one will know if you participated in the study. The information that you will share will remain strictly confidential and will be used solely for the purposes of this research. The only people who will have access to the research data are the research team members mentioned above. Additionally, the Research Ethics Board (REB) and The University of Alberta Auditors may also have access to the data. In order to minimize the risk of security breaches and to help ensure your confidentiality we recommend that you use standard safety measures such as signing out of your account, closing your browser and locking your screen or device when you are no longer using them/ when you have completed the study. Results will be published in pooled (aggregate) format. Anonymity is guaranteed since you are not being asked to provide your name or any personal information.

In order to link the pre- and post- survey data, we kindly ask you to provide a unique code at the start of the survey (by utilizing the last three letters of the participant's mother's maiden names and the two digits of your birth day e.g. ITH23) which by no means will identify you as a participant.

Data Storage: Your survey answers data will be stored in REDCap, a secure password-protected database hosted at the University of Alberta. The data will be stored for a minimum of 5 years.

Voluntary Participation: You are under no obligation to participate and if you choose to participate, you may refuse to answer questions that you do not want to answer. Should you choose to withdraw midway through the electronic survey simply close the link. This will not remove your results from the database: to do so you must email the Principal Investigator at the contact information provided in this consent page, and provide your identifying code to remove your results. Once the identifiers are removed it will no longer be possible to withdraw the data from the study.

Information about the Study Results: Given the anonymous nature of the survey, research findings will not available to the participants. However, we intend to publish the research findings in a peer reviewed journal

CONTACT lnformation:lf you have questions at any time about the study or the procedures, you may contact the research team members: Dr. Dalia A. Hamdy at [masked] or Dr. Sherif Mahmoud at [masked]

The plan for this study has been reviewed by a Research Ethics Board at the University of Alberta. If you have any questions regarding your rights as a research participant or how the research is being conducted, you may contact the Research Ethics Office at 780-492-2615.

Please print a copy of this form for your records.

ELECTRONIC CONSENT:

By proceeding with the survey, you are providing consent to the researchers and allowing your results to be used in the study as described above.

Please proceed to the next page to begin the survey.

An electronic survey form will be created in REDCAP (Pre and Post survey questions are the same)

Evaluation of the Effectiveness of a Didactic and Case-Based Education Program on Pharmacist Knowledge and Comfort in Pharmacogenomics

Principal Investigator: Dr. Dalia ElSayed **Co-Principal Investigator:** Dr. Sherif Hanafy Mahmoud

[implied consent text, per approved document]

Please proceed to the next page to begin the survey.

Please provide us with some information about yourself.

1. Please provide the last three letters of your mother's maiden name, and the day of the month you were born, for anonymized coding purposes. (i.e. if these answers Smith & January 24th you would enter ITH24) _____
2. Please indicate if you are completing this survey prior to or after the education program portion of this study: Pre-education survey____ Post-education survey_____
3. Please indicate if you attended the pharmacogenomics education program portion of this study synchronously (attended both live sessions), asynchronously (viewed both recorded sessions), or mixed (one live session and one recorded session). Full Synchronous_____ Full Asynchronous____ Mixed_____ [post-course survey only]

[questions 4-11: pre-course survey only]

4. **What gender do you identify as? Male _____ Female _____ Other_____ prefer not to say ____**
5. **What year were you born? _____**
6. **What year did you graduate with your first pharmacy degree? _____**
7. **In which country did you obtain your first pharmacy degree?**
   Canada _____ USA _____ Other, please specify: _____
8. **What degrees or certifications do you currently hold? (check all that apply)**
   Diploma _____ BSc. ____ PharmD ____ Residency _____ PhD _____ MBA _____MSc_____
9. **How many years have you been practicing pharmacy?**

Less than 2 years _____ 2-5 years _____ 6-10 years _____ Over 10 years _____

10. **What pharmacy/healthcare setting have you worked in throughout your career? (Check all that apply)**

    Community____ Hospital____ Primary Care Network____ Research____ Industry____ Other, please specify ____

11. **What authorizations or credentials do you currently have? (check all that apply)**

    Additional prescribing authorization _____ Certification to administer injections _____ Certified Diabetes Educator _____ Board Certified Ambulatory Care Pharmacist _____ other, please specify ____

Pharmacogenomics is the utilization of individual genetic variation in DNA to predict drug safety and response. The genetic variants could be on the drug metabolizing enzyme, transporter and/or receptor levels. The aim of pharmacogenomic testing is to provide tailored medication therapy, such as drug choice and dose, based on the individual's genetic variants to provide optimal therapy outcomes.

Please respond to the following statements with Yes or No [pre-course survey only]

STATEMENT	**Yes**	**No**
I received education on the topic of pharmacogenomics during my pharmacy degree program		
I received education on the topic of pharmacogenomics during post-graduate studies and/or while completing continuing education activities.		
I have experience with pharmacogenomic testing.		

Please respond to the following statements with Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree.

STATEMENT	STRONGLY AGREE	AGREE	NEUTRAL	DISAGREE	STRONGLY DISAGREE	NOT APPLICABLE
Pharmacogenomics can enhance the provision of medication-related services (e.g., dispensing, medication reviews)						
Pharmacogenomics testing is cost effective.						
I am comfortable identifying patients who may benefit from pharmacogenomic testing.						
I am comfortable answering patient questions regarding pharmacogenomics testing.						
I am comfortable educating patients on the risks and benefits of pharmacogenomics testing.						
I am comfortable explaining ethical and legal considerations to patients in the process of informed consent for pharmacogenomics testing.						
I am comfortable interpreting a genotype in a pharmacogenetic test result into a phenotype.						
I am familiar with the evidence-based resources and websites available for pharmacogenomics.						
I am comfortable educating patients on their pharmacogenetic test results.						
I am comfortable explaining pharmacogenetic test results to other healthcare providers.						

I am comfortable applying the results from pharmacogenomic testing when making drug therapy decisions (e.g., selecting medication, dosing, monitoring).						

The following skill testing questions are designed to assess your knowledge of pharmacogenomics prior to and after receiving pharmacogenomics education as part of this study**.**

Please answer the following questions to the best of your current knowledge. using the response "I don't know" when applicable.

1) Which pharmacogene is most relevant to antiplatelet selection? (drop down list)

- *CYP1A2*
- *CYP2C9*
- *CYP2C19*
- *CYP2D6*
- *COMT*
- I don't know

2) If a patient provides you with a result for a *CYP2D6* test, and is asking you to provide their physician with a recommendation for treatment of depression, which online resource would you find most useful in interpreting their phenotype (metabolism status)?

- Lexicomp
- eCPS
- PharmGKB.org
- PharmacyGenes.org
- Therapeutic Handbook of Psychotropic Drugs
- I don't know

3) Which of the following would be considered the MOST correct definition of incidental findings in the context of pharmacogenomic testing?

    - Coincidental identification of a drug-gene interaction that was not the focus of the test ordered (e.g. *CYP2C19* testing for antiplatelet selection that also shows patient is at higher risk of side effects from their current antidepressant)
    - Identification of polymorphisms that indicate a different risk of an inheritable disease (e.g. *CACNA1S* testing to determine the risk of malignant hyperthermia with volatile anesthetics and succinylcholine that also reveals genetic risk for the development of hypokalemic periodic paralysis, an inheritable and sometimes debilitating disease)
    - Finding a drug-gene interaction for which there is no current drug-related problem (e.g. panel testing shows ultrarapid metabolism of PPIs via *CYP2C19*, however the patient feels GERD is well controlled at current low dosage).

- A pharmacogenomic test ordered and completed in error with identified drug-gene interactions found
- I don't know

4) Pharmacogenetic testing for VKORC1 looks at a change in drug effect at the level of:

- Pharmacokinetics
- **Pharmacodynamics**
- Off-target effect
- Drug-drug interaction
- Drug-environment interaction
- I don't know

5) HLA-B genotyping in patients with Chinese ancestry is suggested in the FDA guidelines for which antiepileptic drugs? (check all that apply)

- Phenytoin
- Valproic acid
- Lamotrigine
- Carbamazepine
- I don't know

5) Which therapeutic classes have known drug-gene interactions, with therapy modification recommendations available through a clinical guideline? (check all that apply)

- SSRIs
- Opioids
- Stimulants
- Statins
- Anticoagulants
- I don't know

7) Which of the following cannot be done <u>without the patient's consent</u> regarding the sharing of pharmacogenetic test results?

i) Sharing results with a life insurance company for policy underwriting
ii) Sharing results with a related patient who may carry the same gene
iii) Sharing results with the patient's employer

- i only
- iii only
- i and ii
- ii and iii
- i, ii, and iii
- I don't know

Supplementary Materials 3.2

Pharmacogenomics for Alberta Pharmacists – Course Outline

Table S3.2.1. Outline of Pharmacogenomics for Alberta Pharmacists, Didactic Component. Within the live course, cases were introduced, discussed, and unfolded between almost every session.

Session Number	Session Title
1	Genetics 101
2	Introduction to Pharmacogenomics
3	Applications of Pharmacogenomics in Cardiovascular Medicine
4	Pharmacogenomics and the Patient Care Process
5	Essential Resources in Pharmacogenomics
6	Applications of Pharmacogenomics in Psychiatry
7	Applications of Pharmacogenomics in Pain Management
8	Ethical, Legal, and Social Considerations within Pharmacogenomic Testing
9	Practical Implementation of Pharmacogenomics in the Pharmacy
10	Applications of Pharmacogenomics in Oncology
11	Pharmacogenomics Expanded

Table S3.2.2. Outline of Pharmacogenomics for Alberta Pharmacists, Case Study Component. Full class in the live session consisted of 10-15 pharmacists, and small groups 3-5 pharmacists. Asynchronous participants received cases as a word document with all questions presented in live sessions (including each question presented to all small groups) and space to provide a response, with answer keys to each question on the following page. In all cases and methods of participation, pharmacists were encouraged to utilize resources and knowledge gained through the course to answer the questions to the best of their ability prior to reviewing answers.

Case Number	**Case Focus**	**Description of Live Course Activity**
1	Cardiovascular PGx	Full class discussion in introduction prior to session 1, in application of pharmacogenomics to this case after session 2, and in formulating care-plan after session 3.
2	Psychiatric PGx	Full class discussion in introduction prior to session 4, small group breakout room simulation with facilitator after session 5 to practice using resources, and full class discussion to discuss findings of each group after session 6.
3	Pain PGx	Full class discussion in introduction prior to session 7, small group breakout room simulation with facilitator after session 7 to discuss therapeutic alternatives, followed by full class discussion to review findings of each group.
4	ELSI of PGx	Full class discussion in introduction prior to session 8, small group breakout room discussion with facilitator after session 9 to discuss specific ELSI question assigned, followed by full group discussion to review responses of each group.
5	Oncology PGx	Full class discussion in introduction prior to session 10, and full class discussion in case unfolding after session 10.
6	Polypharmacy PGx	Full class discussion throughout case presentation as each new problem developed.

Supplementary Materials 3.3

Pharmacogenomics for Alberta Pharmacists – Case Study Example

Pharmacogenomics for Alberta Pharmacists

Case Study #1 – Art Terry (Cardiovascular PGx)

Instructions:

Use resources and knowledge gained throughout the course, in addition to standard pharmacy resources, to answer the questions in the space provided. Once satisfied with your response, you may proceed to the next page in the case study to compare your response to answers provided by the course facilitators and gain additional information to help you with the case as it progresses.

We welcome any questions or comments about these cases. Please forward these to [masked].

Thank You!

The Research Team

Case 1 -Art Terry:

Meet Art:

- 52-year-old married male truck driver
- Previous history of P.Oorly controlled hypertension
  - Last pharmacy visit BP 168/92 mmHg
  - Was taking Losartan 100mg po daily, started amlodipine 5mg dail after BP reading above
- No other previously diagnosed medical conditions or medications

Introduction

Case 1 -Art Terry: Introduction

One day, Art develops chest pain on a hike. After descending it is not resolved and he goes to the emergency department.

Art is diagnosed with an NSTEMI, and transferred to cardiology for percutaneous intervention with stent placement.

Art has an uncomplicated short-stay in the cardiology unit and is discharged from hospital the next day.

Case 1 – Art Terry: Introduction

Art's discharge Rx:

- Losartan 100mg po daily
- Amlodipine 10mg po daily
- Metoprolol 25mg po BID
- ASA 81mg po daily
- Clopidogrel 75mg po daily
- Atorvastatin 80mg po daily

[redacted]

You are the pharmacist assessing Art's medications prior to or after discharge. What other information do you need in your assessment of Art's medications?

(Proceed to next page for answers)

You are the pharmacist assessing Art's medications prior to or after discharge. What other information do you need in your assessment of Art's medications?

KEY

- Family history – Art's father had a fatal myocardial infarction at age 47. No other relevant history.
- Other medication history – originally had tried ramipril for hypertension but switched to losartan due to cough (resolved with switch)
- Lifestyle – Art smokes a ½ pack per day for the last 20 years, and is a casual social drinker
- Weight - 5'11", 210lbs, BMI 29.3kg/m^2
- Vital signs – BP 138/88mmHg, HR 53bpm
- Goals of treatments – wife wants to do a big multi-day hike and he wants to make her happy. Also, he wants to be around for his now adult children and future grandchildren, as he is sad he did not have his dad around
- Laboratory tests – Creatinine 87umol/L, liver function tests all within normal limits, lipids HDL 0.8 mmol/L, LDL 4.62 mmol/L, TC 6.20 mmol/L, TG: 1.6mmol/L, electrolytes all within normal limits
- Adherence – excellent, uses dosette even prior to this hospitalization. That is why he was frustrated about his poor blood pressure control
- Over-the-counter use: none
- Stent type: drug eluting stent (paclitaxel)

Case 1 – Art Terry: Follow-Up

Art returns to the pharmacy 1 month after his NSTEMI.

He says his legs hurt so bad he can hardly walk. He is worried it will affect his cardiac rehab and ability to do hikes with his wife, including a dream trip on the Camino de Santiago.

In desperation to find out if it could be due to his medications, he found a pharmacogenetic test to take, and is hoping you can help him understand and utilize it.

Case 1 – Art Terry: Follow-Up

Consider…

What proteins (metabolizing enzymes, transporters, receptors/drug targets) are involved in Art's response to his current medications?

Art's discharge Rx:

- Losartan 100mg po daily
- Amlodipine 10mg po daily
- Metoprolol 25mg po BID
- ASA 81mg po daily
- Clopidogrel 75mg po daily
- Atorvastatin 80mg po daily

What proteins (metabolizing enzymes, transporters, receptors/drug targets) are involved in Art's response to his current medications?

(Proceed to next page for answers)

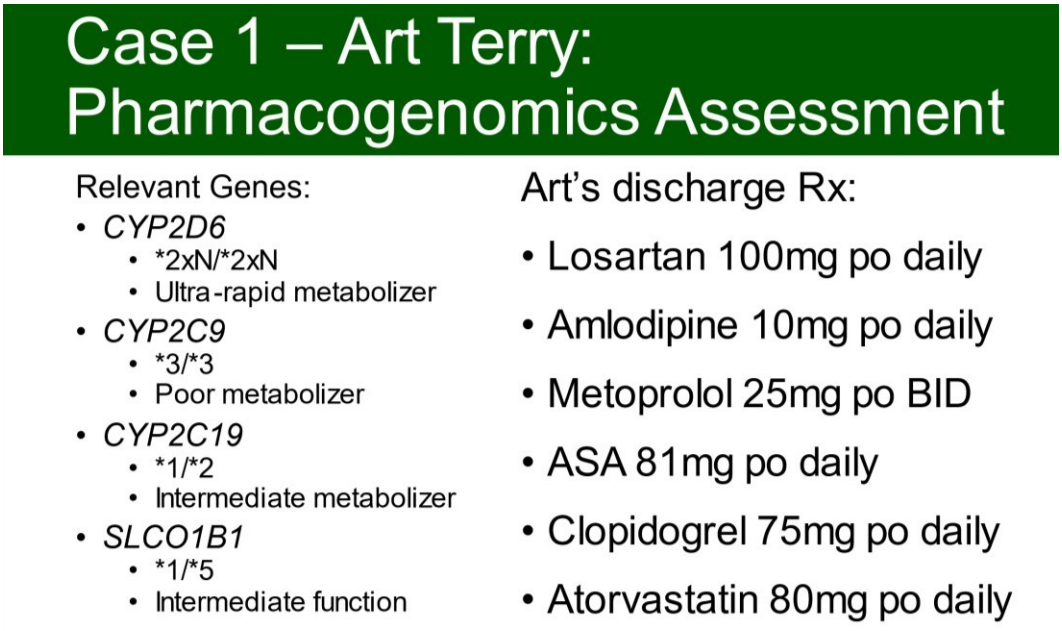
What proteins (metabolizing enzymes, transporters, receptors/drug targets) are involved in Art's response to his current medications?

KEY

- Losartan is metabolized by CYP3A4 and 2C9 into a more potent metabolite
- Losartan acts on the AT_1 receptor to enact its effect
- Amlodipine is metabolized by CYP3A4
- Amlodipine acts on calcium channels in vascular smooth muscle
- Metoprolol is metabolized by CYP2D6 for clearance
- Metoprolol acts on beta-1 receptors in the heart
- ASA covalently binds to COX-1 and COX-2 enzymes
- ASA's metabolite, salicylate (active), is conjugated by saturable UGT enzymes
- Clopidogrel's absorption from the intestine is facilitated by p-glycoprotein
- Clopidogrel is a prodrug activated mainly by CYP2C19
- Clopidogrel acts on $P2Y_{12}$ receptor on platelets
- Atorvastatin is transported by OATP 1B1 (encoded by SLCO1B1)
- Atorvastatin is metabolized by CYP3A4
- Atorvastatin inhibits HMG-CoA reductase enzyme

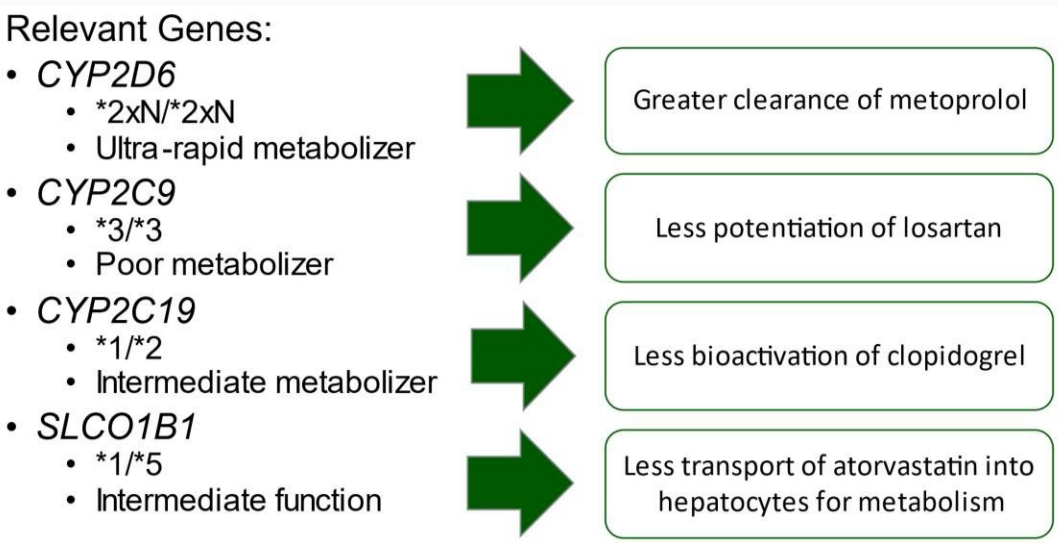
While Art's medications interact with all of these different proteins, we do not necessarily have the capacity to test all of these genes, or the evidence to provide therapy recommendations based on those results we can obtain.

Additionally, it is important to consider non-drug differential in the cause of Art's symptoms. For this case, the patient's physician has ruled out non-drug causes to his myopathy.



What do these test results (and phenotypes) mean for Art's current medications?

(Proceed to next page for answers)



Knowing the drug-gene interactions present, list some drug and nondrug alternatives for management of hypertension and coronary artery disease.

Metoprolol	
Losartan	
Clopidogrel	
Atorvastatin	

(Proceed to next page for answers)

Knowing the drug-gene interactions present, list some drug and nondrug alternatives for management of hypertension and coronary artery disease.

KEY

Metoprolol: The Royal Dutch Pharmacists Association November 2018 guidelines: "For CYP2D6 ultra metabolizers, use the maximum dose for the relevant indication as a target dose, and if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative drug." Considering current heart rate (53 BPM) however, no medication changes are recommended at this time. Suggest home BP/HR monitoring, target HR <110bpm. See BP management below.

Losartan: As blood pressure is currently adequately controlled, could consider maintaining current therapy. If the patient is concerned about pill burden (i.e. is amlodipine necessary if a more potent ARB can be used for this patient?) could consider transitioning to another ARB not affected by known genetics; there are no current dosing guidelines for losartan with pharmacogenomic test results on PharmGKB. If changes in medications, create a monitoring plan with positive and negative parameters with the patient. Blood pressure monitoring as noted above is advisable, to a target <140/<90mmHg and an avoidance of side-effects such as symptomatic hypotension. Encourage lifestyle changes (patient already physically active, advise DASH diet, smoking cessation).

Clopidogrel: The Clinical Pharmacogenetics Implementation Consortium 2013 guidelines advise use of alternative antiplatelet therapy (prasugrel or ticagrelor) due to the increased risk of adverse cardiovascular outcomes (moderate level of evidence). Consider other factors such as drug coverage and cost in this decision, especially given intermediate-metabolism status (evidence is stronger for poor-metabolizers). (Scott SA, et al. Clin Pharmacol Ther. 2013 Sep;94(3):317-23.) General cardiovascular risk reduction measures also advisable as noted above.

Atorvastatin: First, it would be reasonable to consider if the patient is consuming grapefruit juice, which can increase the risk of myopathies. He did in fact start drinking grapefruit juice in the last month, forgetting the education to avoid. The Royal Dutch Pharmacists Association August 2020 Guidelines: “The risk of myopathy can be elevated. The gene variation may lead to reduced atorvastatin transport to the liver, which may increase atorvastatin plasma concentrations.” This may explain this patient’s current adverse drug reaction.

Also from these guidelines: “Rosuvastatin and pravastatin are influenced to a similar extent by the SLCO1B1 gene variation but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.

Fluvastatin is not influenced significantly by the SLCO1B1 gene variation or CYP3A4 inhibitors.” Therefore, some options to consider would be changing to Fluvastatin, dose reduction in atorvastatin with avoidance of grapefruit, or changing therapy to rosuvastatin moderate intensity dose, with follow-up for resolution of myopathy. Other non-drug considerations would be adequate hydration on hikes, avoidance of alcohol (especially in excess) warning and counselling of the signs and symptoms of rhabdomyolysis, and cardiovascular risk reduction as above.

Appendix D: Supplementary Materials for Chapter 4 (Implementation Pilot)

Implementation of pharmacogenomics within community pharmacies in Alberta, Canada: An observational study

SUPPLEMENT

CONTENTS:

CASE EXAMPLES

CASE #1 – CYP2C19 and clopidogrel

CASE 1: Introduction

JM is a 50 year-old black male who presents to the community pharmacy for medication refills. He takes the following medications:

- Clopidogrel 75mg orally daily, for secondary prevention of stroke
- Pantoprazole 40mg orally daily for heartburn
- Atorvastatin 80mg orally daily for vascular protection in diabetes and prior stroke
- Metoprolol __ orally twice daily for hypertension
- Tramadol/acetaminophen 37.5/325mg 1-2 tablets orally every 6 hours as needed for pain
- Bupropion XL 300mg orally daily for depression
- Trazadone 25mg orally at bedtime for sleep
- Gabapentin 300mg orally three times daily for low back pain
- Insulin glargine 35 units subcutaneous daily for diabetes
- Amlodipine 10mg daily for hypertension
- Perindopril 8mg orally daily for hypertension/ vascular protection
- Furosemide 20mg orally daily for fluid retention
- Zopiclone 7.5mg orally at bedtime as needed for sleep if trazodone ineffective

The pharmacist refilling his prescriptions identifies that he may benefit from pharmacogenetic (PGx) testing due to his clopidogrel use. It is also noted that PGx testing may provide useful information in dosing and monitoring with his pantoprazole, atorvastatin, metoprolol, tramadol, and antidepressant therapies.

His most recent set of vitals are: ____

After an explanation of the risks and benefits of PGx testing, JM consents to and provides a buccal swab for analysis.

CASE 1: PGx Test Results

The following report was returned for JM:

REPORT SUMMARY

MEDICATIONS OF INTEREST OVERVIEW		
MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST
Clopidogrel (Plavix)	*CYP2C19*	Major – significant result that may require altering this medication
Pantoprazole (Tecta)	*CYP2C19*	Minor – result should be considered as may affect medication response
Atorvastatin (Lipitor)	*CYP3A4* *SLCO1B1*	Usual prescribing considerations apply
Metoprolol	*CYP2D6*	Usual prescribing considerations apply
Tramadol (component of Ipg-Tramadol/Acet)	*CYP2D6*	Usual prescribing considerations apply
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
valaciclovir (Valtrex), bupropion (Bupropion Hcl Xl), trazadone, gabapentin, lamotrigine (Lamogine), insulin / insulin (Humalog), amlodipine (Norvasc), indapamide / perindopril (Coversyl Plus LD 2.5mg/0.625mg Tablets), furosemide (Furosemide Tablets), zopiclone (Imovane), acetaminophen (component of Ipg-Tramadol/Acet)		

LEGEND: Major prescribing considerations Minor prescribing considerations Usual prescribing considerations

Detailed pharmacogenomic interpretation and recommendations are provided in the *medications of interest* section below.

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PREDICTED PHENOTYPE	GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP2D6	*1/*1	Normal metaboliser	*CYP3A4*	*1/*1	Normal metaboliser
CYP2C19	*2/*2	Poor metaboliser	*CYP3A5*	*1/*1	Normal metaboliser
CYP2C9	*1/*1	Normal metaboliser	*SLCO1B1*	*1/*1	Normal transporter function
VKORC1	AG	Moderately reduced VKORC1 enzyme level	*OPRM1*	AA	Higher opioid sensitivity
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)			

Detailed interpretations of genetic test results are provided in the *pharmacogenomic interpretation* section below.

In addition to the above report, the pharmacist identified that JM was a likely poor metabolizer phenotype for CYP2D6, due to the presence of strong inhibition of the enzyme by bupropion therapy.

Case 1: Care-Plan

Following receipt of JM's PGx results, the pharmacist met with the patient and identified the following drug therapy problems (DTPs):

1. **Secondary prevention of stroke and other adverse cardiovascular or cerebrovascular events:** Poor metabolizer of clopidogrel to active metabolite resulting in inadequate antiplatelet effect. No current adverse effects or inefficacy observed however this is considered a silent drug-gene interaction that may present as treatment failure later. Alternative antiplatelet therapy is indicated. Recommendation made to prescriber to change antiplatelet to ASA 81mg daily as no contraindications or history of treatment failure.

2. Heartburn: Poor metabolism of pantoprazole parent compound to inactive compound resulting in increased plasma concentrations of parent compound. No current adverse drug effects observed. Monitoring plan made with patient; reassess therapy if signs or symptoms of adverse drug effects (e.g. electrolyte imbalance, pneumonia, diarrhea) present.

3. **Pain:** Tramadol interaction with CYP2D6 inhibitor (bupropion) potentially decreasing conversion to active metabolite and decreased pain control. Patient currently reports adequate pain control. No changes advised, continue to monitor.

4. Hypertension: Metoprolol interaction with CYP2D6 inhibitor (bupropion) potentially decreasing conversion to inactive metabolite which may increase the antihypertensive and heart-rate effects. Blood pressure and heart rate are currently within target ranges. Continue to monitor and titrate therapy based on vital signs.

CASE #2 - CYP2D6 and atomoxetine

Case 2: Introduction

DB is a 31 year-old Caucasian male who met with the pharmacist for a comprehensive medication care plan. The pharmacist gathered the following medication history from him:

- Atomoxetine 40mg orally daily for attention deficit hyperactivity disorder (ADHD) and depression (off label)
    - The patients symptoms were not adequately controlled as he had difficulty focusing at work. He was not having any noted side effects to medication therapy.
    - Symptoms of depression were improving with current drug therapy under supervision of a psychiatrist
- Lemborexant 10mg orally at bedtime for sleep
    - No noted concerns

DB was concerned about increasing the dose of atomoxetine due to increased cost of therapy, and difficulty in determining if additional benefit would be seen at the higher dose. The pharmacist determined this would be an appropriate use of PGx testing – in order to determine the likelihood of treatment success with atomoxetine vs. switching to an alternative agent.

PGx testing would also be useful for initial therapy selection if DB wanted to trial an antidepressant for comorbid depression.

After an explanation of the risks and benefits of PGx testing, DB consents to and provides a buccal swab for analysis.

Case 2: PGx Test Results

The following report was returned for DB:

GENE	*CYP1A2*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*OPRM1*	*VKORC1*	*SLCO1B1*
Genotype	*1F/*1F	*1/*2	*1/*1	*2/*41	*1/*1	*1/*3	A/A	G/G	T/C
Phenotype	UM	IM	NM	NM	NM	IM	normal	normal	intermediate

PM: poor metabolizer; IM: intermediate metabolizer; NM: normal metabolizer; RM: rapid metabolizer; UM: ultrarapid metabolizer

Case 2: PGx Follow-Up to Care-Plan

1. Attention Deficit Hyperactivity Disorder: Patient is still symptomatic despite therapy with atomoxetine 40mg orally daily. No side-effects. Dose increase may be indicated. This patient's main barrier to a dose increase (prior to PGx testing) was the cost of therapy. Dose increase recommended based on CYP2D6 NM predicted phenotype and CPIC recommendations. Noted that if the patient knows there is some more evidence to support a dose increase, they may be able to make a more informed decision about cost vs benefit.

2. Depression: Symptoms improving with atomoxetine and psychotherapy. Normal metabolism of CYP2C19 and CYP2D6 allows use of any first-line selective-serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor if treatment desired in the future.

CASE #3 – CYP1A2 and CYP2D6 with duloxetine and bupropion

Case 3: Introduction

VW is a 41-year-old female who notes to her pharmacist that she is still feeling depressed despite adequate trials of her antidepressant therapy. For depression she is taking:

- Duloxetine 60mg orally daily
- Bupropion XL 150mg orally daily
- Quetiapine 50mg orally daily

She also takes:

- Trazodone 100mg orally daily for sleep

She does not indicate any side effects to current medication and denies symptoms of serotonin syndrome. She is a current smoker, which she is also hoping bupropion therapy will help.

VW and pharmacist agree that PGx testing may help determine next steps in antidepressant selection and titration.

After an explanation of the risks and benefits of PGx testing, DB consents to and provides a buccal swab for analysis.

Case 3: PGx Test Results

The following report was returned for VW:

MEDICATIONS OF INTEREST OVERVIEW		
MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST
Duloxetine (Cymbalta)	*CYP1A2* *CYP2D6*	Minor – result should be considered as may affect medication response
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
bupropion (Bupropion Hcl Xl), trazadone, quetiapine fumarate		

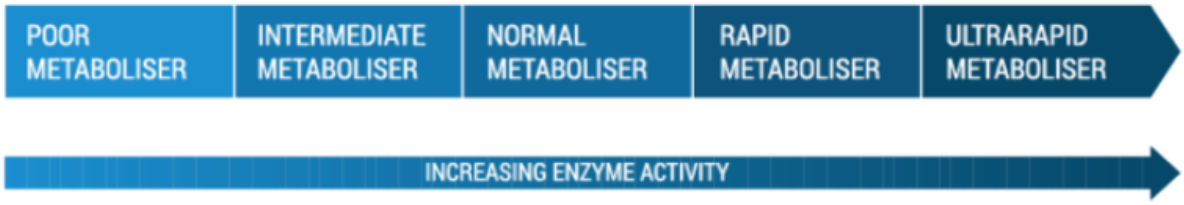
LEGEND: Major prescribing considerations Minor prescribing considerations Usual prescribing considerations

Detailed pharmacogenomic interpretation and recommendations are provided in the *medications of interest* section below.

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PREDICTED PHENOTYPE	GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP2D6	*2/*2	Normal metaboliser	*CYP3A4*	*1/*1	Normal metaboliser
CYP2C19	*1/*1	Normal metaboliser	*CYP3A5*	*3/*3	Poor metaboliser
CYP2C9	*1/*1	Normal metaboliser	*SLCO1B1*	*1/*1	Normal transporter function
VKORC1	GG	Normal VKORC1 enzyme level	*OPRM1*	AG	Intermediate opioid sensitivity
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)			

Detailed interpretations of genetic test results are provided in the *pharmacogenomic interpretation* section below.

The following diagram provides the range of enzyme activity predicted by the myDNA test.



In addition to the above report, the pharmacist identified that VW was a likely poor metabolizer phenotype for CYP2D6, due to the presence of strong inhibition of the enzyme by bupropion therapy. Patient is a smoker thus further increasing CYP1A2 metabolism

Case 3: Care-Plan

Following receipt of VW's PGx results, the pharmacist met with the patient and identified the following drug therapy problems (DTPs):

1. Depression: Patient was still not controlled despite multiple drug therapies at sufficient duration (3 months). Changes in therapy are required

1A: Dose increase indicated for bupropion – given no adverse drug effects, in absence of any relevant genotype data (*CYP2B6*) it is reasonable to trial dose increase to 300mg daily – recommended dose increase to prescriber

1B: unpredictable pharmacokinetics – rapid metabolism via CYP1A2 may render duloxetine ineffective at current dose of 60mg daily, however decreased metabolism via CYP2D6 inhibited by bupropion may increase the risk of side effects if dose is increased to 90mg daily. Alternative drug therapy with an antidepressant unaffected by these pathways (e.g. sertraline, as patient is NM for CYP2C19) may be appropriate – recommended change drug therapy to prescriber

2. Smoking cessation: bupropion dose increase recommended, as noted above.

CASE #4 – CYP2C19 and lansoprazole; history of multi-treatment failure in depression, patient education

Case 4: Introduction

MM is a 29 year old female who consults the pharmacist regarding her problem finding the right treatment for depression. She either experiences adverse drug effects or inefficacy and cannot land on the right medication. She has tried sertraline, which was stopped after 100mg daily for 4 weeks showed no effect, fluoxetine, which is showing no effect after 4 weeks on 20mg daily, and is hoping that pharmacogenomic testing may aid in selecting optimal drug therapy while presenting with a new prescription for augmentation with aripiprazole 5mg po daily.

She also takes:

- Lansoprazole 30mg po BID for GERD (once daily was ineffective)
- Salbutamol 2 puffs inhaled prn for exercise-induced asthma

After an explanation of the risks and benefits of PGx testing, MM consents to and provides a buccal swab for analysis.

Case 4: PGx Test Results

The following report was returned for MM:

GENE	*CYP1A2*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*	*CYP3A5*	*OPRM1*	*VKORC1*	*SLCO1B1*
Genotype	*1A/*1F	*1/*2	*1/*17	*1/*2	*1/*1	*3/*3	A/A	A/G	T/C
Phenotype	NM	IM	RM	NM	NM	PM	normal	intermediate	intermediate

PM: poor metabolizer; IM: intermediate metabolizer; NM: normal metabolizer; RM: rapid metabolizer; UM: ultrarapid metabolizer

By time of post-PGx education, MM had stopped aripiprazole due to adverse effects.

Case 4: Care-Plan

1) The patient discontinued aripiprazole before the results arrived due to AE/lack of effectiveness. Their results did predict poor CYP3A5 metabolism, which is a secondary metabolic pathway for this drug --> this could partially explain the appearance of AEs on a lower dose in the setting of CYP2D6 inhibition by fluoxetine. There was no clinical pharmacogenomic guidance from advisory bodies in regard to CYP3A5 poor metabolism this drug-gene interaction so metabolic theory was used to guide our recommendation along with clinical outcomes. If this medication is retried in combination with a strong CYP 2D6 inhibitor, a lower initial dose is recommended.

2) The patient has been chronically taking lansoprazole for GERD - therapy has been effective at BID doses. Pt is a predicted CYP2C19 rapid metabolizer, which provides some guidance as to why the patient would require BID dosing to relieve symptoms of GERD. CPIC recommends starting at standard daily

dosing, but that higher doses may be required for more serious conditions (H. pylori injection or erosive esophagitis). Given efficacy at higher dose in part due to rapid metabolism, continue current dosing. If lifestyle changes warrant trial discontinuation, a very slow taper is advised due to likely rebound GERD given shorter half-life for this patient.

3) The patient has failed numerous antidepressants in the past, especially when considering medications for pain control and depression/anxiety. The following information was presented to the patient/prescriber for their knowledge and to guide prescribing decisions moving forward: - previously failed sertraline --> pt is a CYP2C19 rapid metabolizer, which may help explain therapy failure - previously failed fluoxetine --> pt is a CYP2C19 rapid metabolizer, CYP3A5 poor metabolizer, CYP2C9 intermediate metabolizer, and CYP2C19 rapid metabolizer. All of these enzymes play a role in fluoxetine metabolism and may contribute to therapeutic failure. Given there may be other reasons for fluoxetine inefficacy, it is reasonable after sufficient cross-taper to trial another antidepressant metabolized by CYP2D6, such as paroxetine, or an antidepressant with multiple pathways of unaffected clearance, such as duloxetine. It is also of important consideration that the patient may have a rare genotype not tested for and therefore patient response must always be considered over genotype.

4) Given how common cardiovascular disease is in the general population, it is important this patient is aware of her *SLCO1B1* intermediate function status and CYP2C9 intermediate metabolism as these genotypes are relevant to statin therapies and may increase risk of myopathies with certain statins. Patient provided education to discuss these results if years later she develops an indication for a statin. Also discussed sharing these results with any prescriber to ensure optimal medication therapy based on predicted responses in addition to her own individual history and factors.

Informed Consent for Participants

[redacted]

Informed Consent for Participants

Study Title: Pharmacogenomics in the Community Pharmacy Setting: A Prospective Observational Study

Principal Investigator: Dr. Dalia El Sayed

Co-Principal Investigator: Dr. Sherif Hanafy Mahmoud

Co-Investigator: Meagan Hayashi

[redacted]

Why am I being asked to take part in this research study?
You are being asked to participate in this study because you are or may be prescribed one or more medications that can be affected by genes.

Our genes can affect how fast or slow some medications are removed from our bodies, and how sensitive we are to the effects of certain medications. These genetic differences are part of the reason why some medications do not work for some people, and why some people have side effects to a medication when others do not. The study of these differences is, and will be referred to in this document, as "pharmacogenomics", and the testing of these genes as "pharmacogenetic testing". Pharmacists may be able to use pharmacogenetic testing in addition to usual care to tailor medication therapy in a process known as "medication therapy management".

About 300 persons will be included in this study.

Study Procedures: What will happen in the study?
Your pharmacy provides pharmacogenomic testing from myDNA within their scope of practice. While the study provides funding for the pharmacogenomic test kit, the way the testing is done and what is done with the test results is decided by your pharmacist and myDNA, and not by the research team. The details of what will be done for pharmacogenomic testing is outlined in the myDNA Consent Form and Patient Information Sheet.

In this study, known as an "observational study," your pharmacist will collect information about you while they are providing this service. This occurs:

1) **Prior to or at the time of pharmacogenomic sample collection**
   What happens: your pharmacist may ask you questions or obtain information from your pharmacy care record.

   Data collected: age, gender, ethnicity, number of chronic medications, medication(s) identified for study inclusion, medication reason(s) for inclusion, other medications that may indicate testing not within inclusion criteria, pharmacist time spent on initial visit.

2) **When pharmacogenomic test results are available**
   What happens: your pharmacist receives information from the pharmacogenomic test company (myDNA) through a secure password-protected online portal. These results are known as your "genotype" to certain proteins (such as drug metabolizing enzymes) that determine how well they work (known as "phenotype").

When a person has a medication affected by a certain "phenotype," this is known as a "Drug-Gene Interaction" (DGI), and this information can be used to formulate a medication therapy care plan with the pharmacist, patient, and other healthcare providers.

The myDNA Medication Test tests for genes to *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5* (drug metabolizing enzymes, indicating how fast or slow drugs are cleared from your body), *OPRM1* (an opioid receptor, indicating sensitivity to opioids), *VKORC1* (indicating sensitivity to warfarin – a blood thinner), and *SLCO1B1* (indicating how fast or slow some medications such as statins and methotrexate are cleared from your body).

Data collected: genotype and phenotype from myDNA report, pharmacist phenotype assignment based on other patient factors, references used in pharmacist phenotype assignment, medications affected by each genotype, pharmacist time spent on test interpretation, test turnaround time.

3) **After the pharmacist and patient agree on a medication therapy care plan**

What happens: your pharmacist will meet with you in person to review your medications with your pharmacogenomic test results, as well as other information pharmacists use to assess medications such as health history, medication and lifestyle factors, and other laboratory tests. They will identify if there are possible drug-therapy problems and formulate a plan with you and your other healthcare providers. The specific recommendations or actions taken by your pharmacist are not determined by this study, but we will collect data on what you choose together. Your pharmacist will ask for your consent to share your health and drug-gene interaction information with your primary care provider.

Data collected: DGIs acted on (pharmacist recommend, prescribe, or form monitoring plan), described DGI, action taken on DGIs (prescribe, recommend, or no action), types of actions taken (discontinue medication, change medication to an alternative, start new medication, dose decrease, dose increase, monitoring without medication change, or no action), non-genetic medication recommendations (brief description), pharmacist time spent on developing care plan.

4) **At the close of study participation**

What happens: you will be asked to complete a survey about the service you received at your pharmacy through a secure and confidential website. There will be an additional electronic consent page at the beginning of this survey.

Data collected: Alberta Pharmacist's Association patient satisfaction survey.

5) **If the pharmacist receives a response on care plan recommendations from the patient's physician**

What happens: your physician or primary care provider may respond to pharmacy recommendations and prescribe medication changes. The specific actions by other healthcare providers are not determined by this study, but we will collect data on what the prescriber response is.

Data collected: physician response to each recommendation (genetic and non-genetic based). Can be a) fully accept; b) accept with modifications; c) reject with different change in therapy; or d) reject with no therapy changes.

What are the risks and discomforts?

The genes tested for within the myDNA medication test carry no known risk of unexpected or disease findings at this time. If we are made aware of new information, we will tell you about these findings. Additionally, you may feel concern or anxiety if you have a drug-gene interaction.

With any research study there may be risks that are not known at this time. If we find out anything new during the course of this research which may change your willingness to be in the study, we will tell you about these findings. No data collected in this study can reasonably be linked to you. Your pharmacist will advise you on the appropriate management of drug-gene interactions to the best of their ability, however you may also contact myDNA or the research team using the contact information provided on the applicable consent forms.

What are the benefits to me?

Taking part in this study will allow you to obtain pharmacogenetic testing at no cost to you (approximate value: $200). With pharmacogenomic testing, your medication therapies may be better informed by your genetic profile, potentially avoiding side-effects or non-effect.

Do I have to take part in the study?

Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the care or treatment that you are entitled to receive at your pharmacy. If you withdraw from the study, your information will not be sent to the research team for use in the study. Your doctor, pharmacist, the research team, or the Research Ethics Board, can stop you from taking part in the study at any time, even if you want to continue to be in the study, for their legitimate reasons.

Are there other choices to being in this study?

You do not have to join this study in order to receive care or pharmacogenomic testing (at cost) from your pharmacist. You will get the standard of care as offered by your pharmacy no matter what you decide. Your pharmacist can provide you with alternative means to receive pharmacogenetic testing without study participation, if you wish to receive this service outside of the study. Your participation in this study is entirely voluntary.

What will it cost to participate in this study? Will I be paid to participate in this study?

There will be no additional cost to you for taking part in this study outside of any costs of standard of care. You will not receive any payment for taking part in this study.

Study Withdrawal

If you change your mind after you have agreed to take part in the study, you can withdraw at any time without affecting your care and without penalty. If you withdraw from the study, we will not collect any more data, but we will keep the data that was already collected, unless you ask for it to be removed.

Privacy and Confidentiality

During this study, we will be collecting information (or "study data") about you. We will use the data to help answer research questions and we will share (or "disclose") your information with

others such as the study sponsor and other researchers in aggregate format that cannot reasonably be linked to you. Below we describe in more detail how your data will be collected, stored, used and disclosed.

What data will we be collecting?
During this study we will be collecting data about you. Examples of the types of data we may collect include where your pharmacy is located, your ethnic background, your age, your health conditions, medications, results of tests or procedures that you may have had, and the medication changes recommended or prescribed by your pharmacist. We will only look for and collect the information that we need do the research. We will get this information as collected and sent by the pharmacist to the research team.

How will the study data be stored?
The study data we collect will be securely stored by the study pharmacist during and after the study in your pharmacy care record. We will also put a copy of this consent form in your pharmacy record, so that doctors you see in the future will know you were in the study. All data collected within the context of this study will be anonymized, all electronic files containing study data will be password protected. De-identified data will be kept in a password protected encrypted memory stick and kept in a locked filing cabinet in the Principal Investigator's office. The research team will collect consent forms from study sites at regular intervals and will keep these forms in a locked filing cabinet and separate from the de-identified study data. Data will be kept for a minimum of 5 years. There are no current plans for reuse.

Storage of your DNA sample and pharmacogenomic test results is outlined in the myDNA consent documents. Please note the following, as found on these documents:

> "After the DNA sample is sequenced and interpreted, myDNA will deliver a personalised myDNA report to your chosen healthcare professionals and you will be notified by myDNA that your report is ready. Your pharmacist will contact you to come in for a consultation to review the results. When registering your test kit with the pharmacy you will set up your login credentials to access myDNA Explore, a secure online website, where you can access copies of your report and other useful myDNA resources…Your personal information and DNA sample will be retained for ten years to allow cost-effective resequencing in the future if new genetic testing or reporting is available. myDNA may perform additional testing at additional cost with your consent. After the ten years, all your personal information (including your DNA sample) will be destroyed in a secure way that ensures protection of your privacy. Your computerized genetic sequence information could be retained indefinitely for research purpose or myDNA program evaluation after the ten year retention period, but it cannot be linked back to you once your personal information is destroyed. During the ten year retention period, you can revoke your consent and request that all personal information held by myDNA be destroyed at any time. If you desire your myDNA genetic information after withdrawing your consent, a new myDNA test would need to be purchased. Your purchase of myDNA testing and advisory services is completely voluntary and is not necessary to continue to receive other pharmacy services."

You and your pharmacist may agree on additional or alternative storage methods at your discretion (e.g. your pharmacy care record).

How will the study data be used?

Your study data will be coded (with a number) and will not contain your name, address or anything else that could identify you (referred to as "de-identified"). Only your study pharmacy will be able to link your coded study data to you. Your coded study data will be sent to the research team for use in this study, and shared in aggregate (summarized) format with study sponsors (the Alberta Pharmacists' Association; RxA), institutions (the University of Alberta), regulatory agencies (Alberta Health, Health Canada, and/or the Government of Alberta), and published in a scientific journal. None of the information shared with these parties will be in a format that could be used to identify you. These parties may work with other parties located outside of Canada, in countries that do not have the same privacy laws as in Canada. However, because nothing that is sent to anyone outside of your pharmacy will contain your name or other identifying information, no one who uses this information in the future will be able to know it came from you. The risk to your privacy, then, is considered small.

Who will be able to look at my health data?
During research studies it is important that the data we get is accurate. Therefore, your study data and original medical records may also be looked at by people from: the study Sponsor, the University of Alberta auditors and members of the Research Ethics Board, Health Canada, and/or other regulatory authorities.

By signing this consent form, you are saying it is ok for the study pharmacist to collect, use and disclose information from your medical records and your study data in coded, de-identified format as described above.

Questions and Concerns
If you have any questions about the research now or later, or if you experience any adverse effects or think that you suffered a research related injury, please contact Dalia El Sayed a[redacted] or Sherif Hanafy Mahmoud at [redacted]. If you have any concerns about any part of this study, or questions about your rights as a research participant, you may call the Health Research Ethics Board [redacted] This office is independent of the study investigators.

Declarations
This study is made possible by the Alberta Pharmacists Association's Innovation Grant. You are entitled to request any details concerning this compensation from the Principal Investigator.

[redacted]

Written Consent

Title of Study: Implementation of Pharmacogenomics in Community Pharmacies in Alberta: Feasibility and Clinical Outcomes

Principal Investigator: Dr. Dalia El Sayed **Phone Number:** [redacted]

Co-Investigator: Dr. Sherif Hanafy Mahmoud **Phone Number:**

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	☐	☐

Who explained this study to you?

_____

I agree to take part in this study:

Signature of Research Participant

_____

(Printed Name)

_____

Date:_____

Signature of Pharmacist _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A SIGNED COPY GIVEN TO THE RESEARCH PARTICIPANT

Data Collection Tool

Pre-Test Research Data

Pharmacy Information

Pharmacy:	
Town/City:	
Means of Recruitment: (choose one)	□ Patient self-referral □ Pharmacist Identified □ Physician referral

Patient Demographics

Age (years):	
Biologic Sex: (choose one)	□Male □Female □Other □Prefer Not to Say
Ethnicity: (answer as per census)	

Relevant Medication History

Number of chronic medications:	
"Chronic Medication" is defined as a medication for which the patient has been or is anticipated to be taking for a period greater than 3 months (including new medications) **PPIs, tramadol, and codeine** can be considered for inclusion regardless of how medication is taken (acute or chronic, scheduled or as-needed)	

Other medication(s) or conditions that may indicate testing per pharmacist assessment: (check all that apply)	□ Family history of poor drug effects □ General history of poor medication response □ Other (please specify)
Ensure eligible for inclusion:	• eGFR is 30ml/min or greater • no moderate or severe liver disease present (defined as Child-Pugh class B or C) • participant is appropriate for PGx testing per clinical pharmacist • no current respiratory illness present • able to provide buccal sample

Approximate pharmacist time spent on initial visit, including consent process:

_____minutes

☐ **Informed consent is documented**

Medications identified for study inclusion:			
□Clopidogrel • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • Any active clopidogrel prescription	□Warfarin • Planning to start	□Simvastatin • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Atorvastatin • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects
□Atomoxetine • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□PPI _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Tramadol • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Codeine • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects
□Antidepressant 1 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Antidepressant 2 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Antidepressant 3 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Antidepressant 4 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects
□Antipsychotic 1 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects	□Antipsychotic 2 _____ • New (within 28 days initial Rx) • Planning to start medication • Inefficacy • Side effects • History of inefficacy/side effects		

Pharmacogenetic Test Results and Assessment

Gene	Allele 1	Allele 2	myDNA phenotype assignment	Pharmacist phenotype assignment (including phenoconversion)	Information used in pharmacist phenotyping (references, interactions)	All patient medications affected by results (regardless of phenotype or therapy problem(s))
CYP1A2			UM / NM / indeterminate	UM / NM / indeterminate		
CYP2C9			NM / High-IM / IM / PM / indeterminate	NM / High-IM / IM / PM / indeterminate		
CYP2C19			UM / RM/ NM / High-IM IM / PM / indeterminate	UM / RM/ NM / High-IM IM / PM / indeterminate		
CYP2D6			UM / NM / low-normal / IM / PM / indeterminate	UM / NM / low-normal / IM / PM / indeterminate		
CYP3A4			NM / IM / indeterminate	NM / IM / indeterminate		
CYP3A5			NM / IM / PM / indeterminate	NM / IM / PM / indeterminate		
OPRM1			High opioid sensitivity, intermediate opioid sensitivity, low opioid sensitivity	High opioid sensitivity, intermediate opioid sensitivity, low opioid sensitivity		
VKORC1			Normal vitamin K metabolism, moderately reduced vitamin K metabolism, significantly reduced vitamin K metabolism	Normal vitamin K metabolism, moderately reduced vitamin K metabolism, significantly reduced vitamin K metabolism		
SLCO1B1			Normal transport, intermediate transport, low transport	Normal transport, intermediate transport, low transport		

Abbreviations in assigning metabolism status of CYP genes: IM = intermediate metabolizer, NM = normal metabolizer PM = poor metabolizer, UM = ultra-rapid metabolizer.

Approximate pharmacist time spent on test interpretation: _____minutes

Test turnaround time (time from sample sent to results received): _____days

Patient Care Plan

Approximate pharmacist time spent on developing care plan with patient: _____minutes

Problem #	**Medication(s) affected**	**Indication(s) / condition**	**Gene(s) affected**	**Brief description of the problem (including other factors such as signs/symptoms, other labs, etc)**	**Action taken**	**Prescribing decision or recommendation made** (e.g.: increase dose, stop medication, change medication, monitoring, etc.)	**Physician response**
1			□CYP1A2 □CYP2C9 □CYP2C19 □CYP2D6 □CYP3A4 □VKORC1 □OPRM1 □SLCO1B1 □non-genetic recommendation	□Drug therapy required □Unnecessary drug therapy □Incorrect drug □Dose too low □Adverse drug reaction □Dose too high □Patient not taking as Rx'd □Monitoring indicated □Other: Interactions:	□Prescribe schedule 1 (APA) □Prescribe OTC/ schedule >1 □Recommendation to physician/prescriber □Monitoring plan made with patient □No action	□Discontinue medication □Change medication to an alternative □Start new medication □Dose decrease □Dose increase □Monitoring without medication change □No action	□Fully accept □Partial accept with revisions (e.g. change to suggested drug but not suggested dose) □Reject and provide

				□Drug-drug □Drug-gene			alternative change not suggested (e.g. change drug but to one not suggested) □Reject with no medication changes □No response □N/A
Problem #	**Medication(s) affected**	**Indication(s) / condition**	**Gene(s) affected**	**Brief description of the problem (including other factors such as signs/symptoms, other labs, etc)**	**Action taken**	**Prescribing decision or recommendation made** (e.g.: increase dose, stop medication, change medication, monitoring, etc.)	**Physician response**
2			□CYP1A2 □CYP2C9 □CYP2C19 □CYP2D6 □CYP3A4	□Drug therapy required □Unnecessary drug therapy □Incorrect drug	□Prescribe schedule 1 (APA) □Prescribe OTC/ schedule >1 □Recommendation	□Discontinue medication □Change medication to an alternative	□Fully accept □Partial accept with

			□VKORC1 □OPRM1 □SLCO1B1 □non-genetic recommendation	□Dose too low □Adverse drug reaction □Dose too high □Patient not taking as Rx'd □Monitoring indicated □Other: Interactions: □Drug-drug □Drug-gene	to physician/prescriber □Monitoring plan made with patient □No action	□Start new medication □Dose decrease □Dose increase □Monitoring without medication change □No action	revisions (e.g. change to suggested drug but not suggested dose) □Reject and provide alternative change not suggested (e.g. change drug but to one not suggested) □Reject with no medication changes □No response □N/A

Problem #	**Medication(s) affected**	**Indication(s) / condition**	**Gene(s) affected**	**Brief description of the problem (including other**	**Action taken**	**Prescribing decision or recommendatio**	**Physician response**

				factors such as signs/symptoms, other labs, etc)		**n made** (e.g.: increase dose, stop medication, change medication, monitoring, etc.)	
3			□CYP1A2 □CYP2C9 □CYP2C19 □CYP2D6 □CYP3A4 □VKORC1 □OPRM1 □SLCO1B1 □non-genetic recommendation	□Drug therapy required □Unnecessary drug therapy □Incorrect drug □Dose too low □Adverse drug reaction □Dose too high □Patient not taking as Rx'd □Monitoring indicated □Other: Interactions: □Drug-drug □Drug-gene	□Prescribe schedule 1 (APA) □Prescribe OTC/ schedule >1 □Recommendation to physician/prescriber □Monitoring plan made with patient □No action	□Discontinue medication □Change medication to an alternative □Start new medication □Dose decrease □Dose increase □Monitoring without medication change □No action	□Fully accept □Partial accept with revisions (e.g. change to suggested drug but not suggested dose) □Reject and provide alternative change not suggested (e.g. change drug but to one not suggested)

							□Reject with no medication changes □No response □N/A

Problem #	**Medication(s) affected**	**Indication(s) / condition**	**Gene(s) affected**	**Brief description of the problem (including other factors such as signs/symptoms, other labs, etc)**	**Action taken**	**Prescribing decision or recommendation made** (e.g.: increase dose, stop medication, change medication, monitoring, etc.)	**Physician response**
4			□CYP1A2 □CYP2C9 □CYP2C19 □CYP2D6 □CYP3A4 □VKORC1 □OPRM1 □SLCO1B1 □non-genetic recommendation	□Drug therapy required □Unnecessary drug therapy □Incorrect drug □Dose too low □Adverse drug reaction □Dose too high □Patient not taking as Rx'd □Monitoring indicated	□Prescribe schedule 1 (APA) □Prescribe OTC/ schedule >1 □Recommendation to physician/prescriber □Monitoring plan made with patient □No action	□Discontinue medication □Change medication to an alternative □Start new medication □Dose decrease □Dose increase □Monitoring without medication change	□Fully accept □Partial accept with revisions (e.g. change to suggested drug but not suggested dose)

				□Other: Interactions: □Drug-drug □Drug-gene		□No action	□Reject and provide alternative change not suggested (e.g. change drug but to one not suggested) □Reject with no medication changes □No response □N/A

Participant Survey

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
I am satisfied with the:					
Type and amount of information discussed by my pharmacist on drug related matters					
Questions asked by my pharmacist before dispensing medications (like any history or previous drug allergy, disease details, etc.)					
Privacy maintained by my pharmacist while talking with me and dispensing medications					
Level of knowledge that my pharmacist demonstrated about drug related issues					
Kind of response pharmacists provide on questions related to drugs					
Language used by my pharmacist in discussing drug related matters					
Amount of time my pharmacist spent with me					
Relationship that the pharmacist tries to maintain with me					
Kind of information my pharmacist provides on disease and other health issues along with information on drugs					

MyDNA Sample Consent Form

PATIENT CONSENT FORM

myDNA is an expert genetic interpretation service that analyses your genetic profile and produces personalised Medication, Nutrition & Wellness reports. The myDNA reports provide insights that enable more informed health and wellness decisions.

In order to receive myDNA testing and advisory services, I understand and consent to the following:

1. That I am 18 years of age or older, and that any sample I provide is either my DNA, or the DNA of a person for whom I am a parent or legal guardian, or have obtained legal authorisation to provide their DNA to myDNA.
2. My pharmacy will collect personal health information from me and from its patient files and will disclose that information to myDNA through myDNA's secure electronic online system including: My name, address, phone number, email address, date of birth, gender, ethnicity, my current prescribed and over-the-counter medication, and the name of my physician(s) if I want to give them access to my personalized myDNA report.
3. That the pharmacy may update my patient file in its system with any new personal health information provided.
4. That I will collect my own DNA sample (a cell cheek swab) and ship it following guidance provided by the pharmacist. My pharmacist will assist me in labelling my sample with my name, address and date of birth.
5. That my DNA sample will be sent to myDNA's Canadian agent who will batch the samples and then forward onto myDNA's accredited laboratory located in Australia and the information collected will be kept confidential and secure, on encrypted servers.
6. That myDNA will conduct testing, analysis and interpretation of my genetic information and provide me with personalised report(s) only for the myDNA test(s) paid. In some cases, an additional sample may be required if the volume or quality of the sample is not adequate.
7. That myDNA will confidentially disclose the results of the test(s) I have requested to me and my authorised healthcare professional(s).
8. My reports and genetic data will be treated as my property and will never be disclosed or shared with third parties including my insurance company and employer. I can formally request for my sample to be destroyed at any time by contacting myDNA.
9. That myDNA will securely store my DNA sample and my personal information for ten years to allow cost-effective re-sequencing in the future if new genetic testing or reporting is available, which myDNA may perform at additional cost with my consent.
10. That after ten years, my personal health information and DNA sample will be destroyed. However my computerized genetic sequence information may be retained indefinitely and could be used for research or myDNA program evaluation. This genetic sequence information cannot be linked to me after the other personal information held by myDNA is destroyed. If I want to have any new test done after that, I must give myDNA another sample and pay for new testing.
11. That myDNA will make my results available to me on a secure online portal.
12. That myDNA will only report on actionable genetic findings that have a high degree of scientific credibility which have been reviewed and signed off by the myDNA scientific team. Anything that falls out of this scope will not be reviewed or reported.
13. That myDNA does not assess any genes related to disease risk or diagnostics.
14. That the myDNA medication report may not cover all medications that I may be taking.
15. That I can revoke my consent and formally request for my sample to be destroyed at any time by contacting myDNA and my pharmacy.
16. That my pharmacist has gone through the myDNA Patient Information Sheet with me and explained the benefits, limits and risks of the service as provided to them by myDNA . I have had the opportunity to ask questions and I understand the myDNA pharmacogenomics test and advisory services available to me.
17. That I can contact myDNA at help.ca@mydna.life or at 1-844-472-7896 if I have questions.

myDNA may contact me in the future to advise me on new information and/or new products available. I may withdraw my consent at any time (please check below):

☐ I consent ☐ I do not consent

Patient Full Name	Signature	Date Signed
Full Name of person assisting participant with consent (if present)	Signature	Date Signed
Full Name and License Number of Pharmacist obtaining consent	Signature	Date Signed
Name of Pharmacy	Address	Phone Number

MyDNA Sample Report

Obtained from https://www.mydna.life/wp-content/uploads/myDNA-Example-Report-Medications-Full.pdf (Accessed August 25, 2022)

myDNA Medication

Personalised Medication Report
for *Test Patient*

Name:	Test Patient	DOB:	00-00-0000	Collected:	01-Jan-2018
Address:	123 Example St, Example Suburb, 3000	myDNA ID:	0000	Received:	03-Jan-2018
		Pathology No:	00-0000000	Reported:	08-Jan-2018
Doctor:	Example Doctor	Test performed by:	GenSeq Labs	Genetic interpretation by:	myDNA
Copy to:	Example Pharmacist				
Clinical Notes:	Inadequate analgesic effect. ? Medication side effects: sweating, gastrointestinal upset and muscle pain.			Associate Professor Les Sheffield, MB.BS. FRACP Approved Pathology Practitioner 23077	

REPORT SUMMARY

CURRENT MEDICATIONS OVERVIEW		
MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST
Codeine (component of Panadeine Forte)	*CYP2D6* *OPRM1*	Major – significant result that may require altering this medication
Fluvoxamine	*CYP1A2* *CYP2D6*	Major – significant result that may require altering this medication
Simvastatin	*CYP3A4* *SLCO1B1*	Major – significant result that may require altering this medication
Esomeprazole	*CYP2C19*	Minor – result should be considered as may affect medication response
Clopidogrel	*CYP2C19*	Usual prescribing considerations apply
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
clarithromycin, candesartan (Atacand), paracetamol (component of Panadeine Forte)		

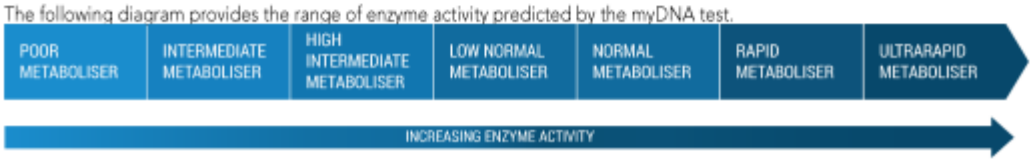
LEGEND: Major prescribing considerations · Minor prescribing considerations · Usual prescribing considerations

Detailed pharmacogenomic interpretation and recommendations are provided in the *current medications* section below.

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PHENOTYPE	GENE	GENOTYPE	PHENOTYPE
CYP2D6	*4/*4	Poor metaboliser	*CYP3A4*	*1/*1	Normal metaboliser
CYP2C19	*1/*1	Normal metaboliser	*CYP3A5*	*3/*3	Poor metaboliser
CYP2C9	*1/*3	Intermediate metaboliser	*SLCO1B1*	CC	Poor Transporter Function
VKORC1	GG	Normal VKORC1 enzyme level	*OPRM1*	GG	Lower opioid sensitivity
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)			

Detailed interpretations of genetic test results are provided in the *pharmacogenomic interpretation* section below.

The following diagram provides the range of enzyme activity predicted by the myDNA test.



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CURRENT MEDICATIONS

PERSONALISED INTERPRETATION AND RECOMMENDATIONS		
MEDICATION	**INTERPRETATION**	**RECOMMENDATION**
Codeine (component of Panadeine Forte)	*CYP2D6* - Poor metaboliser *OPRM1* - Lower opioid sensitivity: Greatly reduced metabolism of codeine into its active metabolite morphine. There is a high likelihood of an inadequate analgesic response to codeine. The OPRM1 genotype predicts reduced sensitivity to morphine and, by extrapolation, to codeine as well.	Based on the CYP2D6 genotype CPIC[1] provides a strong recommendation to avoid codeine use due to the lack of efficacy. CPIC states that tramadol and to a lesser extent oxycodone are not suitable alternatives. (However, given that oxycodone itself has analgesic activity, it may be effective even in a CYP2D6 poor metaboliser). Examples of opioids not metabolised via CYP2D6 (and therefore not affected by this genetic variation) include morphine and buprenorphine. Based on the OPRM1 genotype, there is no genotype-guided dosing recommendation available.
Fluvoxamine	*CYP2D6* - Poor metaboliser *CYP1A2* - Ultrarapid metaboliser (with inducer present): Fluvoxamine is metabolised by both CYP2D6 (predominant pathway) and CYP1A2. Negligible metabolism by CYP2D6 and increased metabolism by CYP1A2 in the presence of enzyme inducers such as cigarette smoke are predicted. Note that fluvoxamine itself will inhibit CYP1A2, which could negate the effect of enzyme induction, especially with increasing dose. Fluvoxamine exposure is likely to be increased. There is some evidence that increased drug exposure is associated with adverse effects, such as gastrointenstinal upset.	Based on the CYP2D6 genotype, CPIC[2] provides an optional recommendation to consider a 25-50% reduction of the recommended starting dose and titrate to response. Alternatively, CPIC recommends using an alternative drug not metabolised by CYP2D6.
Simvastatin	*SLCO1B1* - Poor Transporter Function *CYP3A4* - Normal metaboliser: This SLCO1B1 result is associated with a high risk of myopathy (up to twenty-fold at 80mg daily).[3] Other factors expected to further increase this risk include higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism. Normal metabolism of simvastatin by CYP3A4 is predicted.	Based on the SLCO1B1 genotype, CPIC guidelines[4] provide a strong recommendation to be alert to the increased risk of myopathy, to use low-dose therapy (e.g. 20mg daily) or consider an alternative statin (e.g. pravastatin or rosuvastatin). If using simvastatin, creatine kinase (CK) measurement may be considered. No genotype-guided dosing recommendation based on the CYP3A4 genotype is available.

CURRENT MEDICATIONS

PERSONALISED INTERPRETATION AND RECOMMENDATIONS		
MEDICATION	**INTERPRETATION**	**RECOMMENDATION**
Esomeprazole	*CYP2C19* - Normal metaboliser: This genotype predicts normal metabolism of esomeprazole. However, this rate of metabolism has been associated with a potentially incomplete clinical response in conditions such as oesophagitis and H. pylori. The effect of this genotype in predicting a reduced PPI response is less pronounced with esomeprazole than with several other drugs in this class (omeprazole, lansoprazole, pantoprazole).	If response is inadequate, consider 1) increasing the dose, 2) using divided dosing (i.e. at least twice daily) even of the same overall daily dose and 3) trial of rabeprazole as an alternative.
Clopidogrel	*CYP2C19* - Normal metaboliser: Normal formation of clopidogrel's active metabolite is predicted.	CPIC guidelines[5] provide a strong recommendation to use the label-recommended dosage if clopidogrel is being prescribed for acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI).

POTENTIAL DRUG INTERACTIONS

The effect of drug-drug interactions can be additive to the effect of genotype on drug metabolism. Inhibitors can decrease and inducers can increase metabolism, leading to changes in drug concentration and clinical effects.

Comments in the current and future medications sections only consider the effects of the patient's genotype, not those due to interacting drugs. For the health professional's consideration, the table below identifies which of the patient's current drugs may inhibit or induce those enzymes tested by myDNA. The extent of the inhibition or induction depends on the dose and duration of the therapy. The overall effect on metabolism by a specific enzyme may be estimated by considering both the genetic finding and the potential interacting drug.

MEDICATION	INHIBITOR – MODERATE	INHIBITOR - STRONG	INDUCER
Clarithromycin		CYP3A	
Esomeprazole	CYP2C19		
Fluvoxamine	CYP3A	CYP1A2, CYP2C19	

FUTURE MEDICATIONS

The following tables outline personalised recommendations for future medications.

NOTE: These tables do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of medications but includes many commonly prescribed medications.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
ADHD - miscellaneous agents	Atomoxetine	*CYP2D6*	Adverse effects	*FDA*[6]
Antianginals	Perhexiline	*CYP2D6*	Adverse effects	-
Antiarrhythmics	Flecainide	*CYP2D6*	Adverse effects	*DPWG*[7]
Anticholinergics (genitourinary)	Tolterodine	*CYP2D6*	Adverse effects	*FDA*[8]
Anticoagulants	Warfarin	*VKORC1* *CYP2C9*	Significantly increased warfarin sensitivity	*FDA*[9]

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antidepressants - other	Vortioxetine	*CYP2D6*	Adverse effects	*TGA*[10], *FDA*[11]
Antidepressants - serotonin noradrenaline reuptake inhibitors	Venlafaxine	*CYP2D6*	Adverse effects	*DPWG*[7]
Antidepressants - SSRIs	Fluoxetine	*CYP2D6* *CYP2C9*	Adverse effects	*FDA*[12]
	Fluvoxamine	*CYP2D6* *CYP1A2*	Adverse effects	*CPIC*[2]
	Paroxetine	*CYP2D6*	Adverse effects	*CPIC*[2]
Antidepressants - tricyclic antidepressants	Amitriptyline	*CYP2D6* *CYP2C19*	Adverse effects	*CPIC*[13]
	Clomipramine	*CYP2D6* *CYP2C19*	Adverse effects	*CPIC*[13]
	Dothiepin	*CYP2D6* *CYP2C19*	Adverse effects	*CPIC*[13]
	Doxepin	*CYP2D6* *CYP2C19*	Adverse effects	*CPIC*[13]
	Imipramine	*CYP2D6* *CYP2C19*	Adverse effects	*CPIC*[13]
	Nortriptyline	*CYP2D6*	Adverse effects	*CPIC*[13]
Antiemetics	Ondansetron	*CYP2D6*	Increased therapeutic and/or adverse effects	*CPIC*[14]
	Tropisetron	*CYP2D6*	Adverse effects	*CPIC*[14]
Antiepileptics	Phenytoin	*CYP2C9*	Adverse effects	*CPIC*[15]
Antipsychotics	Aripiprazole	*CYP2D6*	Adverse effects	*DPWG*[7], *TGA*[16], *FDA*[17]
	Brexpiprazole	*CYP2D6*	Adverse effects	*FDA*[18]
	Haloperidol	*CYP2D6*	Adverse effects	*DPWG*
	Risperidone	*CYP2D6*	Adverse effects	*DPWG*[7]
	Zuclopenthixol	*CYP2D6*	Adverse effects	*DPWG*[7]
Antitussives	Dextromethorphan	*CYP2D6*	Adverse effects	-
Beta blockers	Metoprolol	*CYP2D6*	Adverse effects	*DPWG*[7]
Drugs for sexual dysfunction	Dapoxetine	*CYP2D6*	Adverse effects	*TGA*[19]
Glaucoma - ocular preparations	Timolol	*CYP2D6*	Adverse effects	-
Immunomodulators and antineoplastics	Tamoxifen	*CYP2D6*	Reduced / inadequate response	*CPIC*[20]
Miscellaneous	Eliglustat	*CYP2D6*	Adverse effects	*TGA*[21]
Neurological drugs	Tetrabenazine	*CYP2D6*	Increased therapeutic and adverse effects	*FDA*[22]
Opioid Analgesics	Codeine	*CYP2D6* *OPRM1*	Reduced / inadequate response	*CPIC*[1]
	Tramadol	*CYP2D6*	Reduced / inadequate response	*DPWG*[7]
Statins	Simvastatin	*SLCO1B1* *CYP3A4*	Adverse effects	*CPIC*[4]

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MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Angiotensin receptor blockers	Irbesartan	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Losartan	*CYP2C9*	Reduced / inadequate response	-
Anticholinergics (genitourinary)	Darifenacin	*CYP2D6*	Adverse effects	-
Anticholinesterases	Donepezil	*CYP2D6*	Adverse effects	-
	Galantamine	*CYP2D6*	Adverse effects	-
Antidepressants - other	Agomelatine	*CYP1A2*	Reduced / inadequate response	-
	Mianserin	*CYP2D6*	Adverse effects	-
	Mirtazapine	*CYP2D6* *CYP1A2*	Altered response	-
Antidepressants - serotonin noradrenaline reuptake inhibitors	Duloxetine	*CYP2D6* *CYP1A2*	Reduced / inadequate response	-
Antidiabetics	Glibenclamide	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Gliclazide	*CYP2C9* *CYP2C19*	Increased therapeutic and/or adverse effects	-
	Glimepiride	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Glipizide	*CYP2C9*	Increased therapeutic and/or adverse effects	-
Antiemetics	Metoclopramide	*CYP2D6*	Adverse effects	-
Antihistamines	Chlorpheniramine	*CYP2D6*	Adverse effects	-
	Dexchlorpheniramine	*CYP2D6*	Adverse effects	-
	Promethazine	*CYP2D6*	Adverse effects	-
Antipsychotics	Chlorpromazine	*CYP2D6*	Adverse effects	-
	Clozapine	*CYP1A2*	Reduced / inadequate response	-
	Olanzapine	*CYP1A2*	Reduced / inadequate response	-
Beta blockers	Carvedilol	*CYP2D6*	Adverse effects	-
	Nebivolol	*CYP2D6*	Adverse effects	-
	Propranolol	*CYP2D6* *CYP1A2*	Altered response	-
Hypnotics	Melatonin	*CYP1A2*	Reduced / inadequate response	-
NSAIDs	Celecoxib	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Diclofenac	*CYP2C9*	Adverse effects	-
	Ibuprofen	*CYP2C9*	Adverse effects	-
	Indomethacin	*CYP2C9*	Adverse effects	-
	Mefenamic Acid	*CYP2C9*	Adverse effects	-
	Meloxicam	*CYP2C9*	Adverse effects	-
	Piroxicam	*CYP2C9*	Adverse effects	-
Opioid Analgesics	Morphine	*OPRM1*	Associated with reduced response to morphine	-
	Oxycodone	*CYP2D6*	Reduced / inadequate response	*DPWG*[7]
Proton pump inhibitors	Esomeprazole	*CYP2C19*	Reduced / inadequate response	-
	Lansoprazole	*CYP2C19*	Reduced / inadequate response	-
	Omeprazole	*CYP2C19*	Reduced / inadequate response	-
	Pantoprazole	*CYP2C19*	Reduced / inadequate response	-
	Rabeprazole	*CYP2C19*	Reduced / inadequate response	-
Psychostimulants	Dexamphetamine	*CYP2D6*	Adverse effects	-
	Lisdexamfetamine	*CYP2D6*	Adverse effects	-

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MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Statins	Atorvastatin	*SLCO1B1* *CYP3A4*	Adverse effects	-
	Fluvastatin	*SLCO1B1* *CYP2C9*	Increased therapeutic and/or adverse effects	-

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antidepressants - other	Moclobemide	*CYP2C19*	No altered effect predicted by genotype	-
Antidepressants - SSRIs	Citalopram	*CYP2C19*	No altered effect predicted by genotype	*CPIC*[2]
	Escitalopram	*CYP2C19*	No altered effect predicted by genotype	*CPIC*[2]
	Sertraline	*CYP2C19*	No altered effect predicted by genotype	*CPIC*[2]
Antifungals - Azoles	Voriconazole	*CYP2C19*	No altered effect predicted by genotype	*CPIC*[23]
Antiplatelet drugs	Clopidogrel	*CYP2C19*	No altered effect predicted by genotype	*CPIC*[5]
Antipsychotics	Quetiapine	*CYP3A4*	No altered effect predicted by genotype	-
Benzodiazepines	Clobazam	*CYP2C19*	No altered effect predicted by genotype	-
	Diazepam	*CYP2C19*	No altered effect predicted by genotype	-
Calcineurin inhibitors	Tacrolimus	*CYP3A5*	No altered effect predicted by genotype	*CPIC*[24]
Miscellaneous	Cyclophosphamide	*CYP2C19*	No altered effect predicted by genotype	-
	Naltrexone	*OPRM1*	No altered effect predicted by genotype for naltrexone	
	Proguanil	*CYP2C19*	No altered effect predicted by genotype	-
Statins	Pravastatin	*SLCO1B1*	No altered effect predicted by genotype	-
	Rosuvastatin	*SLCO1B1*	No altered effect predicted by genotype	-

LEGEND:
CPIC = Clinical Pharmacogenetics Implementation Consortium
DPWG = The Royal Dutch Pharmacists Association – Pharmacogenetics Working Group
TGA = Therapeutic Goods Administration (Australia)
FDA = Food and Drug Administration (US)

CPIC and DPWG guidelines are available on the PharmGKB website www.pharmgkb.org/view/dosing-guidelines.do

mydna Medication

PHARMACOGENOMIC INTERPRETATION

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
CYP2D6	*4/*4	*CYP2D6* - Poor metaboliser Due to the presence of two null alleles, this individual is predicted to have a poor metaboliser phenotype. For a drug extensively metabolised by CYP2D6, drug exposure and clinical effects may either be greatly increased (for an active drug) or greatly decreased (for a prodrug). The individual is at risk of experiencing adverse effects (active drug) or therapeutic failure (prodrug).
CYP2C19	*1/*1	*CYP2C19* - Normal metaboliser Due to the presence of two normal function alleles, this individual is predicted to have a normal metaboliser phenotype. For a drug extensively metabolised by CYP2C19, drug exposure and clinical effects may be expected to lie within the normal range.
CYP2C9	*1/*3	*CYP2C9* - Intermediate metaboliser Due to the presence of one normal function allele and one decreased function allele, this individual is predicted to have an intermediate metaboliser phenotype. For a drug extensively metabolised by CYP2C9, drug exposure and clinical effects may either be increased (for an active drug) or decreased (for a prodrug). This may increase the likelihood of adverse effects (active drug) or therapeutic failure (prodrug).
VKORC1	GG	*VKORC1* - Normal VKORC1 enzyme level The VKORC1 enzyme is predicted to be present in normal amounts and the response to warfarin will be normal. The *CYP2C9* genotype should also be considered together with the *VKORC1* genotype for calculating the initial warfarin dose.
CYP1A2	*1F/*1F	*CYP1A2* - Ultrarapid metaboliser (with inducer present) Due to the presence of two *1F alleles, this individual is predicted to have an ultrarapid metaboliser phenotype. Enzyme activity is highest in the presence of inducers, such as tobacco smoke, regular consumption of cruciferous vegetables or chargrilled meats, and certain drugs. For a drug extensively metabolised by CYP1A2, drug exposure and clinical effects may either be reduced (for an active drug) or increased (for a prodrug).
CYP3A4	*1/*1	*CYP3A4* - Normal metaboliser The *22 allele is not present and this individual is expected to have a normal metaboliser phenotype. Whilst many drugs are known to be metabolised by CYP3A4, relatively few genetic variations have been found that affect metabolism of a limited number of these drugs.
CYP3A5	*3/*3	*CYP3A5* - Poor metaboliser Due to the presence of two no function alleles, this individual is predicted to have a poor metaboliser phenotype (CYP3A5 non-expresser). CYP3A5 is known to metabolise certain drugs, including tacrolimus. Note that this individual's genotype is the most common one amongst Caucasians.
SLCO1B1	CC	*SLCO1B1* - Poor Transporter Function Due to the presence of two decreased function alleles, this individual is predicted to have poor function of the *SLCO1B1* encoded transporter. Decreased clearance of certain medications such as simvastatin is expected.

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
OPRM1	GG	*OPRM1* - Lower opioid sensitivity The GG genotype contains two variant alleles for the OPRM1 gene which encodes the mu opioid receptor. Whilst the evidence around OPRM1 genetic variation continues to develop, it appears that the G allele is associated with a reduced response to certain opioids (in particular, morphine). These findings are supported by a number of cohort studies and at least two meta-analyses[25,26] however, this is not shown in all studies. For naltrexone in the management of alcohol use disorder, some studies have shown an association of the G allele with superior clinical outcomes. Note the frequency of the variant allele (G) is higher in people of Asian ancestry (around 40%) than European ancestry (around 15%).

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Laboratory Results provided by: GenSeq Labs (NATA 20082)

Disclaimer: The pharmacogenomic test result in this report is just one factor that the prescribing doctor will take into consideration when determining a patient's appropriate medication and dose. These interpretations are being provided to the prescribing doctor as a tool to assist in the prescription of medication. Patients are advised not to alter the dose or stop any medications unless instructed by the doctor. The interpretation and clinical recommendations are based on the above results as reported by GenSeq Labs (NATA 20082) and also uses information provided to myDNA by the referring doctor. This report also assumes correct labelling of sample tubes and that the sample is from the above patient.

MYDNA CLINICAL SUPPORT

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Alleles Tested for in the MyDNA (Melborne, Australia) Medication Test

Gene	Alleles
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *14A, *14B, *17, *29, *36, *39, *41 and gene duplications
CYP2C19	*2, *3, *17
CYP2C9	*2 and *3
VKORC1	-1639G>A
CYP1A2	*1F
CYP3A4	*22
CYP3A5	*3
SLCO1B1	*5 (reported as the C allele at SLCO1B1 rs4149056)
OPRM1	118A>G

The 'wild-type' allele *1 is assigned when none of the tested variants are identified.