Pharmacogenomics: From Experimental Design Through Patient Interactions

by

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Abstract

In this study 180 patients were consented and enrolled for pharmacogenomic testing based on their current antidepressant/antipsychotic usage. Samples from patients were genotyped by PCR, massARRAY, and targeted for next generation sequencing. We also conducted a quantitative, frequency-based analysis of participants' perceptions using simple surveys. Pharmacogenomic information, including medication changes and altered dosing recommendations were returned to the pharmacists and used to direct patient therapy. Overwhelmingly, patients perceived pharmacists/pharmacies as an appropriate healthcare provider to deliver pharmacogenomic services. In total, there were 81 medication changes in 33 unique patients, representing 22% of all genotyped participants. We performed a simple drug cost analysis and found that medication adjustments and dosing changes across the entire cohort added $24.15CAD per patient per year for those that required an adjustment. Comparing different platforms, we uncovered a small number (1.7%) of genotype discrepancies, none of which impacted medication suggestions. We conclude that: 1）Pharmacists are competent providers of pharmacogenomic services. 2) The potential reduction in adverse drug responses and optimization of drug selection and dosing comes at a minimal cost to the health care system. 3) Changes in drug therapy, based on PGx tests, result in inconsequential changes in annual drug therapy cost with small cost increases just as likely as costs savings. 4) Pharmacogenomic services offered by pharmacists are ready for wide commercial implementation. This thesis details the methods and results from this study in relation to pharmacogenomics as a concept and its practice across British Columbia and Canada.

Lay Summary

Our genotype can predict details on how one might respond to certain medications and the efficacy of those drugs. Inexpensive DNA tests, which allow us to query a patient's individual genotype, are likely to help reduce drug costs for the province of British Columbia and increase positive health outcomes for patients by reducing the trial-and-error nature of current treatment. Despite its potential, Pharmacogenomic testing and implementation is not widely available for residents of British Columbia nor is there a system in place for interpretation and distribution of the test results. We sought to investigate the use of pharmacists as providers of PGx testing and to determine the cost-benefit of this service, as well as define its history and use. Our study concluded that there would be minimal upfront cost to the healthcare system and that there was enthusiastic support by patients for community pharmacists as the point-of-care for pharmacogenomics.

Preface

A portion of this thesis has been published:

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Ms. Samantha Breaux was responsible for the initial draft of the manuscript, reviewed and revised each draft and reviewed and approved the final manuscript. In addition, she completed the patient sample processing, data extraction, R-based analysis, pharmacist communications and return of results. Mr. Derek Desrosiers helped design the project and provided input on the initial draft and reviewed and revised each version. He also handled communication with the pharmacists and funding partners as well as completing aspects of the cost-benefit analysis. Dr. Mauricio Neira provided data analysis assistance. Dr. Sunita Sinha provided project support during sample processing and assisted in revising the manuscript. Dr. Corey Nislow was responsible for project management and design. He also revised each version of the draft and approved the final manuscript.

Associated work can be found in all chapters of this thesis.

The project this thesis is based off received approval from the University of British Columbia's Research Ethics Board; certificate number H16-02326.

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List of Abbreviations

A - Adenine

AMA - Amino Acid

ADR - Adverse Drug Reaction

BC - British Columbia

C - Cytosine

CAD - Canadian Dollar

CAP - College of American Pathologists

CDS - Clinical Decision Support

CLIA - Clinical Laboratory Improvement Amendments

CMS - Centers for Medicare & Medicaid Services

CN - Corey Nislow

Cn' - n Prime Carbon

CNS - Central Nervous System

CPIC - Clinical Pharmacogenomics Implementation Consortium

CPNDS - Canadian Pharmacogenomics Network for Drug Safety

CYP450 - Cytochrome p450

DAP - Diagnostic Accreditation Program

dbSNP - Single Nucleotide Polymorphism database

DD - Derek Desrosiers

DIN - Drug Identification Number

DNA - Deoxyribonucleic Acid

DPWG - Dutch Pharmacogenomics Working Group

EF - Environmental Factors

EHR - Electronic Health Records

EM - Epigenetic Modifications

eMERGE - Electronic Medical Records and Genomics Network

EU - European Union

FDA - Food and Drug Administration

G - Guanine

GOF - Gain-of-Function

GWAS - Genome Wide Association Studies

ID - Identity

IGNITE - Implementing Genomics in Practice Network

Indel - Insertion and Deletion

LDT - Laboratory Diagnostic Tests

LOF - Loss-of-Function

MALDI-TOF - Matrix-Assisted Laser Desorption/Ionization — Time of Flight

MHC - Mental Health Compounds

mRNA - Messenger RNA

N - Number

NA - Not Applicable

NCBI - National Center for Biotechnology Information

NIH - National Institute of Health

NTP - Nucleotide

PCR - Polymerase Chain Reaction

PD - Pharmacodynamics

PGRN - Pharmacogenomics Research Network

PGx - Pharmacogenomics

PharmGKB - Pharmacogenomics Knowledge Base

PharmVar - Pharmacogene Variation Consortium

PK - Pharmacokinetics

PREPARE - Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions

QC - Quality Control

qPCR/ RTqPCR - Quantitative PCR / Real-Time Quantitative PCR

REB - Research Ethics Board

RNA - Ribonucleic Acid

SB - Samantha Breaux

SEAPharm - Southeast Asian Pharmacogenomics Research Network

SNPs - Single Nucleotide Polymorphism

SOP - Standard Operating Procedure

T - Thymine

tRNA - Transfer RNA

TRS - Target Rich Sequencing

UBC - University of British Columbia

U-PGx - Ubiquitous Pharmacogenomics Consortium

USA - United States of America

USD - United Stated Dollar

WES - Whole Exome Sequencing

WGS - Whole Genome Sequencing

Glossary

1000$ Genome Barrier - Previous challenge to providing affordable sequencing was cost. NGS brought the cost of sequencing a full genome below 1000$ USD.

3D/Tertiary Structure - Interactions between distal parts of the same molecule, creates dimensional structure.

3rd Generation Sequencing - Long-read sequencing technology; nanopore.

4-Point Likert Scale - Survey design, excludes neutral option to force participants to strongly disagree, disagree, agree, or strongly agree.

Absorption - Act of taking up a drug into a cell or tissue.

Activation Energy - Energy required for a reaction to proceeded; difference in free energy between substrate and transition state.[1]

Active Site - Site where a drug produces its effect; site of function of an enzyme.

Adherence - Maintenance of a medication regimen.

Adverse Drug Reaction - Unwanted unintended effect of a drug.

Allele – An alternative gene sequence

Alternative Transcript - Alternative mRNA produced through differential splicing from a single gene.

Amino Acid - Acidic molecule with an amino group; building block of proteins.

Anneal - Bind two DNA strands; can also refer to the process of heat denaturation and reformation of the double strand.[2]

Antidepressant - Class of medications indicated in the treatment of major depressive disorder.

Antipsychotic - Class of medication indicated in the treatment of psychosis.

Apoptosis - Programed cell death.

Array/Panel Based Genotyping - Method for uncovering genotype/ phenotype in a massively parallel fashion that infers base identity; for this study refers to microarrays and massARRAYs.

Assemble - Building of an ordered genome from sequence reads.

Barcode - Unique identifier can be a unique sequence of DNA.

Base Pair - Two hydrogen bond bound nucleotides.

Bioavailable - Portion of the drug available for the body to use.

Biological Pathway - System process involved in maintaining an organism.

Biology - Study pertaining to living and organic systems.

Biomarker - A biological feature that is predictive of a disease state or phenotype.

Bridge Amplify - Process during Illumina sequencing that amplifies and creates paired end reads.

Cancer - Malignment mutations charactered by uncontrolled cell growth.

Catalyze - Reduce activation energy required for a reaction to go forward.

Cell - Smallest living unit; makes up tissues, organs, and organisms or itself can be a full organism; carries out work required to maintain the organism.

Chromatin - Compacted/supercoiled DNA.

Chromosome - Fully compacted DNA as found in the nucleus; diploid organisms (humans) have two copies of each chromosome for a total of 46.

Clinical - Relating to in practice patient or medical treatment.

Clinical Decision Support System - Tool used to inform prescribers of a patient's specific pharmacogenomic dosing guidelines.

Clinical Laboratory Improvement Amendments - United States amendment to the regulations of laboratory diagnostic tests.

Coding Region - Sequence of DNA which produces a gene.

Codon - 3 base sequence that codes for an amino acid.

Co-Factor - Additional factor required for the proper function of a drug/enzyme.

College of American Pathologists Certification - Additional certification, more stringent than CLIA, that one can receive for their laboratory diagnostic test.

Community Pharmacist/Pharmacy - Pharmacy or pharmacist that works in a community setting as opposed to a clinical or hospital practice.

Consent - Active and informed agreement to participation.

Consideration - A returned minor, usual, or major dosing guideline.

Contig - Short DNA read that assemble by overlapping ends.

Copy Number - Number of copies of a gene an individual has; entire genes can be duplicated or deleted.

Cost Benefit - Analysis to determine how financially reasonable an action is.

CPIC - Unites States institution that issues pharmacogenomics dosing guidelines.

Current Medication - Medications that we recorded the patients taking at the start of the study.

Cytochrome P450 - Enzyme class found mainly in the liver. Involved in phase 1 metabolism; 6 were evaluated in this study CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, AND CYP3A5.

Cytogenetic Analysis - Analysis that interprets chromosome structures.

dbSNP - Assigns SNP reference numbers.

Diagnostic Accreditation Program - Accreditation agency in British Columbia for laboratory diagnostic tests.

Diploid - Having two copies of each chromosome.

Disease - A state which disrupts an organism's ability to maintain homeostasis.

Distribution - Where the drug localizes within an organism.

DNA - Heritable information in the cell; encodes proteins and dictates cell function.

DNA Methylation - Epigenetic modification which adds a methyl group to the DNA strand; can silence or induce genes.

Dose - Amount of drug given/taken.

Dosing-Guidelines - Guidelines to help prescribers ensure patients are taking the optimal amount of their medications.

Double Stranded - DNA or RNA when base-paired.

Down Regulate - Inhibit a gene's expression.

Downstream - A relative location in the genome; occurs in the direction of transcription/replication.

DPWG - Dutch working group to establish clinical pharmacogenomics dosing guidelines.

Drug - Compound, molecule, or element capable of molecularly attenuating biological systems.

Drug Class - Related drugs; similarities in structure and modes of action.[3]

Drug Identification Number - Reference number used in Canada to identify drugs.

Drug Metabolism - The process of biotransformation of drugs to aid in excretion or activation.

Drug Target - Intended site of action of the drug or molecule said drug interacts with.

Efficacy - Maximum ideal effect of a drug.[4]

Elderly - Person older than 60.

Electronic Health Records - Electronic tool to assist physicians in storing and tracking patient information.

Electrophoreses Gel - Test to characterize molecule size by diffusion time in presence of an electrical current.

Endogenous - Produced locally in/by the organism.

Enhancer - Distal region of the DNA which induces transcription.

Enzyme - Protein capable of catalyzing a reaction.

Epigenetic - Relating to modifications made to DNA after replication; can impact expression; can be caused by environmental factors.

Eukaryotic - Cell type found in multicellular organism; cells contain a nucleus; in contrast to prokaryotes.

Excretion - Process of drug removal from the body.

Exon - Part of a gene which is translated to mRNA; not spliced out.

Exonuclease - Enzyme capable of cleaving nucleic acids.

Expression - Translation of a protein.

Extensive/Normal Metabolizer - CYP450 metabolizer state characterized by normal function of the protein.

FDA - Agency of the United States that regulates drugs and genetic tests.

Flow Cell - Platform where a genetic test is performed; capable of being washed with sample or reagent.

Fluorophore - Molecule that when excited fluoresces.

Frameshift Mutation - Mutation that disrupts the 3 base codon reading frame.

Gain-of-Function - Mutation which improves or adds functionality to a protein.

Gene - Region of the genome which produces a protein.

Genetic Factor - Gene influenced.

Genetic Polymorphism – Variability in DNA sequence.

Genetics - Study of genes; related or pertaining to genes.

Genome - An organism's total DNA sequence.

Genome Wide Association Study - Studies used to make associations between phenotype and genotype.

Genomics - Study of the genome/total DNA sequence.

Genotype - Description of an individual's set of genes; details the copy of a gene on each chromosome.

Genotyping - Process of determining the alleles present in an organism.

Germ Cell - Reproductive cell; not a somatic cell; haploid.

Gibbs Free Energy - Measure of thermodynamic potential and free energy.

Haploid - Cell or organism with only one copy of its genome.

Haplotype - Group of genes commonly inherited together.

Hardy-Weinberg Equilibrium - P2 + 2pq +q2 =1; describes allele frequency in an ideal population.

Health Canada - Canada's regulatory agency that oversees drug and genetic test approval.

Health Care System - Total network in place to treat human ailments.

Hepatic/ Hepatocyte - liver cell.

Heterozygote - Organisms with two different copies of an allele.

Homeostasis - Biological state maintained as normal operations in organisms.[5]

Homozygote - Organisms with two copies of the same version of an allele.

Human Genome Project - Major effort that sequenced the first human genome.

Hybridize - Act of single stranded DNA annealing to the antisense strand.

Hydrophilic - Water soluble.

Hydroxyl - A molecule of an oxygen and hydrogen atom.

Illicit Substance - An illegal substance taken for its addictive effects.

Illumina - Next generation sequencing technology; uses reversable termination paired with imaging to determine sequence.

Imputation - Process of determining SNPs based of a patient's haplotype data.

In-Vitro - Experiment conducted in a lab/outside a living organism.

Indel - Insertion and deletion; types of mutation that cause frameshifts.

Indication - A minor, usual, or major dosing guideline.

Induce - Facilitate expression or function.

Inhibit - Reduce expression or function.

Insurer - Party who assumes medical costs; party that insures against risk of disease/injury.

Interindividual Variability - Change in outcomes due to individual factors.

Intermediate Metabolizer - CYPP450 metabolizer state characterized by loss of function alleles.

Intron - Part of the gene which is spliced out.

Iplex Massarray - Array-based genotyping method; uses mass spectrometry and mass difference to determine sequence identity.

Karyotype - Genetic test where the chromosomes are visualized.

Laboratory Diagnostic Test - Test used to determine disease or conditions in humans.

Ligate - Join two DNA fragments together.

Lipophilic - Soluble in lipids.

Liver - Major organ; major site of drug metabolism.

Loss-of-Function - Mutation that reduces an enzymes capacity to work.

Major - Dosing consideration returned on myDNA reports; indicates that medication or dosing changes may be required.

Map - Process of aligning sequencing reads with a reference genome.

Mass Spectrometry - Test that assesses substance identity based on mass and charge.

McKesson Canada Wholesale Drug Price - Wholesale pharmaceutical sellers (https://www.mckesson.ca/).

Mechanism of Action - Route through which a drug takes effect; how it impacts the cell/organism.

Medication - Drug used in treatment of a patient's condition.

Medication Labeling - Drug prescribing and usage information.

Medication Therapy Management Programs - Programs undertaken to assist patients in taking medications and reduce adverse drug reactions.

Medicine - The field of patient treatment and disease management.

Meiosis - Process of germ cell replication.

Mental Health Compounds - Medication used in the treatment of psychiatric disorders.

Mental Illness - Psychiatric disorder often chartered by psychosis or inapposite moods.

Metabolism - The set of chemical reactions in the body.

Microarray - Array/panel-based sequencing methods; uses hybridization to determine sequence identity.

Microscopy - Use of a microscope.

Minor - Dosing consideration returned on myDNA reports; indicates that results should be consider as there is some evidence of an impacted phenotype.

Missense Mutation - Mutation that changes an amino acid.

Mitochondria - Organelle; site of energy production in the cell.

Molecule - A compound made of multiple atoms.

Monooxygenase - Enzyme that catalyzes the addition of an oxygen atom.[6]

mRNA - Intermediate molecule between DNA and protein.

Mutation - A variation in genomic sequence.

Nanopore - 3rd generation sequencing technology; uses fluctuation in electric signal to determine bases.

Next Generation Sequencing - High throughput short read sequencing technology; often uses reversable termination to make base calls; Illumina.

Nitrogenous Base - A guanine, cytosine, adenine, thymine or uracil molecule.

Nonsense Mutation - Mutation that produces a premature stop codon and a nonfunctional or truncated copy of the protein.

Nonsynonymous Mutation - Mutation that changes the amino acid sequence.

Nucleic Acid - DNA or RNA.

Nucleoside - Ribose/deoxyribose sugar + nitrogenous base.

Nucleotide - Phosphate + nucleoside.

Null Mutation - Mutation that produces a nonfunctional copy of a gene.

Nutrigenomics - Field of study looking to investigate how our genomes impact food metabolism.

Off-Target Discovery - Unintended finding of a genomic inquiry.

Oligonucleotide - Short synthetic DNA sequence, often used as probs/primers.[7]

One-Size-Fits-All - Prescribing model that gives standardized doses to all patients.

Organism - A living unit.

Paired-End - Sequencing reads stemming from both the forward and reverse strand of DNA.

Patients/Participants - Those enrolled in the study.

Personalized Medicine - Individualized treatment, may include genetic factors.

Pharmaceutical - Medication

Pharmacist - Professional involved in the compounding and prescribing of drugs.

Pharmacodynamics - Study of how drugs impact the body.

Pharmacogenes - Gene relevant in the metabolism or function of a drug.

Pharmacogenetics - The study of drug-gene associations.

Pharmacogenomic Testing - Using a person genomic information for personalized prescribing.

Pharmacogenomics - The study of drug-genome associations.

Pharmacokinetics - Study of how the body impacts drugs.

Pharmacology - Study of drug action.

Pharmacy - A store which sells drugs; where pharmacists work.

PharmGKB - Curator of pharmacogenomic information.

PharmVar - Organization that reviews and assigns *alleles.

Phase 1 - Refers to the Pharmacogenomics at the Point of Care: Phase 1 Study.

Phase 1 Metabolism - Transformation of molecules to aid in their excretion; majorly preformed in the liver.

Phase 2 - Refers to the Pharmacogenomics at the Point of Care: A Community Pharmacy Project in British Columbia study.

Phenotype - An organism's displayed characteristics.

Physician - Practitioner of medicine.

Ploidy - Relates to the copy number of the genome.

Point Mutation - Mutation in one base in the DNA sequence.

Polymerase - Enzyme that catalyzes the addition of nucleotides during replication/transcription.

Polymerase Chain Reaction - Method for DNA amplification.

Polymorphism - Natural genetic variation.

Polypeptide - Chain of amino acids.

Poor Metabolizer - CYP450 metabolizer state defined by two copies of the null allele.

Population Frequency - Frequency of the gene/event in a large global or mixed group.

Potential/Future Drugs - 93 compounds for which myDNA relate guidelines for.

Preemptive Pharmacogenomic Testing - Pharmacogenomic testing done to inform on potential risk based on many genes, not just on single drug-gene pairs; done not just at the time of treatment but to inform on future prescribing.

Prescriber - Person who prescribes drugs.

Prescribing - Act of assigning medications and doses to individuals.

Prescription - An assigned medication.

Primer - DNA sequence used to initiate replication or transcription.

Probe - DNA with a known sequence used to capture sequence of interest in samples.

Procarcinogen - Agent associated with cancer causation.

Prodrug - Inactive form of a drug which needs to be metabolized to function properly.

Promoter - Region of a genome that facilitate transcription.

Proof Reading - Process of correcting errors that occur during replication/transcription.

Protein - Folded polypeptide chains of amino acids, capable of doing cellular work.

Pseudogene - Non-functional gene copy in the genome.

Psychiatric - Relating to the mind.

Pucker - Carbon atom forced out of plane due to steric hinderance.

P-Value - Confidence score of false positives.

qPCR/RTqPCR - Methods used to quantify level of expression.

Qualitative Survey - Examination of participant and pharmacist experience.

Quencher - Molecule which represses fluorescence.

R - Statistical programming language.

Rare Variant - Uncommon mutation found in <1% of the population.

Reading Frame - Coding region of the gene as defined by the 3 base codons.

Recombination - Process during miosis where the gene on each copy of the chromosomes are transposed.

Reference SNP Number - Ascension number used to identify small mutations.

Replication - Process of copying the genome.

Research Ethics Board - Ethics board of the University of British Columbia; approves procedures used in study.

Reversable Terminator - Sequence terminator that may be removed to continue the addition of nucleotides.

Reverse Transcription - Process of going from RNA to DNA.

Ribosome - Molecule involved with the formation of polypeptides.

Ribozyme - RNA molecule with enzymatic capabilities.

RNA - A macromolecule and nucleic acid; intermediate between DNA and protein; has other enzymatic activities.

Route of Administration - Way a drug enters the body.

Sample ID /Sample Barcode - Unique identifier used to identify participants in the study.

Sanger/Shotgun Sequencing - First generation sequencing technology; uses termination-based sequencing.

Secondary Structure - Local interaction in the same molecule, can produce structure such as DNA's helix.

Sequence - Order of nucleic acids.

Sequencing - Determinization of the order of nucleic acids.

Sequencing Library - Set of DNA samples prepared for sequencing.

Short Tandem Repeats - Short repeating sequences in the genome.

Short-Read - Read of a DNA sequence shorter than 500bp.[8]

Single Nucleotide Polymorphism – Common type of genetic variation. Point mutations which exists in >1% of the population.

Single Strand – Molecule of DNA which is not base paired.

Smooth Endoplasmic Reticulum - Organelle in cells involved in the metabolism of molecules.

SNPedia - Wiki of SNP information.

Somatic Cell - Cell in a body tissue; not a germline cell.

Splice Site - Site in the coding region of a gene where an intron may be spliced out.

Standard Operating Procedure - Study protocol.

Star (*) Allele - Common genetic haplotypes.

Strand Slippage - Mutation process where a strand pairing misaligns.

Substrate - Compound which is acted on; precursor molecule

Supercoil - Compaction or winding of DNA.

Supplements - Extra dietary compounds; generally, vitamins or nutrients; often produced endogenously.

Synonymous Mutation - Mutation which produces an identical protein.

Target Rich Sequencing - Using specific probes with NGS to sequence genes of interest.

Therapy - Treatment.

Threptic Window - Range where a drug treatment is effective without being toxic.

Throughput - Related to the amount of DNA processed.

Tidy - Long data; data preprocessed for analysis.

Tissue - Group/type of cells in an organism with specialized characteristic.

Transcription - Act of copying DNA sequence into an RNA molecule.

Transcription Factor - Protein which regulates transcription.

Transition State – State between the substrate and product in a chemical reaction; has highest free energy.[1]

Translation - Act of forming protein from mRNA.

Transport - Act of bringing a molecule into a cell or tissue.

Trial and Error - Prescribing approach based on standardized dosses and modifying dosses if problems arise.

tRNA - Molecule responsible for bringing the correct amino acid to the growing polypeptide chain.

Truncated Protein - Protein translated with a premature stop codon and is missing amino acids; may prevent function.

Tumor - Abnormal growth of cells.

Ultra-Rapid Metabolizer - CYP450 metabolizer state characterized by a gain of function allele.

Usual - Dosing consideration returned on myDNA reports; indicates that normal prescribing considerations should be followed.

Variant - A genetic polymorphism; a mutation.

Warfarin - Anticoagulant and a major cause of adverse drug reactions.

Whole Exome Sequencing - Sequencing of the coding region.

Whole Genome Sequencing - Sequencing of an individual's entire DNA sequence.

Wiki - Open-source encyclopedia.

Work - Energy expended towards a goal in a cell; energy is stored as ATP.

Xenobiotic - Foreign compound capable of attenuating biological function.

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I am also extremely grateful to the pharmacists and participants who chose to enroll in our study as well as their respective pharmacy chains for showing interest in pharmacogenomic concepts and making my research possible.

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Dedication

This thesis is dedicated to everyone who said:

“You should apply for your Masters.”

Chapter 1: Introduction

1.1 Rationale

Completion of the Human Genome Project in 2003 brought expectations that the information would revolutionize the practice of medicine and introduce new scientific, business, and medical models.[9–11] While many of those hopes are just beginning to be realized, the resulting discipline of pharmacogenomics (PGx) has matured considerably in the past decade. PGx uses genetic information to classify patients who may benefit from personalized medication or who may respond negatively to a particular treatment. Differences in treatment outcomes can be attributed to genetic, environmental, physiological and psychological factors.[12–16] The influence of genetic factors has been associated with 15% to 30% of the variability in drug treatment; for some specific compounds genetic components may contribute up to 95% of interindividual variability.[13,15–17] PGx can help ensure that patients receive the most appropriate medication and dose; can reduce the number of adverse drug reactions (ADRs), and aid in medication adherence. The most appropriate provider of PGx testing, however, remains a subject of debate.

In British Columbia (BC) Canada, pharmacists are the recognized drug experts.[18] Furthermore, over the past two decades their scope of practice has expanded to provide more aspects of comprehensive patient care.[19] Such emphasis on a more patient-centered, individualized, and preventative approach to wellness is an antidote to the frustration of the one-size-fits-all paradigm of evidence-based medicine.[20] Implementation of PGx testing based on these benefits has, however, proven to be challenging. Causes include low acceptance of pharmacist recommendations by the physician and prescriber, mixed patient receptivity, low rates of reimbursement to pharmacists, inadequate human resources, and the physical layout of the pharmacy.[21] Our supposition for potentially unproductive interactions between pharmacists and physicians was due to the (self-reported) high levels of unfamiliarity with regards to genomics and by extension being uncomfortable with making drug therapy changes based on a participant's drug metabolism genotype.[22,23] An additional barrier is the cost of PGx testing which ranges from $200–$500, often left to the consumer because insurers have been hesitant to cover genetic testing for non-diagnostic purposes.[24] Fears include concerns over data security

and actual clinical impact.[25] These barriers are surmountable and have been addressed in other contexts.[26]

1.1.1 Adverse Drug Reactions

PGx testing is a powerful way to address the fact that every year in BC alone over 200,000 people are admitted to hospitals due to ADR of which 10,000–20,000 die; these patients' treatments costs an estimated $49 million per year.[27] These numbers are likely to be higher because up to 95% of ADRs go unreported.[28] ADRs are complications or unintended effects of medications. These can range from mild allergic reactions such as localized rashes to life-threatening conditions like liver failure. ADRs can also include attenuation of gene expression and complications arising from affected downstream drug metabolism. ADRs are frequently influenced by age, medication conflicts, wrong or suboptimal prescribing, and poor adherence.[29,30] Up to 50% of drugs are not taken as prescribed.[30] PGx offers a promising way to combat ADRs by assessing genetic factors that may inhibit medications from working properly or causing unwanted side effects, and guide correct dosing. Additionally, ADRs may be associated with genetic polymorphisms. From 27 drugs commonly cited as causes for ADRs, 59% are metabolized by an enzyme with a known loss-of-function (LOF) allele compared to 7%-20% of randomly selected drugs.[13,31] In 2011, the American Pharmacists Association acknowledged the importance and practicality of integrating genomics with medication therapy management programs to optimize patient drug therapy.[32] Almost 4% of new drugs are also withdrawn from the market due to ADRs.[13,33] Identifying ways to determine who would be helped by these medications may allow these compounds to stay on the market and for individuals to receive the appropriate treatment.

1.1.2 Mental Health Compounds

Antidepressants and antipsychotics are both medication classes indicated in the use of psychiatric disorders.[14] While all drug targets and their mechanisms of action have yet to be elucidated, antidepressants broadly function by blocking monoamine reuptake to increase neurotransmission – Antipsychotics generally work by blocking receptors to reduce mesolimbic dopaminergic neurotransmission.[14,34] The effectiveness of these drugs are suboptimal however, and two out of

three people will need to try multiple/different antidepressants until they find one that works for them; the most common reason for needing to switch was due to side effects, which can leave a person physically debilitated and worsen mood disorders.[35] Additionally, antidepressant use is linked with age, with the elderly (those over 60) being 40.2% more likely to use an antidepressant than the rest of the United States (USA) population.[36] The elderly also take multiple classes of drugs with 51.6% of seniors in Canada taking 1–4 drugs of different classes chronically and an additional 35.3% taking 5 or more.[29,37] Some of these drugs are used to mitigate ADR symptoms from their other medications. Identifying problematic medications can reduce the drug cost if other medications can be discontinued because they are no longer needed to manage ADRs. It also allows us to capture a wide range of medications to test the validity of our results. Antipsychotics face a similar problem in their prescribing and like antidepressants have an efficacy rate of 30-40%.[14,38]

In addition, development of new mental health compounds (MHC) in recent years have diminished.[14] The compounds currently on the market to treat psychiatric disorders are likely to remain the standard of care, and as such, PGx testing may offer a way to maximize their current utility.[14] Mental health disorders have a large financial burden. It is estimated that in the next 30 years Canada's total mental health burden will be above 2.5 trillion dollars with a fifth of the population living with a mental illness.[39] This is an issue insurers wish to address. Offering PGx testing can reduce the trial-and-error approach in prescribing. Two enzymes, CYP2C19 and CYP2D6 are responsible for the phase 1 metabolism of two thirds of available psychiatric compounds; these enzymes also exhibit a wide degree of polymorphism with altered phenotypes that exhibit different rates of metabolism.[40–42] These two enzymes have clinical utility in prescribing some psychiatric medications and genotyping these enzymes may improve patient outcomes.[14] For these reasons and due to interest from our funders use of antidepressants or antipsychotics were included as criteria for enrollment in the study.

1.1.3 Aims

Phase 1 of this project in which we concluded that the community pharmacist is the appropriate healthcare expert for PGx deployment laid the ground work for the current research.[43] In Phase 2 we tested the hypothesis that medication changes as a result of PGx testing have a minimal

impact on the overall cost of a patient's drug therapy, as well as build on the hypothesis that the Pharmacist is an ideal PGx provider. During this study we gained the opportunity to partner with two genotyping agencies that offered PGx test panels. While one PGx test was used to return patient results the other was maintained for in-house analysis, to assess the utility of a targeted rich sequencing (TRS) approach to PGx testing as compared to an established commercial service,

The objectives of this study were to i) test the feasibility and appropriateness of community pharmacists as a conduit for pharmacogenomics information, ii) gauge the receptivity of patients in this setting, iii) assess the cost-effectiveness of this approach, iv) review the genomic information, and v) conduct a basic analysis. Despite the limited size of the study, we satisfied these objectives and discuss how the lessons learned here can be applied broadly to guide the application of PGx testing in community pharmacies. This document also wishes to highlight the theory, background, and future directions of PGx testing as a whole.

1.2 DNA and Mutations

1.2.1 DNA in Cells

Deoxyribonucleic acid (DNA) contains an organism's heritable information. It is a primarily double stranded molecule made up of nucleotides (NTPs) containing one of 4 nitrogenous bases: adenine (A), thymine (T), guanine (G), cytosine (C).[44] DNA also imparts a cell's function and structure. This is done through the expression of diverse ribonucleic acids (RNA)s and proteins, which are made up of folded chains of Amino Acids (AMAs).[44,45] The function of a protein derives, in part, from its folded 3D structure; this function however, is limited by the protein's abundance, its co-factor's availability, or the availability of its active sites which can be overwhelmed by the presence of its substrate or altered by sequence variation.[50] The 3D structure and functionality of a protein can also be altered by changes in AMA order. AMAs are encoded in DNA in groups of three bases called codons.[56,62] DNA is first transcribed into a RNA molecule which is then translated into protein.[44] DNA can be maintained in a multitude of ploidies or copy numbers. Common in the Eukaryotic kingdom are diploid (2 copies) and haploid (1 copy) cells. Human somatic cells are diploid, which increases genetic diversity, and

may protect the cell if one copy of the DNA is damaged.[49] The diploid state also protects against the expression of recessive mutations.[49] Genomic DNA contains regions known as genes and these stretches of sequence code for a protein.[44,50] DNA however, is not composed solely of coding regions or regions which contain genes. The majority of DNA is noncoding; with much of this non-coding DNA serving regulatory purposes, and a larger proportion being of unknown function.[51] Additionally, within genes portions of transcript are spliced out (introns) with the exons being maintained and translated into protein.[44] Introns are less well characterized and may have regulatory functions, as-yet-unknown functions, or be deployed to produce alternative transcripts to produce multiple gene products from the same gene.[51]

1.2.2 Types of Common Genetic Mutations

A genetic mutation represents a change in DNA sequence as compared to the average (or reference) sequence in the species. Mutations can be either recessive or dominant. Dominant mutations require only one copy of the gene to be mutated to impact phenotype while recessive mutations require both. These mutations can have (at least) three effects on an encoded protein. Synonymous mutations produce the same AMA and typically do not impact protein folding; because the redundancy in AMA-codon pairs (64 codons for 21 AMAs) single base changes may not affect the resulting AMA.[44,47,48] In contrast, a nonsynonymous substitution changes an AMA. This may produce a premature stop codon (nonsense mutation) and often a non-functional protein; or it may substitute an AMA with a new AMA with varying degrees of effect of the resulting protein (missense mutation).[47]Additionally, there are frameshift mutations which disrupt the downstream codons due to 1-2 base insertions or deletions (indels). This can have dire consequences for the organism or cell who inherits or develops such a mutation. Many times, embryos or cells which acquire such LOF mutations do not survive.[47,52] However, indels of three bases keep the transcript in frame and can produce functional proteins. Indels can occur during replication when polymerase mistakenly adds or skips bases, strand slippage, or during some DNA damage events and make up 15-21% of human polymorphisms.[53,54] Mutations moreover, can arise outside the coding region and may contribute significantly to the disease risk if occurring in a regulatory region.[55]

By far the most common DNA variations in living cells are point mutations, referred to as single nucleotide polymorphisms (SNPs) if they persist in the population at >1%.[15,54,56,57] These occur when a single letter base in the nucleic acid sequence is substituted. This can result in synonymous and nonsynonymous changes in sequence when in the coding region of a gene.[47,54] This commonly occurs during replication of the genome and in response to cellular damage/epigenetic modifications (EM). While DNA replication is a high fidelity process with proofreading methods there is still a baseline mutation rate of 3.0×10^{-8} mutations/nucleotide/generation leaving 100-200 new mutations per generation in humans.[58,59] If a mutation persists within a germline cell it will get passed down to future progeny. A mutation in a somatic cell is often less detrimental in the resulting organism as the cell may be targeted for apoptosis or supported by the surrounding normal tissue; however, this may lead to the formation of tumors and cancers in healthy tissues.[47,60] SNPs additionally may give rise to new protein functionality or gain-of-function (GOF) mutations such as the CYP2C19 *17 SNP which improved therapeutic responsiveness to clopidogrel when compared to the wild type.[61] More common, however, are LOF mutations in proteins. For example, out of the 6 cytochrome p450 (CYP450) enzymes we investigated in this study only 2 maintain relevant GOF phenotypes that are not induced.[62,63]

Within the genome, there are also transposable elements, these are mobile genetic elements capable of moving in the genome; this can cause a duplication in the gene, and it may insert a gene out of frame or under a new promoter which changes its functionality or rate of replication.[64] Changes in gene copy number can be important for the final displayed phenotype of the organisms. For example, an increase in copy number of CYP2D6 gene will increase the levels of its protein which in turn increases its metabolic activity; each copy of CYP2D6 increases the rate of function significantly and individuals will require higher doses of drug digested by the enzyme for optimal therapeutic function.[41,65] The variation in gene copy number is thought to be a large part of the variation in individual phenotype as thousands of genes, ~12% of the human genome, are variable in copy number.[66,67]

1.2.2.1 Single Nucleotide Polymorphism (SNPs) and Nomenclature

SNPs, allele, gene, and genotype all refer to heritable changes in DNA sequence, and in some cases can be used interchangeably. SNPs, alleles, and genes all refer to sequences on a single copy of the chromosome. A SNP may be considered an allele; however, an allele may be made up of different or multiple mutations. An allele is a noted mutation in a gene, while gene more accurately describes the heritable open reading frame regardless of specific allele.[50] Genotype specifically refers to the ensemble of genes/alleles on both copies of the chromosome.

Information about genotypes has traditionally been indicated as star (*) alleles. Star alleles are common genetic haplotypes often with a known phenotype; haplotypes being groups of alleles that are commonly inherited together.[68,69] Written '*number' for each gene, there is a default allele with the normal phenotype, often *1; the normal allele is often assigned when other variants in the gene are absent or not detected.[68] Star alleles are assigned and reviewed by the Pharmacogene Variation Consortium (PharmVar) (https://www.pharmvar.org/).[69] Genotypes or mutations are commonly listed by their reference SNP number. This written as (rs12345: A/A) and includes an accension number to allow researchers to easily access and catalogue genetic polymorphism for the genome location and the genotype at the site.[70] RS numbers may also be written to include the common allele at the site. In this case allele is written as rs12345: c121A> C, where the A is the major or common allele while the C is the minor. RS numbers can also be given as star alleles, compiled if the gene contains multiple mutations, although short multi-nucleotide changes, small indels, short tandem repeats, and some retro transposable elements are also recorded in RS numbers.[70–72] These numbers are assigned and annotated from submitted research by the National Center for Biotechnology Information's (NCBI) Single Nucleotide Polymorphism database (dbSNP).[70,71] To further aid in discovery SNPedia (https://www.snpedia.com/) describes significant dbSNP polymorphism in a wiki style to allow for understanding of the mutations.[73]

1.3 Methods of SNP/Mutation Detection

There are many different methods of SNP detection, the most common of which have been listed here. While there are other methods for primary sequence detection, these have either fallen out of common use, are irrelevant to the study, or are still in development.

An issue shared by the short-read sequencing methods is that they struggle assembling repetitive sequences as well as identifying indels/transpositions of genes.[8,52] Polymerase chain reaction (PCR) and its amplification applications can additionally have biases against GC rich regions due to the stability of the 3-hydrogen bond base pairing.[8,74,75]

1.3.1 Sequencing-Based Detection

The most direct method to determine genetic mutations is sequencing the genome. There are several different types and generations of sequencing technologies. These methods can detect genetic mutations in a global and unbiased fashion or can be combined with specific probes to select for genes or regions of interest.[75]

One of the initial first-generation sequencing methods, Sanger sequencing, was used in the human genome project to create the assembly.[76] In this method genetic material is extracted, and copied with dideoxy NTPs lacking a OH on the 3' carbon and tagged with a radioactive group or fluorophore; this prevents the further addition of NTPs and the DNA chain replication terminates; the library is then run through an electrophoresis gel with single base pair resolution and the identity of the NTP is assessed by excitement of the base-paired fluorescent marker.[77,78] These short-medium length (300-1000bp) reads are made into contigs and concatenated and mapped back to a reference genome or assembled de novo based on overlapping sequences.[79] These methods have the lowest throughput but have been considered the gold standard of sequencing technologies.[76,78]

The next generation of sequencing methods introduced by the Solexa/Illumina sequencing platform has significantly brought down the cost of sequencing and broke the $1000 genome barrier.[80] It is the most widely used sequencing platform allowing for the sequencing of whole genomes and has allowed for it to be feasible for small scale research projects to sequence novel genomes.[81] In this method DNA fragments are ligated to a barcoded adapter sequence and hybridized to flow cells; the sequences are then bridge amplified and the flow cell washed with tagged reversible terminator NTPs which are allowed to bind; the fluorophore is excited and an image captured of the spot to read the fluorescent identity of the paired bases; next the terminator is cleaved, the flow cell is washed again and the next base is allowed to pair.[82] This method

produces relatively short sequences (typically of around 150bps) and with an accuracy rate of 99.9% or greater for the majority of bases called.[75,83]

In recent years newer methods of sequencing have started being used commercially and in research, the most notable being Nanopore Sequencing. Nanopore sequencing runs tagged DNA fragments through an artificial pore embedded through a flow cell in the presence of an electrical current. The passing of the bases causes a change in the electrical current which is measured and recorded; this signal is decoded to give the sequence identity which can be hundreds of kilobases long.[78,84] Nanopores can also directly sequence RNA, proteins, and epigenetic modifications.[84] However, this method currently only has an accuracy rate of >98%.[85]

1.3.2 Array/ Panel Based

In addition to sequencing methods, genomic identity can be assessed through hybridization of sequences to a probe known as microarrays. Microarrays can have hundreds of thousands of probe oligos (often tailored to question of interest) bound to their surface; the surface is washed with tagged DNA fragments which are allowed to bind and sequence identity is determined by binding.[77,86] To make up for loss of throughput or genome coverage in this method, further genetic information can be imputed based on genetic haplotype.[87] Imputing takes advantage of the fact that there are groups of genes that are often inherited together. However, rates of inheritance differ by ethnicity.[88] Microarrays have been the "bronze" standard of the industry, often employed in commercial ventures.[89] Appropriately designed and run tests can have accuracy rates of >99% and are less expensive (often by a factor of 10) than other methods.[90] A single test can cost less than 100$ USD.[87]

Additional methods take advantage of the mass differences of the DNA fragments. The iPLEX massARRAY System, a non-fluorescent platform utilizes mass spectrometry to accurately measure PCR-derived amplicons. MALDI-TOF (matrix-assisted laser desorption/ionization — time of flight) mass spectrometry, coupled with end point PCR, enables highly multiplexed reactions. Polymorphic sites are detected by primer extension where the targeted region is amplified; remaining NTPs are neutralized and then a terminating extension reaction using a promoter that binds immediately upstream of the polymorphic site as a 'mass modified' NTP

lacking the 3'-hydroxyl extends the product by a single base; This allows detection and determination of sequence based on final weight and the available primers.[91–94] This systems also has a high degree of accuracy on validated assays (>99.7%).[95]

1.3.3 Copy Number Detection

Because most systems struggle with detection of gene duplications and deletions, or can be seen as too expensive or time consuming to perform at scale, the presence of these features is often verified using other methods, commonly through PCR amplification. This method has the advantages of being quick, cheap, and highly reliable.[96,97] In long-range PCR, in the presence of the gene duplication a new primer site becomes active giving two distinct sized bands on the gel analysis; in terms of a gene deletion, a distant primer site becomes energetically favorable for the reaction. Again, giving two distinct bands in the presence of a deleted allele.[98]
Quantitative PCR/ Real time PCR is also widely used. Here a PCR reaction is conducted in the presence of either nonspecific fluorescent dsDNA dye or a fluorescently labeled DNA probe, which only becomes active after the quencher is removed by the polymerase's exonuclease. [97,99] The level of fluorescence is measured at the end of each cycle or in real time and compared to the standard curve of a reference gene to determine the copy number of the gene of interest.[97,99] A similar method may also be used to detect SNPs.[97,100]

Similarly, microarrays also can detect changes in copy number. The tagged DNA of interest is hybridized to a probe and fluorescence measured. Copy number variation is determined by the ratio of relative fluorescence of each probe.[67] Microarrays can function in a broad manner to detect these types of changes across the genome.[67,77] However it cannot detect copy number variants smaller than ~80kb and is more expensive when compared to other approaches.[77]

An additional method, cytogenetic analysis, interprets chromosome structure to determine the presences of certain mutations.[86,101] Here the chromosomes are karyotyped (extracted, imaged, and paired). This can inform if the organism has a duplicated chromosome and can also detect some changes in structural features such as large gene duplications and deletions, as well as transpositions.[77] This may also be paired with fluorescent probes and microscopy to visualize presence of features of interest.[86,101]

1.4 Pharmacology of Medications

Pharmacology is broadly defined as the study of drug action.[102–104] Drugs themselves can be any substance natural or manmade, aside from a nutrient or essential dietary ingredient, that can modulate biological function.[103,104] These are mostly foreign substances, plant-derived natural products, xenobiotics, as compared to endogenous molecules.[105,106] Drugs can function by interacting with cellular products such as hormones; can act as cell products; interact with the genome, cell, or cellular machinery; directly, impede transcription and translation; and can potentially up or down regulate cell functions depending on its specific mode of action.[103,104] Drugs themselves can be made up of anything from basic elements to RNA fragments, to gene editing systems.[103] The main function of drugs today is use in medicine and helping impaired biological systems achieve and maintain homeostasis to improve or prolong health. However, the effect is highly dependent on the dose administered and too much or too little can cause adverse reactions and death.[102] Additionally, drugs need not be limited to only medicinal purposes and exist ubiquitously in today's society from components in food and manufacturing to cosmetics.[107]

The study of drugs and their effects is both a branch of medicine and one of the oldest fields of study with practitioners dating back to 150AD.[102] However, the field as we know it today came about in the mid-1800s with a focus on structure and function of drug and target.[102,103]

1.4.1 Pharmacokinetics and Pharmacodynamics of Medications

In its goal of determining the relationship between drug concentration and whole-body physiological effect, pharmacology is split into the two complementary disciplines of pharmacokinetics (PK) and pharmacodynamics (PD).

PK concerns itself with the absorption, bioavailability, distribution, metabolism, and excretion of drugs. PK can be considered as the impact of the body on drugs; conversely PD is often described as the impact of drugs on the body and studies drug dosage, route of administration, and frequency of administration.[104] Its focus is on how drug concentration at the receptor site influences intensity and time course of effect; as for most drugs, the intensity of their presence at the receptor site determines the intensity of action.[108] However, drug action is highly dependent

on host factors, such as how much of the receptor is present or the amount of metabolizing enzyme available; additionally, some drugs have a narrow therapeutic window meaning their therapeutic and toxic concentrations are close and are easily impacted by host factors.[103,104,108] Currently, the field places a large emphasis on the liver as the major location of phase 1 metabolism of drugs within the body; the smooth endoplasmic reticulum and mitochondria of liver cells contain a large number of CYP450 enzymes which catalyze the bulk of phase 1 drug metabolism.[13,106] Metabolism refers to the set of chemical reactions that take place within a cell/organism.[109] Phase 1 metabolism mainly involves breaking down lipophilic compounds to hydrophilic molecules to aid in excretion by increasing the chemical's solubility.[106] The majority of pharmaceutical compounds on the market today are lipid soluble.[110] This allows them to more easily bypass the lipid bilayer of cell membranes; however it also impacts their ability to be excreted.[111] Some drugs additionally are administered as prodrugs and are not active in their ingested form but need first be metabolized to produce therapeutic effect.[106] PK and PD surveil these interactions mainly through monitoring drug serum levels as this is correlated to levels at the active site.[103,104,108] As such, the fields of PK and PD work together to describe the pharmacological impact of drugs and increase medication efficacy while reducing toxicity.[108]

1.5 Pharmacogenomics

Pharmacogenomics, sometimes thought of as personalized or precision medicine, is a relatively new field of study, coming into real prominence in 2003 with the addition of patient genotype considerations to medication labels by FDA, and in 2004 with the first test for CYP2D6 and CYP2C19 genotypes.[24,112,113] However, the notion of individual variability impacting drug response has been well recorded since the 6th century BC where an interindividual response in fava bean poisoning was noted; this response was later shown to be attributable to a G6PD phenotype.[10] Subsequent centuries have continued to build the field, importantly in the 1950s the notion that genes can control drug response was popularized and in the 1980s and 1990s with the purification of the CYP450 enzymes.[10,13,15] PGx evolved from the field of pharmacogenetics which primarily looks at single gene associations.[10,15,26,112] The terms however have become somewhat interchangeable.[15] PGx today combines pharmacology with genomics. Taking into account both how genes interact with each other and how they are influenced by certain

medications to produce the optimal therapeutic outcome for patients.[15,113] In short, PGx wishes to describe how your personal genomic variability impacts your response to medication. The current paradigm of prescribing is a ‘one-size-fits-all’ or a ‘trial-and-error’ approach that fills standardized doses and then seeks to adjust if problems arise or if desired therapeutic effect is not achieved.[114] Currently, drugs seem to be effective only in 25% - 60% of cases.[115,116] PGx stands in contrast to that by seeking to provide targeted medication regimens tailored to each patient's individual physiology by studying the gene-drug-phenotype relationship. It seeks to identify patients likely to experience ADRs and those most likely to benefit from treatment; in addition PGx aims to establish rational dosing guidelines and inform clinical trial guidelines.[15]

New drug-gene associations are made in two main ways, through genome wide association studies (GWAS) or through studying drug PK and PD.[15,113,117] If a drug is designed to interact with a specific protein, then structure and copy number of the protein will be important to the drug's ability to function. Likewise, if a drug is known to be metabolized by a specific protein variant function will impact drug clearance. Once the identity of these enzymes and affected biological pathways have been uncovered the corresponding genes and variants can be analyzed on impact to drug efficacy both computationally and experimentally.[15,103,104,108,117] GWAS can serve to help make those associations and other correlations between genotype and phenotype. GWASs collect large amounts of patient genome and qualitative data and compare them for shared variants and any associated phenotype.[118] While powerful in making phenotype-genotype associations, GWAS studies need to be very tightly controlled and need to have sufficient statistical power to allow for any conclusions to be made. These will further need to be validated with additional directed research.[15,118]

1.6 Pharmacogenes

Genes which exhibit pharmacological importance, able to attenuate drug PK or PD, are labeled pharmacogenes.[117,119] Pharmacogenes additionally can be thought of as genetic biomarkers. These are DNA sequences associated or indicated in disease.[16] Alleles in these pharmacogenes are strongly associated with the variety of drug responses we see in individuals.[117] Clinical pharmacogenes are graded on their relevance and withstanding evidence of significance for impacting a specific drug; to this end these genes are often found as drug targets or in

metabolism or transport pathways, which would impact clearance of the compounds.[117,120–122] The CYP450 class of enzymes are responsible for metabolizing 70%-80% of pharmaceuticals on the market.[62] The CYP450 enzymes are responsible for the clearance of foreign compounds by breaking them down into their water-soluble forms, as well as the production and activation of some endogenous molecules such as hormones; they are primarily monooxygenases, but they are also capable of catalyzing reduction, hydration, and a variety of other reactions.[62,106] While their expression is differentially regulated, they are distributed through all tissues with high levels of activity in the liver as well as the gut and central nervous system (CNS).[62,106,123] Currently, 115 genes and pseudogenes have been found to encode human CYP450 enzymes; of these 57 are genes which are broken into 18 families and 44 sub families.[62,123] A large degree of polymorphy, including change of copy number, is seen in the genes to which a wide degree of enzyme function ranging from ultra-rapid metabolizers of a substrate to complete LOF phenotypes can be attributed. The CYP450 alleles are categorized by their phenotype and generally reported as ultra-rapid, extensive/normal, intermediate, and poor metabolizers of their substrate.[41,124] Their activity can also be attenuated by certain medications which will impact the metabolism of all compounds processed by the enzyme; often pharmaceuticals will only be metabolized by one or few of CYP450 gene products allowing clear associations to be created.[62,123,124] This makes them an important class of molecules to research when making personalized medicine assumptions.

Six CYP450s are evaluated in this study in addition to two pharmacogenes involved in cellular transport. While in the CYP 1, 2, and 3 families, approximately 12 of the CYP450 genes are known to be involved in drug metabolism; 6 of those CYP450s metabolize the majority of the drugs acted on by the enzyme family.[62,106]

CYP1A2 is the metabolizing enzyme for around 9% of all clinical drugs, but is often not the most important factor.[62,63,125] It is highly expressed in the liver where expression can be induced by some polycyclic aromatic hydrocarbons such as those found in cigarette smoke. These may be broken down by the enzyme into some procarcinogen compounds.[62,63,125–128] CYP1A2 appears to have a preference for aromatic amines and heterocyclic compounds.[62] It is involved in the metabolism of pharmaceuticals such as olanzapine, clozapine, duloxetine, acetaminophen and propranolol, while caffeine, clozapine, clopidogrel are most significantly metabolized by

it.[62,63,126,129,130] CYP1A2 activity may also be impacted by some medications such as being reduced by oral contraceptives and fluvoxamine and induced by omeprazole and caffeine.[63,131] The most clinically significant variant of the CYP1A2 allele is *1F which consists of a single SNP (rs762551:C > A) and is characterized as an ultrarapid metabolizer.[62,63] This allele is phenotypically relevant in the presence of an inducer such as patient smoking.[130,132] The AA genotype has been associated with nonresponse to clozapine and reduced efficacy of olanzapine.[63,129,133] The C allele has been associated with increased risk of ADRs from some antipsychotic substrates.[63,134]

CYP2C9 is expressed predominantly in the liver where it is the second highest expressed CYP450 enzyme.[62,135,136] It is responsible for 15%-20% of the phase 1 drug metabolism and has preference for weakly acidic substances.[62,136] Its substrates include nonsteroidal anti-inflammatory drugs, oral antidiabetic agents, and angiotensin II receptor blockers. It is also the major enzyme involved in the clearance of warfarin.[62,136,137] However, it is estimated to contribute to only 10% of the variability in warfarin response with the remainder made up by other gene variants, age, sex and other individual factors.[138,139] CYP2C9 is induced by rapamycin which can increase the system clearance of other medications.[136,140] It is inhibited by a variety of compounds including fluconazole, amiodarone, and sulphathiazole.[136,141] This may lead to ADRs in polypharmacy patients as some compounds processed by CYP2C9 have a narrow therapeutic window.[136] Both the *2 and the *3 alleles have clinically relevant phenotypes and are characterized as poor metabolizers, resulting in lower rates of clearance of substrates.[62,136] The *2 allele is characterized by the rs1799853: C > T mutation that replaces an arginine residue with a cysteine; this does not appear to affect substrate binding, but does decrease enzyme activity by approximately 50% when compared to the wild type.[136] Homozygotes for the allele have impaired clearance of phenytoin, tolbutamide, ibuprofen, nateglinide, fluvastatin, and phenprocoumon by 68%-90%.[136,142] The variant exists in Caucasian populations at 10%-20% but is rare in populations of Asian or African descent.[136,143] The *3 allele defined by rs1057910 A > C and clearance of substrates is reduced.[62,136,142] Heterozygotes for this variant have been estimated to have about half the clearance of S-warfarin, tolbutamide, fluvastatin, glimepiride, tenoxicam, candesartan, celecoxib, phenytoin.[136,142]

CYP2C19 is responsible for metabolism of drugs such as antidepressants, benzodiazepines, mephenytoin, the antiplatelet prodrug clopidogrel and it is the major enzyme for metabolizing proton pump inhibitors (PPI).[42,62,144] The enzyme is expressed predominantly in the liver but also appears in the gut.[42,128] Steroid oral contraceptives can down regulate the gene and some SSRIs have an inhibitory effect such as omeprazole; CYP2C19 is inducible by some endogenous hormones and some drugs including rifampicin, ritonavir, and dexamethasone.[42,62] Three allele variants are commonly clinically evaluated, the *2, *3 and *17 alleles. The *2, rs4244285 G > A, allele for an additional splice site.[62,144,145] The rs4986893 G > A mutation which characterizes the *3 allele and results in a premature stop codon.[62,144,146] Both the *2 and *3 result in truncated protein products and LOF mutations.[62,144–146] Additionally, both alleles are more common in Asian populations, 25%-29% and 2%-9% respectively; the *2 allele is more common in general and is found at 12% in Caucasians and 15% in African Americans while *3 has an allele frequency of below 1% in other populations.[62,143–147] The *17 mutation is characterized by the rs12248560: C > T allele; this mutation is in the promoter region of the gene to create an enhancer site.[42,62,148] This results in increased expression and a GOF and ultrarapid metabolizer phenotype.[144,148] The allele is predominantly expressed in Caucasian populations (21%); it can also be found in those of African American (15%) and Asian (3%) descent.[143,144,148] This gene however is evaluated with CYP2D6 to make prescribing decisions for some antidepressants.[42,149]

While CYP2D6 makes up only ~2% of CYP450 content in the liver, this enzyme metabolizes up to 25% of all commonly prescribed drugs and is required for the metabolic activation of several others.[13,41,62] In addition, CYP2D6 can be found expressed in the intestines and central nervous system (CNS).[62,128] The gene is the only functional member of the CYP2D family and is considered not inducible; though, there are many substances that may inhibit its activity by binding to the enzyme such as the drug methadone[41,62,150,151]. The CYP2D6 gene is highly polymorphic with over 100 characterized alleles, alternative splicing events, and even full gene deletions[152]. In addition, changes in copy number can dramatically increase enzyme function and fold changes between 2-13 have been observed[41,153]. Protein function for CYP2D6 is also dynamic with GOF, LOF, and null mutations present in all populations[41,143,152,154]. The null

mutation exists most frequently in Caucasian populations with the *4 allele at 20%-25%.[62,143,147] The allele meanwhile is rare in African and Asian populations, however, the gene deletion *5 is found in most populations at 3%-5%; the presence of the LOF mutations *10 in Asians and the *17 in Africans persist with a frequency of up to 50% and 30% respectively, while Caucasians have a 10% chance of carrying both LOF allele and a null mutation[62,143,147]. Changes in copy number also can occur frequently, upwards of 50% in some populations. In Caucasians copy number duplicates exist at 1%-5%[62]. The medication classes metabolized by CYP2D6 are extensive and include those involved with the CNS (various classes of antidepressants, anti-psychotics, and opioids) or cardiovascular systems (such as antiarrhythmics and beta-blockers), as well as antihistamines, antimalarials, and amphetamines[41,62]. Phenotype will be impacted by the metabolizer state of the individual which is determined by the most functional version of the allele present[41].

CYP3A4 is predominantly expressed in the liver and intestines where it is the most abundant CYP450 isoform making up 15%-20% of hepatic and 70% of gastrointestinal CYP450 content.[62,128,155–157] Despite this, enzyme levels between individuals has been found to have up to 100-fold variability in its expression; this variability has not been well linked with changes in CYP3A4 genotype.[62,156,158,159] However, the *22, rs35599367: C>T, allele has been shown to decrease enzyme activity and increase plasma serum levels of metabolized substrates.[62,156,160,161] The enzyme is thought to metabolize 30% to 50% of oxidized pharmaceuticals and is sensitive to both induction and inhibition.[116,156] The enzyme itself is large and can accommodate big lipophilic molecules along with some smaller substrates.[62] CYP3A4 metabolizes drugs from most classes of medications and the *22 genotype is known to impact the metabolism of some substrates such as erythromycin, cyclosporin, tamoxifen, and fluticasone.[159,160] The allele is present in between 3 and 5% of Caucasians but is rarer in other ethnic groups.[147,160]

The CYP3A5 gene is related to CYP3A4 and the proteins share a >85% sequence similarity.[62] In some individuals a functional copy of CYP3A5 can partially substitute for impaired CYP3A4 expression.[62,160] The two enzymes overlap in substrate specificity however still show some preferences, such as for atorvastatin which is catalyzed 16-fold more effectively by

CYP3A4.[62,162] The functional version of the allele *1 exists predominantly in populations of African descent at levels up to 60%.[62] The non-functional copy of the gene *3 is the major allele in Americans, Europeans, and East and South Asians with population frequencies of 80%, 94%, 71%, and 67% respectively; the allele also exists in African populations at 17% along with two other null mutations *6 and *7 which have frequencies of 15% and 10%.[62,147,160,163] The *3 rs776746: A>G mutation creates an aberrant splicing forming a truncated protein. This mutation is most notably associated with increased plasma concentrations of tacrolimus and additionally may impact the metabolism of statins.[62,160,164,165]

In addition to the 6 main hepatic CYP340 isoforms, our study also focused on 2 other genes necessary for the proper clearance or function of commonly prescribed pharmaceuticals:

The VKORC1 gene encodes the rate limiting step in the vitamin K cycle; the VKORC1 enzyme, a vitamin K epoxide reductase, converts vitamin K epoxide to vitamin K which is a cofactor of several coagulation factors.[138,166] The enzyme is localized to the endoplasmic reticulum of hepatic cells and other tissue types.[128,138] VKORC1 is inhibited by Warfarin—this decreases vitamin K levels and increases the risk of hemorrhagic bleeding.[138,166] Warfarin has a small therapeutic window and a large degree of phenotypic response is seen in individuals. VKORC1 accounts for up to 25% of this variability.[138,139] The rs9923231: G>A SNP changes a nucleotide in the transcription factor binding site and reduces levels of VKORC1 expression up to 44% when compared to the wild type allele.[138,167] The effects of the allele are also additive and each allele is predicted to reduce the necessary warfarin dose by 28%.[168] This variant is the major allele in some populations and has a frequency of 90% in people of Asian descent and is common in other ethnicities such as Caucasians with an allele frequency of around 40%.[138] This allele is the most important determining factor for initial warfarin dose.[138,139,168]

SLCO1B1 encodes the transporter protein OATP1B1 which is responsible for the active transport of many drugs and endogenous compounds into hepatocytes where the enzyme is localized to the basal lateral membrane.[169,170] OATP1B1 is especially important to the statin drug class as it is primarily responsible for transport of the molecules; additionally, the site of action

for statins is in hepatocytes where they impact the production of cholesterols. [169,171] LOF mutations in SLCO1B1 genotypes may affect the efficacy of some statins but also increase the risk of myopathy due to increased plasma concentrations.[169,171] The SLCO1B1 allele rs4149056: T > C defines the *5 variant and is present in the *15, *16, *17 haplotypes.[169] The *5 allele is most predictive of myopathy risk in simvastatin patients.[171] In addition, *5 has been associated with increased plasma levels of medications of other classes such as repaglinide, irinotecan, and bilirubin.[169] The allele is most common in Caucasians and Asians with a frequency of between 12%-20% and 6%-19% respectively, followed by between 1%-4% in African Americans.[169]

1.7 Accreditation Agencies – CLIA, CAP, DAP, and the FDA Regarding LDT

1.7.1 Sources of Information: PharmGKB and CPIC

In order to collect and disseminate PGx information several different working groups have been formed. The Pharmacogenomics Knowledge Base (PharmGKB) (https://www.pharmgkb.org/) is part of the National Institute of Health's (NIH) Pharmacogenomics Research Network (PGRN) (https://www.pgrn.org/); which additionally supports the Clinical Pharmacogenomics Implementation Consortium (CPIC)(https://cpicpgx.org/) and PharmVar.[172] PharmGKB is an online resource that parses the available scientific literature to form an annotated database that helps researchers understand genotype variant-drug associations and the impacted biological pathways.[121] PharmGKB ranks associations based on four levels of evidence, Figure 1.1. The lowest level 4 is described by case reports, studies unable to meet significance, or in vitro assays; level 3 includes uncorroborated studies with statistically significant findings. [121] Levels 1 and 2 are split into 2 subcategories each. 2b describes variants with replicated evidence although the studies may show significance; 2a builds on that by including variants in already important pharmacogenes. [121] Level 1b shows a strong level of evidence collaborated by multiple studies with significant p-values while level 1a is reserved for those variants which have medical endorsed guidelines or implemented labeling. [121] In order to provide the most accurate information, risk is given as a relative risk based on the other variant genotypes.[121]

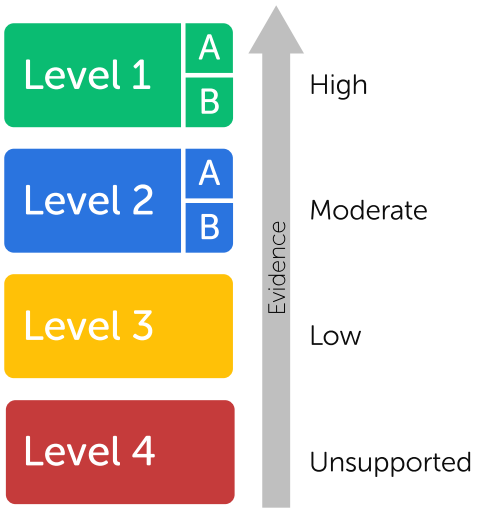


Figure 1.1 PharmGKB levels of evidence. PharmGKB annotates important pharmacogenes for which there is moderate evidence into VIP reference summaries.[121] Image taken from PharmGKB.org under their creative commons licence (PharmGKB, 2021).[173]

Specifically, in order to help guide clinical implementation of PGx PharmGKB has branched into the CPIC which aims to give standardized information on dosing-guidelines for genotype variations.[120,121] CPIC uses a similar 3 level scale for clinical significance as PharmGKB. Level 3 indicates a lack of sufficient information; level 2 the evidence is sufficient but limited and level 1 provided strong validated evidence. [120] A rating system is also used to denote the strength of the recommendation; C indicates sub-optimal, B moderate, and A strong evidence.[120] In addition, CPIC provides the information needed to interpret genomics tests, including the severity of the disease, therapeutic index of the drugs, availability of tests, and alternative medications as well as guidelines for polygenetic variation.[120]

Some countries have their own version of the CPIC such as the Dutch Pharmacogenomics Working Group (DPWG). The DPWG consists of a multidisciplinary consortium that publishes PGx dosing guidelines and surveils PGx implementation for the Netherlands.[122] DPWG has published over 80 dosing guidelines from which there appears to be a high rate of concordance with CPIC.[174]

1.7.2 Role of Drug Approval Agencies: The FDA as an Example

The USA Food and Drug Administration (FDA) reviews, oversees and approves clinical trials, new drugs, medical tests, and medication labeling, as well as oversees general drug safety. The agency supervises the world's largest pharmaceutical market, making up 40.4% of total global sales in 2018.[175] This emphasis on the FDA may be due to the fact that the USA does not control drug pricing which incentivizes all drug manufacturers to seek first approval of novel compounds and tests through the FDA. For example, 43.7% of novel active compounds have their first patent filed in the USA.[176] Because of this, other agencies such as the equivalent, Health Canada and European Medicines Agency have measures for acceptance of FDA approved compounds.[177] Due to its share of drug approvals the FDA has become a prominent source for drug and medical device testing information.

The FDA's department of pharmacology includes The Genomics and Targeted Therapy Group which assists in applying PGx to the research and development process as well as integration into clinical practice.[178] The FDA supports the application of PGx by publishing guidelines for conducting clinically relevant PGx research; conducting regulatory reviews and sponsoring researchers; promoting educational outreach; and developing guidelines and policy for the use of PGx information.[178] To this end the FDA lists the pharmacogenetic associations for gene variants related to drug metabolizing enzymes, drug transporters, and certain ADRs. The FDA lists 109 drug-gene associations that it has found evidence for significant response and has approved over 125 nucleic acid based companion diagnostic test.[179,180] Additionally, the FDA (as of August 2020) lists 431 drugs that have edited labeling to include information about relevant PGx biomarkers.[181]

1.7.2.1 Laboratory Diagnostic Tests

Laboratory diagnostic tests (LDTs) are medical devices used in determination of disease or condition from bodily substances such as sputum, blood, or tissue.[182] This may be developed as a commercial product which is shipped to a laboratory or done as in-house testing. PGx tests fall under this category. LDTs have additional regulation and oversight from the FDA and related agencies. The Clinical Laboratory Improvement Amendments (CLIA) modified the Public Health Services Act in 1988 with quality and certification standards for LDTs.[183,184] CLIA

standards have continued to be amended and are applied and enforced by three agencies: The FDA, the Centers for Medicare & Medicaid Services (CMS), and the Center for Disease Control .[184,185] However, the CMS is the agency primarily responsible for regulating laboratory testing. The goal of CLIA legislation is to ensure that care received is standardized, reliable results regardless of diagnostic test or provider.[184] All providers of LDTs in the USA must become CLIA certified.[184] In addition to CLIA certification providers of LDTs may opt to receive College of American Pathologists (CAP) diagnostic testing certification. CAP is the largest association of pathologists and offers stringent peer-reviewed regulation of laboratory diagnostics.[186,187] CAP standards are updated yearly and laboratories are assessed every 2 years.[186] CAP accreditation is recognized both internationally and by the CMS in place of CLIA certification.[187]

In Canada, the College of Physicians and Surgeons of British Columbia offer a Diagnostic Accreditation Program (DAP). DAP establishes and monitors performance standards for LDTs and other diagnostic services in only in BC.[188] However, DAP includes that all private and public facilities must be accredited.[188] The governmental regulatory agency Health Canada accredits and monitors LDTs within the country when offered as medical devices. However, a loophole in Canada's regulatory law allows LDTs to be offered without accreditation in some provinces if not offered as a test kit.[189]

Chapter 2: Experimental Design – Experimental Setup

Our project took place in community pharmacies around BC in partnership with practicing pharmacists. Designing and implementing a study which allowed us to estimate the economic and emotional impact of preemptive PGx testing as well as a basic genetic analysis required input from all study members. Derek Desrosiers (DD) and Corey Nislow (CN) were responsible for the study design. Some pharmacists, pharmacies, and standardized operation procedures (SOP)s were maintained from Phase 1 of the project which provided the framework for Phase 2 and the current study. A goal of Phase 1 was to facilitate the entry of PGx testing into pharmacy practice and to create SOPs that would allow quality care at any pharmacy location. The current study aimed to build on that base, refining some SOPs and expanding our network of pharmacies. We also returned the results of PGx testing to patients and their pharmacists/physicians in Phase 2. This included monitoring resulting medication changes. We further completed a comparison of TRS and array based genotyping methods. This chapter highlights the experimental design of the study and the methods completed by the graduate researcher, Samantha Breaux (SB), for the Pharmacogenomics at the Point of Care: A Community Pharmacy Project in British Columbia (Phase 2) project of which this thesis is based on.

2.1 Pharmacy and Pharmacist Selection

Community pharmacies were selected to reflect a diversity in geography and practice environments in BC, Figure 2.1. Pharmacies were required to have expressed interest in participating, a corporate membership with the BC Pharmacy Association, a sufficiently private counselling area, and adequate staffing to ensure that the pharmacist could have uninterrupted time with participants during the education and consent process. Additional pharmacies were added throughout the project as needed. At the start of this study we recruited 34 pharmacists at 21 different community pharmacies in 15 different communities. Taking into account individual turnover, we ended up with 21 pharmacists recruiting patients at 17 participating community pharmacies in 13 locales across the province as shown in Table 2.1.

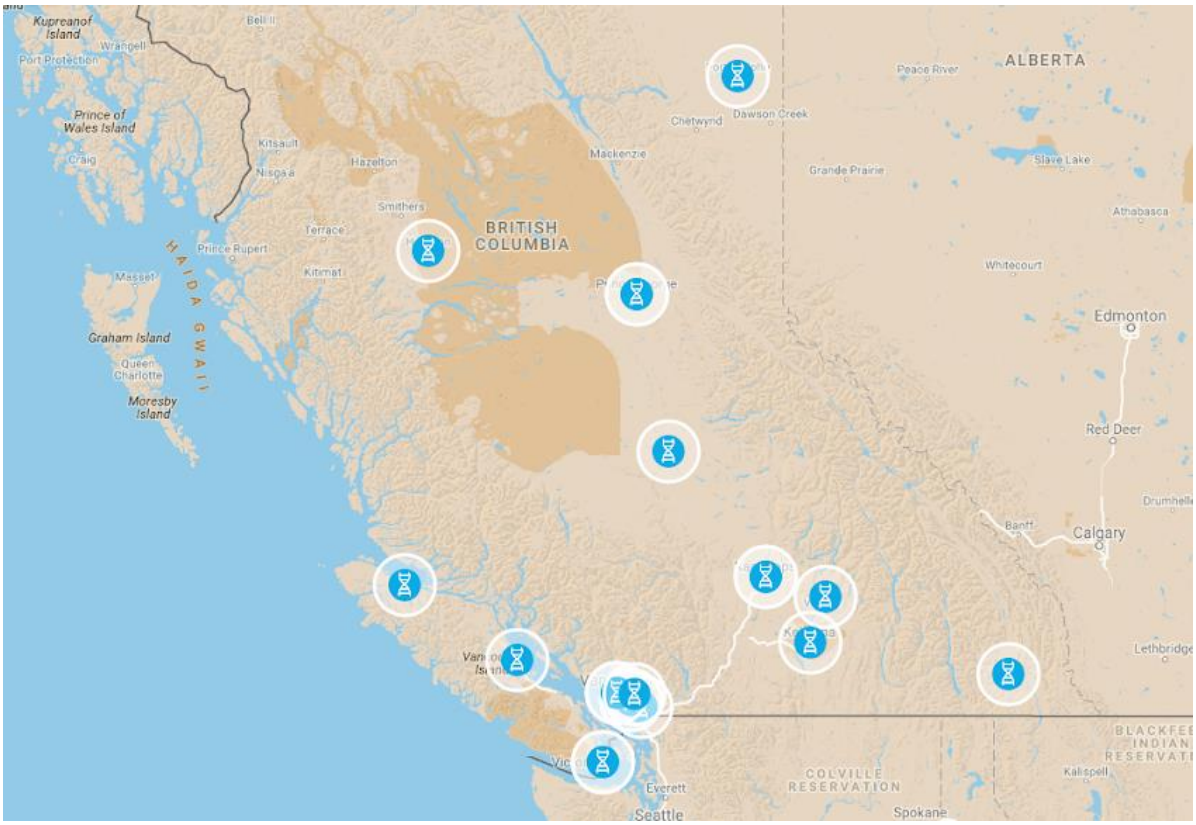
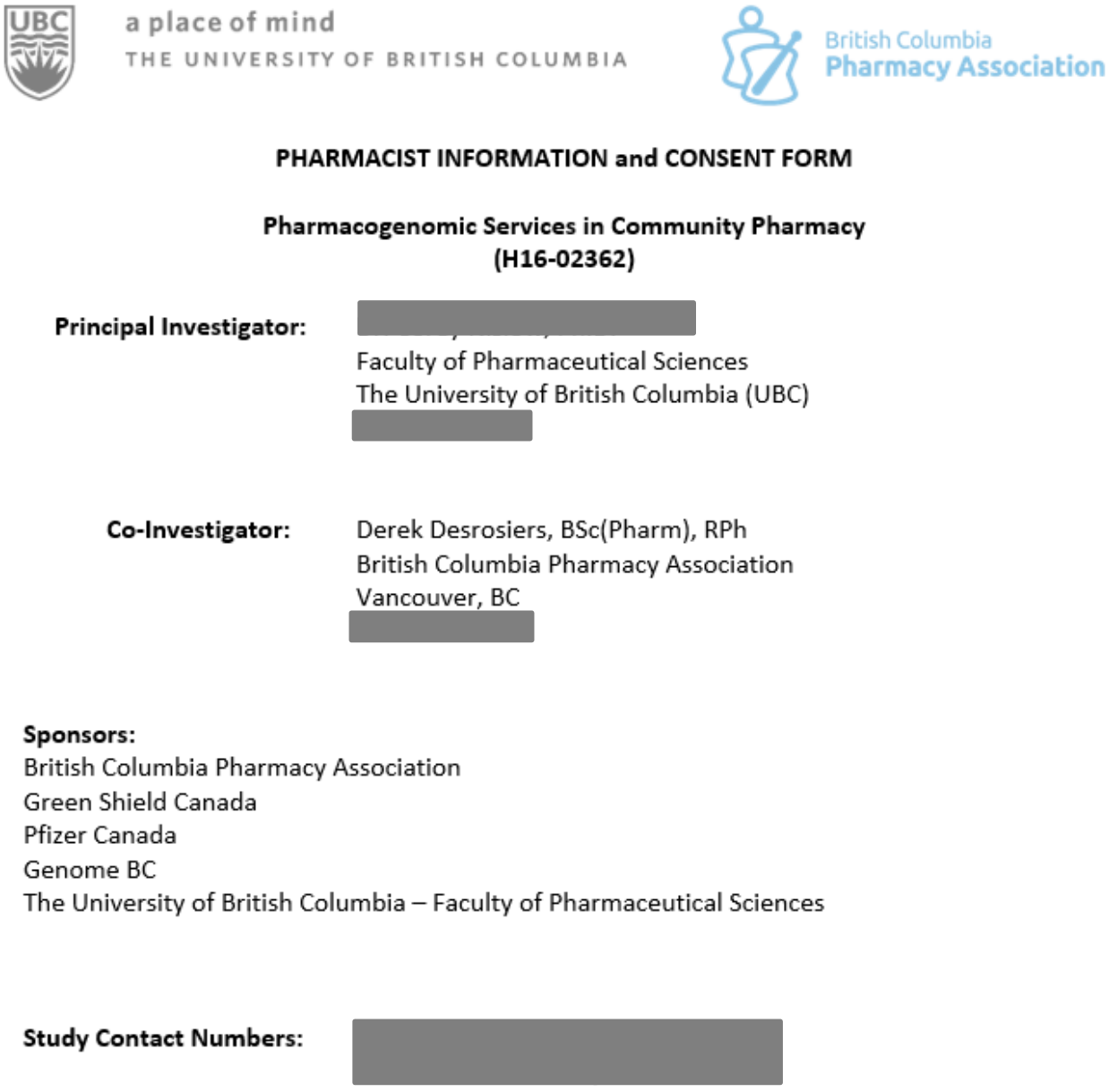


Figure 2.1 Map of participating Pharmacies.

Table 2.1 Participating pharmacies and their locations.

Pharmacy	City
Armstrong Pharmacy	Armstrong
BC Pharmacy Association	Kamloops
Harbourside Pharmachoice	Port McNeill
Hart Drug Mart	Prince George
Heart Pharmacy Ida	Victoria
Lakeside Medicine Centre	Kelowna
London Drugs #67	Courtenay
Naz's Pharmacy No. 2 Ltd.	Surrey
Pharmasave #032	Houston
Phoenix Dispensary	Prince George
Pratt's Compounding Pharmacy	Kamloops
Quadra Village Drug Mart	Victoria
Safeway #4918 (Willow brook)	Langley
Save-on-foods Pharmacy #987	Williams Lake
Shoppers Drug Mart #2212	Surrey
Wellness Pharmacy #1	Vancouver
Wilson Pharmacy	Port Coquitlam

Pharmacists were either self-selected or identified by their supervisors. They had to be able to participate in the study in addition to their usual responsibilities. Most new sites started with one pharmacist. However, as the study proceeded additional pharmacists were trained in order to increase enrollment.



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British Columbia
Pharmacy Association

PHARMACIST INFORMATION and CONSENT FORM

Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Principal Investigator: [redacted]
Faculty of Pharmaceutical Sciences
The University of British Columbia (UBC)
[redacted]

Co-Investigator: Derek Desrosiers, BSc(Pharm), RPh
British Columbia Pharmacy Association
Vancouver, BC
[redacted]

Sponsors:
British Columbia Pharmacy Association
Green Shield Canada
Pfizer Canada
Genome BC
The University of British Columbia – Faculty of Pharmaceutical Sciences

Study Contact Numbers: [redacted]

Figure 2.2 Page 1 of 6 of the pharmacist information and consent form. Details study contacts and sponsors. Blacked-out sections contains contact information. For full form see Appendix-I.

In order to be enrolled in our study the pharmacists had to read and fill out the Pharmacist Information and Consent Form, Figure 2.2. This 6-page document is an invitation to the study and describes in detail the expected role of the pharmacists, the purpose of the study, the benefits of their participation, and how their information will be kept confidential. They then have a place to sign and consent to follow all pharmacists' codes of ethics and rules laid out by the study. With the study team member, the pharmacist discussed the project's principles of informed consent, privacy requirements, patient education, information collection, and reviewed a consent checklist designed to guide the education and process. At the conclusion of this session, the pharmacist was asked a series of questions based on the training they received.

2.1.1 Pharmacist Training

In addition to the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans Course on Research Ethics the pharmacists had to complete a study training program done remotely via webinar and phone. The goals of the training were two-fold, i) to ensure pharmacists followed all the requirements of the law and Research Ethics Board of the University of British Columbia (UBC), especially with respect to patient privacy; and ii) to ensure that the patient experience was consistent regardless of the pharmacy type or location.

2.1.1.1 Operations Logistics and Report Interpretation

The details of sample collection, handling, return, and documentation were discussed with a team leader. Pharmacists were required to complete the myDNA online pharmacist training program for PGx. This provides an overview of PGx as well as interpretation of the myDNA reports they would receive. The learning objectives for this training were, i) understand the basis of CYP450 genes/enzymes associated with clinical dosing guidelines; ii) understand how variants affect an individual's ability to metabolise medications; and iii) how to apply this knowledge in clinical practice to improve their patients' outcome.

2.1.1.2 Quality Control

Before the pharmacists enrolled patients in our study, a phone call to role play the registration and consent process with a study team member was conducted. The study team member

completed the consent checklist during the process and at the end of the session reviewed the terminology, phrasing, and content with the pharmacist.

The patient recruitment checklist was designed to ensure that the proper consent protocol was followed for each patient and to ensure study team members that all ethical and legal compliances had been followed, Figure 2.3. It also guided the pharmacist through the enrollment process to ensure standardization of enrollment between pharmacists, pharmacies, and patients.

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PARTICIPANT RECRUITMENT CHECKLIST
Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Date		
Ensure you complete and document the following steps when recruiting a participant for the study so they may provide consent. **Write down any relevant notes/discussion that come up during the process.**		
☐	Move participant into private area – verify they have about 20-25 mins.	
☐	UBC Pharmaceutical Sciences leading the research, funded by Genome BC, Pfizer and Green Shield.	
☐	Participation is voluntary, won't have any effect on healthcare they receive from pharmacy or other healthcare providers whether they participate or not.	
☐	Project is looking to recruit participants who: • are currently taking or have previously taken one of the qualifying drugs • understand English or have a competent translator • are 19 years or older • are able to provide consent & info required	
☐	You and the research team have been trained on consent procedures, handling saliva samples and maintaining privacy & confidentiality in compliance with applicable laws.	
☐	Identify the purposes of the research project: 1. Assess public and patient receptivity to receiving pharmacogenomic sequencing and advice in community pharmacies.	
☐	2. Outcome analysis of the test results.	
☐	3. Validate storage and communication of actionable data	
☐	4. Capture patient experiences.	
	5. Creating digital database of DNA sequence info for future research.	
	6. Inform the heath care case and financial case for PGx implementation.	
☐	Participation advances genomic research. Participant will receive test results and medication may be altered.	
☐	Clearly explain what you require of the participant and re-iterate what the study requires: • Consent	
☐	• Saliva sample	
☐	• Personal info (may contact if something missing or for future research)	
☐	• Medication/medical history – will be linked to DNA info for research purposes	
☐	Explain/reassure the participant about what will happen to their personal info: • Protected by privacy laws at all times.	
☐	• Only project manager, principle investigator or his designate will have access to identifying info.	
☐	• Once participant info & saliva sample received at UBC, will only be identified by participant code.	

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☐	• Key file will be only link between participant codes & identifying info. The key file, will be transferred to a separate drive which will be kept in a secure location within UBC with limited access.	
☐	• No personal info sold or used for commercial purposes. Identity will not be disclosed in any report.	
☐	• All identifying info and saliva samples will be destroyed by December 31, 2020. De-identified digital DNA sequences retained until no longer useful for research.	
☐	Re-iterate: A project goal is to create a digital database of DNA sequence info – means that de-identified DNA info could be used for other research (with ethics approval).	
☐	Can withdraw any time without giving reason (until key filed destroyed - Dec 31, 2020).	
☐	Can contact you or contacts listed in info package for questions or withdrawal.	
☐	By consenting, participant does not give up any legal rights if they become ill or injured as a result of participation. • Risk is extremely low since – only providing saliva sample & some personal/medical info.	
☐	Study will not cost anything except their time. Will receive a report for participation.	
☐	Show video to explain some science and procedures. Stay with them to answer questions.	
☐	Ask participant to explain what they understand and think of the info they've heard and seen. Any questions or more information required?	
☐	Explain what the participant needs to do next: 1. Take Participant Info Package and Consent Form home to review.	
☐	2. Understand their obligations and how their info, saliva and DNA is going to be used.	
☐	3. If they still want to participate, a second meeting is required to: a. Sign the consent form. b. Collect the saliva sample. c. Obtain some personal and medical info. i. Show Data Collection Form & Participant Identifying Form	
☐	Arrange follow-up meeting. • Bring in meds or list of meds. • Must not eat, drink, smoke, or chew gum 30 mins prior to second meeting for saliva collection.	

Pharmacy Name			
Pharmacy Address			
Pharmacist Name		License #	
Pharmacist Signature			

Figure 2.3 Pages 1 and 2 of the patient recruitment checklist.

2.2 Patient Selection and Consent

To be enrolled in the study a potential participant must have been over 19, speak English, and needed to be taking at least 1 of the MHCs listed in Table 2.2. Pharmacists were prohibited to search patient records to identify eligible participants. Despite this, 5 patients were enrolled by pharmacists who were not on one of the listed MHCs.

Table 2.2 Study compounds. Patients had to be currently taking at least one of the medications in the table to be included in the study. Included is the usage frequency of each drug. Some patients were taking multiple compounds.

Antidepressants	Usage	Antidepressants	Usage	Antipsychotics	Usage
Agomelatine	0	Mianserin	0	Aripiprazole	9
Amitriptyline	12	Mirtazapine	12	Clozapine	0
Citalopram	26	Moclobemide	2	Haloperidol	0
Clomipramine	0	Nortriptyline	6	Olanzapine	5
Dothiepin	0	Paroxetine	2	Quetiapine	24
Duloxetine	10	Sertraline	17	Risperidone	4
Escitalopram	27	Trimipramine	0	Zuclopenthixol	0
Fluoxetine	12	Vanlafaxine	23		
Fluvoxamine	1	Vortioxetine	2		
Imipramine	1				Total: 195

The patient consent and enrollment process, like the pharmacist training, was rigorous and uniform, regardless of location or the pharmacist. A participant information session took approximately 30-45 minutes and proceeded as follows. In a private area of the pharmacy, the pharmacist explained the project and summarized the Participant Information & Consent Form, Figure 2.4. A checklist was completed for each potential participant. The potential participant was then shown a video specifically developed for this project. The video, Appendix - II, introduced the key concepts of PGx and the goals of the research project. The pharmacist watched the video with each patient to ensure that concepts were clear and to answer questions as necessary. The potential participant was then given the Patient Information & Consent Form to review, and was required to wait at least 24 hours before committing to the study. This allowed patients time to reflect, to discuss the project with other family members or caregivers, and to obtain additional information to make an informed decision about their participation.

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Pharmacogenomic Services in Community Pharmacy
Principal Investigator: [redacted], Associate Professor, UBC

Principal Investigator: [redacted]

Co-Investigator: [redacted]

Participant Consent Form

My pharmacist explained the research project objectives, the benefits and potential harms and discomforts to me and answered the questions posed by me. In addition, I have read and understood the information provided to me by my pharmacist, in writing and presented in a video. I have been able to reflect on the request for information and ask for advice if needed.

I understand that:

- my pharmacist will collect my saliva, identifying information, demographic information and medical information
- the information collected will be kept confidential and secure as described in the participant information section
- my participation is completely voluntary and I can withdraw from the study at any time
- this study may not provide me any direct benefits for participation
- I will receive a copy of this signed consent form for my records
- I may contact the pharmacist or study team at any time to access or correct my personal information
- I will not be provided my DNA sequence however I will be provided genetic test results in a clinically actionable report
- I am not waiving any of my legal rights as a result of signing this consent form

I consent to:

- participate in this study
- the pharmacist identified below collecting my identifying, demographic and medical information from me and sending it to University of British Columbia for use in the research study "Pharmacogenomic Services in Community Pharmacy"
- the pharmacist, on behalf of the study team, taking my saliva sample for use in the study as described in the participant information section
- my saliva sample with my identifying, demographic and medical information to be sent to the University of British Columbia for use in the research study "Pharmacogenomic Services in Community Pharmacy" as described in the participant information section
- my genetic data being sent securely, along with my demographic and medical information in a de-identified manner to myDNA Australia to have a clinically actionable report generated
- the pharmacist reviewing the results of my genetic tests (clinically actionable report) with me

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- my DNA sequence information to be securely stored at UBC for as long as it remains useful for research purposes for this study or by other researchers
- my DNA sequence information to be shared with other research groups who have obtained necessary ethical and legal approval
- being contacted to participate in additional research to providing additional medical information or clarifying information provided

Participant 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**

Figure 2.4 Pages 11-12 of the participant consent form. Details what knowledge the participant is responsible for and what they are agreeing to. Places to sign for participants and witness, if required. Blacked-out sections contains contact information. For the full document see Appendix – III.

The participant information and consent form is a 12-page document combining all the study information for the patients to review and sign if they agree to participate, Figure 2.4. Along with study contacts the manuscript overviews the concept of consent and how to withdraw, study background and procedures, researcher, pharmacist, university and participant responsibility, benefits and risks to participating, and discusses what happens to data at the end of the study. The consent form itself verifies that the participant understood the information they received both through the information packet and from their pharmacist and records their interests in participating in the study.

In addition to the patient information and consent form we included information on what would happen in case clinically actionable results were found during the course of the study, Figure 2.5. This goes over the options that the participants can take: do nothing, make a change, or recommend a change to their primary care provider. It also lists the role of the pharmacist in interpreting the patients results and role in medication changes.

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Clinically Actionable Results Plan

If a "clinically actionable result" is detected;

The pharmacist will review all report results with the participant including recommendations related to all clinically actionable results. The pharmacist will then review other pertinent information on the participant's medication profile in the pharmacy as well as on PharmaNet. Taking all the available information into account, the pharmacist will decide on a potential course of action and discuss the options with the participant. A decision will then be made jointly by the pharmacist and participant to act in one of three possible ways as follows:

(i) Do nothing and send a copy of the report to the participant's physician for addition to their medical record.

(ii) Make a change to the participant's drug therapy by either changing a dose, discontinuing a medication or making a therapeutic substitution to change a medication. In this instance, the pharmacist would initiate the change in drug therapy and immediately (within 24 hours) report the details of the change, in writing, to the participant's physician along with a copy of the report.

(iii) Make a recommendation to the participant's physician to either changing a dose, discontinue a medication or make a therapeutic substitution to change a medication. It will be up to the physician to act upon any such recommendation or not.

If a decision is made to alter the medication dose, based on the pharmacogenomics report, this will be conveyed using protocols that are already in place. As per Profession Practice Policy 58 (PPP-58) of the College of Pharmacists of BC, the pharmacist will complete the Documentation and Notification Form and send it to the physician.

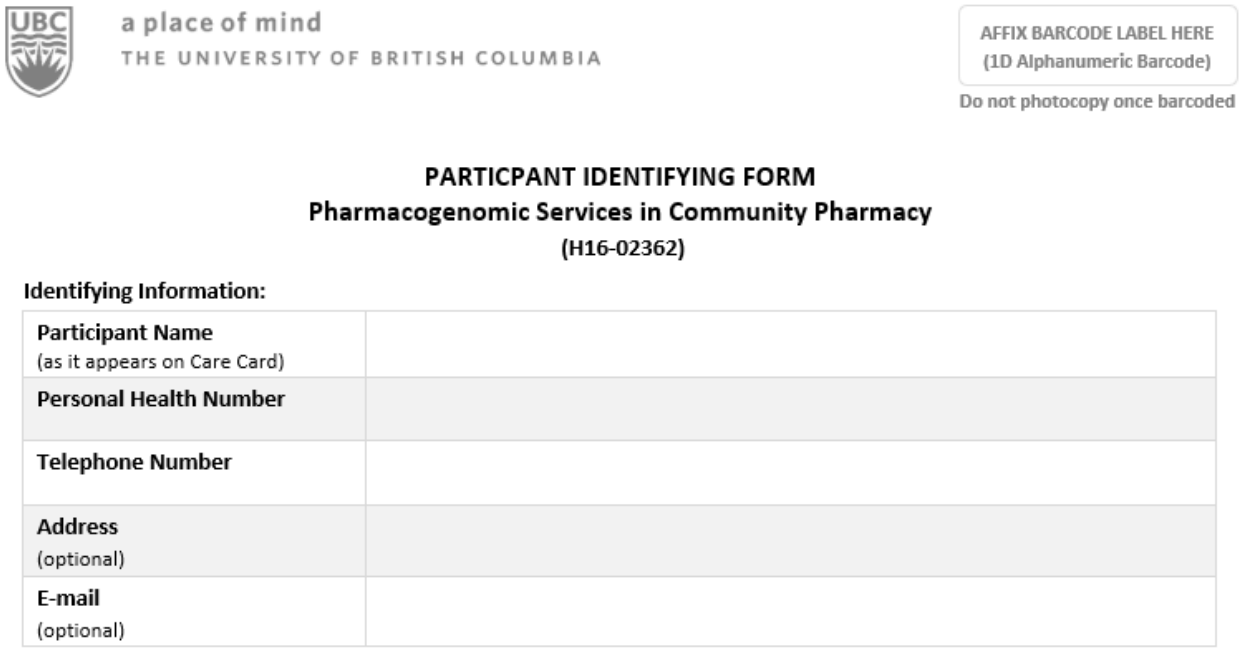
If the participant does not have an ongoing and regular physician, the pharmacist will send a copy of report and a record of prescription adaptation (if completed) to the physician who originally prescribed the drug for the participant.

Figure 2.5 Clinically actionable results plan, given to patients to review.

After a potential participant agreed to the study, the enrollment process took approximately 30-60 minutes. It started with the pharmacist answering questions generated in the contemplative (take-home) phase. Next, patients signed the consent form and were given a copy for their records. Following their consent, the patients provided a saliva sample and their pharmacist collected the required enrollment information. To avoid external incentives (or the appearance thereof) we specified that each pharmacist be limited to recruiting a maximum of 10 patients.

2.2.1.1 Patient Data Collection

After consent of the participant was received the participants' data was recorded by the pharmacist. The participant identifying form was provided specifically to collect patient contact information, Figure 2.6.



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PARTICPANT IDENTIFYING FORM
Pharmacogenomic Services in Community Pharmacy
(H16-02362)

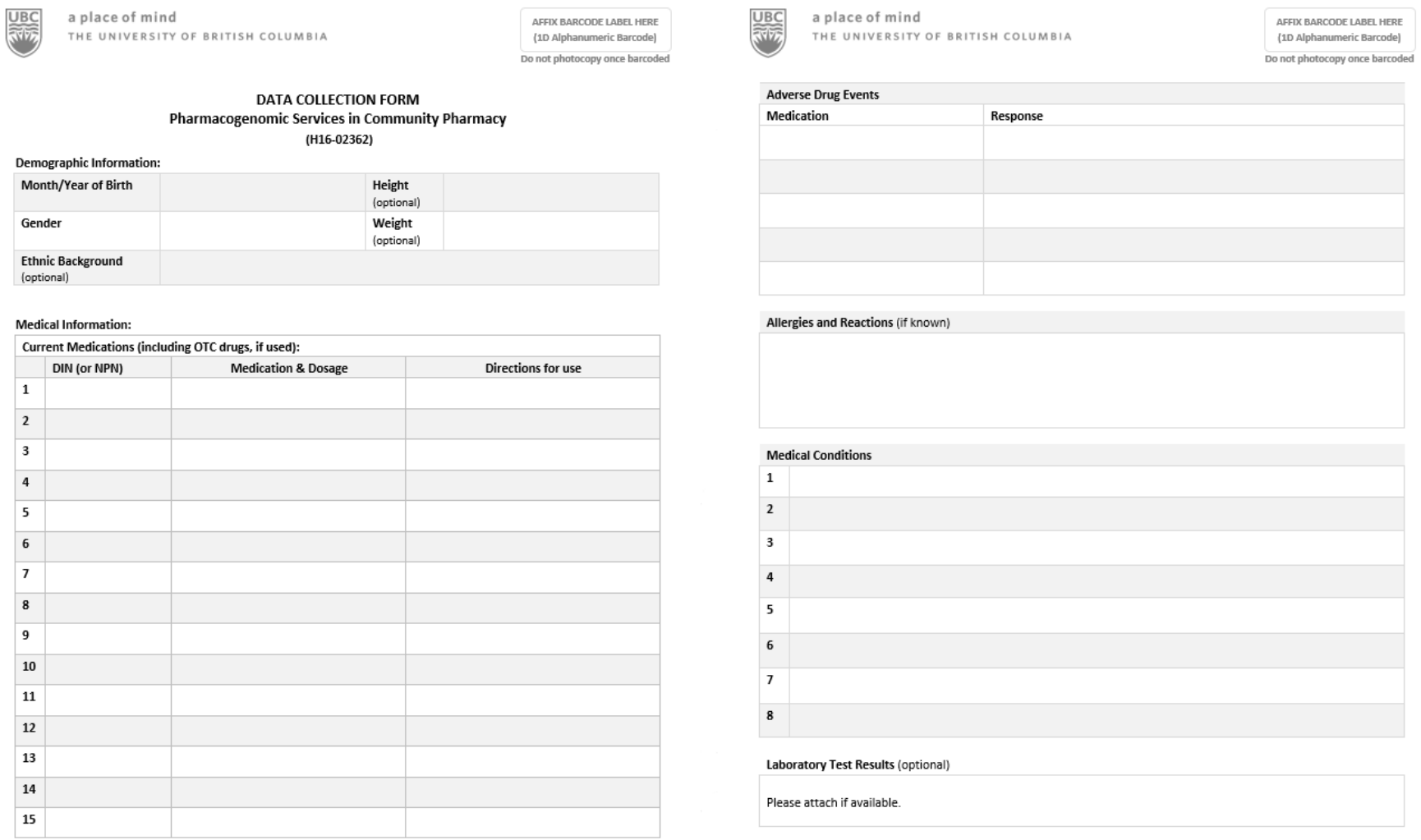
Identifying Information:

Participant Name (as it appears on Care Card)	
Personal Health Number	
Telephone Number	
Address (optional)	
E-mail (optional)	

Figure 2.6 Patient identifying form as provided to participants.

A weakness of this form was making a patient's email address optional, especially as contact with some participants was lost during the course of the study. Emailing is a low stakes way to get in contact with people and in some cases may be less awkward than a phone call.[190] While calling is still an important form of contact and allows subjects to feel connected, emailing additionally offers utility of easily sending batched or automated updates.[190,191] However, many of our participants were older and therefore less likely to have an email address than younger participants.[192]

The patient data collection form, Figure 2.7, allowed us to gather our study subjects' critical information. The form allows for collection of birthdays, gender, height, ethnic background, allergies, known medical conditions, previous history of ADRs, and current medications.



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DATA COLLECTION FORM
Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Demographic Information:

Month/Year of Birth		**Height** (optional)	
Gender		**Weight** (optional)	
Ethnic Background (optional)			

Medical Information:

Current Medications (including OTC drugs, if used):

	DIN (or NPN)	Medication & Dosage	Directions for use
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			

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Adverse Drug Events

Medication	Response

Allergies and Reactions (if known)

Medical Conditions

1	
2	
3	
4	
5	
6	
7	
8	

Laboratory Test Results (optional)

Please attach if available.

Figure 2.7 Data collection form, provides space for pharmacists to record participant demographics and current medications.

The form however does have some weaknesses that should be modified in future iterations. Most notably ethnic background is an optional space. Patient ethnicity should always be included when considering any test that uses haplotyping to call genotypes. This is important as haplotyping imputes gene identity based on known associations and likelihood of recombination during mitosis. As these recombination groups are different in different ethnic groups (Africans for examples have the shortest haplotype blocks with highest rates of recombination between their chromosomes), not properly stratifying for patient ethnicity can lead to incorrect genotyping[193]. Additionally, array-based paneling needs to account for different population frequencies of alleles when choosing SNPs to include. As different alleles are present at different levels in different ethnic populations not accounting for the natural variance can lead to false associations/correlations: both in determining genotype/phenotype correlations and in drawing conclusions about cost effectiveness. For example, the CYP2D6 ultra rapid metabolizer phenotype is found at a prevalence of 30% in Ethiopian populations.[194] People with this phenotype require higher doses of drugs for maximum effect. If our study had been comprised of people of mostly Ethiopian descent this could lead to false assumption that there is actually more of a need for CYP2D6 genotyping and that this would lead to a higher cost burden to the health care system.

Another major weakness with this form was the lack of a space to collect smoking information. Cigarette smoke consists of a plethora of different compounds that can affect our gene expression and drug metabolism. For example, cigarettes are well known inducers of the CYP1A2 genes which lead to impaired metabolism.[126] Omitting this information means that we were further missing out on collection of important drug/gene, drug/drug, and gene/gene information. This could have further impacted our cost-benefit analysis.

An unexpected problem with the data collection form was in interpreting the pharmacists handwriting. Although Drug Identification numbers (DIN) were included in the collection process, not all pharmacists recorded the DIN for easy drug identification. Some pharmacists also simply had handwriting so unique to be almost unreadable. Another notable issue was the inclusion of medicinal supplements as part of the current medication. As we were not looking at supplement use or impact on drug metabolism, this was unnecessary information.

2.3 Sample Processing

2.3.1 Sample Handling

The patient's saliva sample was collected at the pharmacy along with the required patient history. In the 30 minutes prior to saliva collection, it was ensured that participants had not eaten, drunk, smoked, or chewed gum. The collection tube and an instruction sheet detailing how to submit a saliva sample were provided. This process took 2-5 minutes in most cases, although there were participants who took longer and a small number who were unable to provide usable saliva samples. The reasons for this varied, but the common theme was that these participants complained of 'dry mouth'. The pharmacist then collected the sealed tube for transport. Although it was beyond the scope of this study, we expect that alternative collection methods (i.e., buccal swab) would have been a suitable alternative. To ensure that the project was completed in a timely manner, we chose a cut-off deadline for patient recruitment 8 months after the project began.

After de-identification, the original copy of the patient enrollment documentation and the patient's saliva sample were sent via secure courier to UBC. A copy of the demographic information was kept and secured at the pharmacies. Saliva samples were received and catalogued and stored at our sequencing facility (https://sequencing.ubc.ca/). Participant information was used to update a key file linking identifying information to the participant code. All non-identifying information was transcribed and linked only to the participant code. Sample IDs were then subsequently linked to unique, randomized sample barcodes for downstream analysis and report tracking.

2.3.2 DNA Extraction

DNA was extracted from 250 µl of saliva sample. Any remaining saliva was stored at room temperature for up to a week prior to long term storage at -20 °C. The "prepIT.L2P" reagents were used according to the manufacturer's instructions (DNA Genotek). DNA was eluted in 50 µl molecular-grade water and DNA quality was assessed by gel electrophoresis and quantified by Nanodrop (Thermofisher Scientific) and fluorometry using the Qubit dsDNA HS Assay Kit. The

gel analysis provided a go/no-go step for the samples, in other words, if samples were extensively degraded at this quality control (QC) step, we attempted a second extraction. DNA was stored at -20 °C until genotyping or TRS library preparation.

2.3.3 Target Rich Sequencing (TRS)

DNA was extracted as described above and processed according to the manufacturer (https://www.kailosgenetics.com/).[195] Briefly, to prepare the sequencing library: DNA samples are annealed with guide oligos which contain the targeted sequences of interest and fragmented by a restriction digest PCR. After this Illumina adapter sequences and a unique sample identifier (barcode) are patch ligated to the library samples. The samples are then enzymatically cleaned to remove single strands and the sample is further purified via AMPure magnetic beads. They are then universally PCR amplified and purified a final time by AMpure beads. QC of the samples was conducted by agarose gel electrophoresis and the total volume of DNA was quantified with Qubit. Pooled amplicons were sequenced on an Illumina Miseq platform, generating paired-end 78 bp reads.[196]

Long range PCR was used to determine duplication as according to the manufacturer (https://www.kailosgenetics.com/).[98] Briefly for both duplication and deletions events participants' DNA samples are mixed with primers for the CYP2D6 gene. Additionally, in separate reactions primers for sites that become active in only gene duplications or deletions are added. Samples are then amplified by PCR and analyzed by gel electrophoresis.

2.3.4 Panel Based Sequencing

We worked with myDNA (https://www.mydna.life/en-ca/) to perform SNP analysis using the iPLEX massARRAY system. Samples were processed as described above (see Array/Panel based). The number of CYP2D6 gene copies were detected by qPCR, as described above (see Copy Number detection) using a 7900HT PCR system.[197]

2.3.5 Data Collection and Analysis

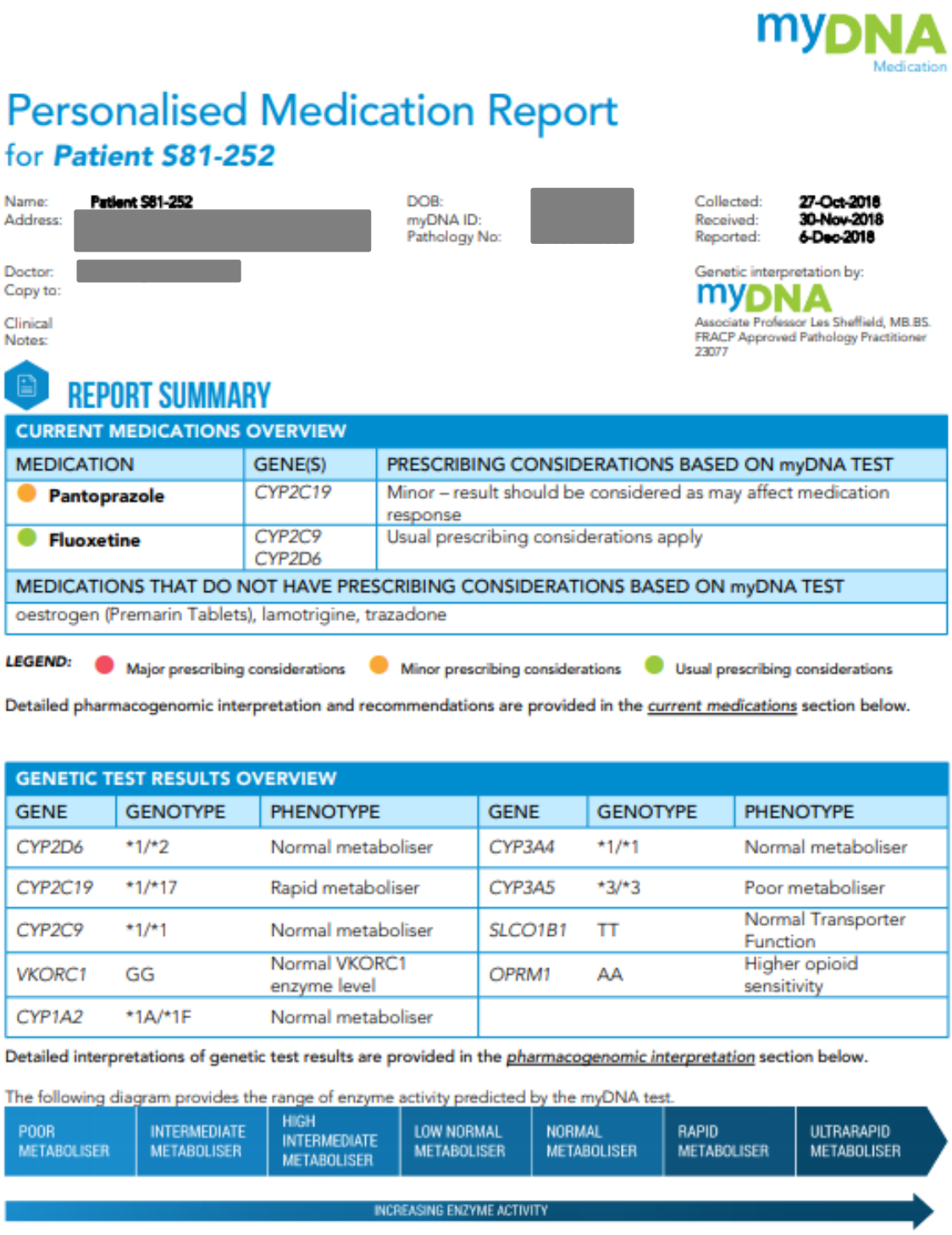
To process the myDNA reports for our meta-analysis, each participant's medical considerations and genotypes were extracted from PDFs using tabula.[198] Files were then manually edited to include a patient ID and any potential drug-drug interaction information.

Genotype information from the TRS reports were manually entered into a .csv file and further tidied, such as conversion from wide to long data, using R (version 3.6.1), a programming language for data analysis.[199] To compare genotype calls between TRS and myDNA, only shared alleles were analyzed. A file containing every unique myDNA call was matched with the corresponding TRS genotype.

Population frequencies for the genotypes CYP2D6, CYP2C19, CYP2C9, and VKORC1 were taken from an analysis of an Australian population.[197] The frequency of CYP2D6 *36 was taken from an American population.[152] The population frequencies of the SLCO1B1, CYP1A2, CYP3A4, CYP3A5, and OPRM1 genotypes were calculated from the global SNP frequency. Global Frequency of the SNPs were gathered from the Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/).[200] Hardy-Weinberg equilibrium was used to calculate the genotype frequencies in an ideal population.[201]

All genotype data manipulation and analyses for the manuscript were completed in R version 3.6.1. Later analysis was completed in version 4.0.3, Appendix - IV. Analysis depended on R packages: Tidyverse, data.table, reshape2, compare, plyr, and rowr.[205–210] Cost-benefit analysis and tabulation of survey results was completed in Excel. Drug prices were retrieved from the McKesson Canada wholesale drug price list in effect at that time.

2.3.6 Data Reporting



myDNA Medication

Personalised Medication Report

for *Patient S81-252*

Name: **Patient S81-252**
Address: [redacted]

DOB:
myDNA ID:
Pathology No: [redacted]

Collected: **27-Oct-2018**
Received: **30-Nov-2018**
Reported: **6-Dec-2018**

Doctor: [redacted]
Copy to:

Clinical Notes:

Genetic interpretation by:
myDNA
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
Pantoprazole	*CYP2C19*	Minor – result should be considered as may affect medication response
Fluoxetine	*CYP2C9* *CYP2D6*	Usual prescribing considerations apply
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
oestrogen (Premarin Tablets), lamotrigine, trazadone		

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	*1/*2	Normal metaboliser	*CYP3A4*	*1/*1	Normal metaboliser
CYP2C19	*1/*17	Rapid metaboliser	*CYP3A5*	*3/*3	Poor metaboliser
CYP2C9	*1/*1	Normal metaboliser	*SLCO1B1*	TT	Normal Transporter Function
VKORC1	GG	Normal VKORC1 enzyme level	*OPRM1*	AA	Higher opioid sensitivity
CYP1A2	*1A/*1F	Normal metaboliser			

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.

POOR METABOLISER | INTERMEDIATE METABOLISER | HIGH INTERMEDIATE METABOLISER | LOW NORMAL METABOLISER | NORMAL METABOLISER | RAPID METABOLISER | ULTRARAPID METABOLISER

INCREASING ENZYME ACTIVITY

Figure 2.8 First page of a myDNA PGx report. Provides a summary of impact on current compounds and an overview of the participant's genotype. Blacked-out sections contains identifying information. For full document see Appendix – V.

Patient reports were generated using myDNA's PGx software (https://www.mydna.life/en-ca/), Figure 2.8. These reports were uploaded to a secure website accessible to the primary project team by the CN, DD, and SB. Data was encrypted and only de-identified to the appropriate pharmacist after review by the project team. Genomic reports and patient IDs were sent separately in encrypted Excel spreadsheets. GitHub (https://github.com/) was used to store all analysis routines and to ensure version control.

2.3.7 Patient Consult at the Pharmacy

The reports were released directly to the project leads CN, DD, and SB, at which point they were reviewed before being released to the pharmacist. Reports were reviewed with each participant in a face-to-face appointment with the pharmacist following a standardized script. The pharmacist delivered results, discussed possible therapy change recommendations, and asked if the participant wanted the report shared with the patient's physician. Participants had the option of sharing the report directly themselves or having the pharmacist send a copy. Pharmacists were responsible for recording medication changes. Although, all medication changes were made by the patient's physician.

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OUTCOMES SUMMARY of CLINICALLY ACTIONABLE RESULTS

Pharmacogenomic Services in Community Pharmacy (H16-02362)

Instructions

1. Only list medications for which there was a change such as dose/strength change, discontinuation, new drug started.
2. Include ALL changes whether you made the change or the prescribing physician made the change.
3. Use the following codes in the Code column on the table.
4. Codes for Code (column 2) in chart below:
   DC = Discontinued
   ND = New Dosage
   NM = New Medication
5. Make additional copies if needed or more medications.

		Current Medications including OTCs if used				New Medications or Dosages or Directions		
	Code	DIN (or NPN)	Medication Name & Dosage	Directions for use		DIN (or NPN)	Medication Name & (Dosage)	Directions for use
Example	ND	02239607	Celexa 20mg	one tab daily		02246057	Apo-citalopram 40mg	one tablet daily
Example	NM	02250160	Teva-simvastatin 20mg	one tablet qhs		02302683	Novo-atorvastatin 20mg	one tablet qhs
Example	DC	02252787	Apo-clopidogrel 75mg	one tablet daily				
1								
2								
3								
4								
5								

Figure 2.9 Outcomes Summary of clinically actionable results. Pharmacists complete for patient and returned at the end of the study.

The patient outcomes survey collected information on changes to a patient's prescribed medications after return of their genotyping/PGx test, Figure 2.9. Only medications that had changes made to them after the study were to be recorded. The table allowed us to track changes to dose, frequency of doses, route of consumption, and the addition of new medications. A weakness of this form, again was simply pharmacist handwriting that could make it hard to read. Additionally, some pharmacist would send back entirely blank forms or would not send forms back for people who had no changes made. So additionally, having a line to inform the pharmacists to send back forms even if no changes were made and potentially include an NA, to allow researchers confidence in their interpretation of the form may be beneficial.

Further, all participating pharmacists and patients were asked to complete a qualitative survey on their experience in the study, Figure 2.10.

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British Columbia
Pharmacy Association

PHARMACIST EXPERIENCE SURVEY
Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Please indicate how much you agree or disagree with the following statements:

	Strongly Disagree	Disagree	Agree	Strongly Agree
1. The training for participation in this study was adequate and appropriate.				
2. The support from the study team met my needs.				
3. The study team responded to my queries in a timely manner.				
4. The materials I received for the study were thorough.				
5. I feel my patients appreciated the opportunity to participate in this study.				
6. Overall, I had a positive experience participating in this study.				

Additional Comments:

PARTICIPANT EXPERIENCE SURVEY
Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Please indicate how much you agree or disagree with the following statements:

	Strongly Disagree	Disagree	Agree	Strongly Agree
1. My pharmacist gave me enough information about the study.				
2. I understood the purpose of the study and the terms used by my pharmacist were not overly technical.				
3. I was given enough time to ask questions and discuss the study with my pharmacist.				
4. I feel comfortable participating in this study.				
5. I think the community pharmacy is a good location for genetic testing.				
6. I am comfortable with the idea of pharmacists using genetic information to help them make drug therapy decisions.				
7. I would be willing to participate in this type of research again.				

Additional Comments:

Figure 2.10 Pharmacist and participant experience surveys. Each have their own form and were completed by either the pharmacist or patient, respectively. Forms were returned to the study team by the pharmacist

Independent of pharmacist or patient influence they agreed or disagreed with statements on their participation in the study, the support they received, the appropriateness of pharmacists as providers and pharmacies as a location of service. Respondents also had additional room for comments. The surveys consisted of 4-point Likert scale which does not include a neutral option. This type of survey is well suited for conducting market research and capturing respondents' experience, as they are required to provide an opinion.[208,209]

2.4 Research Ethics Board Approval and Legal Compliance

Many different pieces of legislation were considered pertaining to personal and health information, pharmacy and pharmacist obligations, and the consent requirements of healthcare interventions. Legal review was obtained to ensure the highest standard of legal compliance. In developing our Research Ethics Board (REB) procedure, we considered the following Canadian and British Columbian legislation:

1. The Personal Information Protection Act, The Freedom of Information and Protection of Privacy Act, The Health Professions Act and its Bylaws, The Health Care (Consent) and Care Facility (Admission) Act, and The Pharmacy Operations and Drug Scheduling Act. These laws lay out the obligations of the pharmacist, the pharmacy, and the University of British Columbia with respect to personal and health information.
2. The Health Professions Act and its Bylaws and The Personal Information Protection Act. These laws governed the pharmacist with respect to the collection, use, disclosure and security of personal and health information.
3. The Freedom of Information and Protection of Privacy Act and the policies of UBC and its Research Ethics Board.

Pharmacists were obligated to follow REB-approved protocols with respect to collection, use, disclosure, and security of patient/participant personal and health information under The Health Professions Act and its Bylaws (governing the profession of pharmacists and other healthcare professionals), and the BC College of Pharmacists Code of Ethics and Bylaws (self-governed entity entrusted with protecting public safety by regulating the pharmacy profession).

Researchers were bound by the Protection of Privacy Act (which articulates the access and privacy rights of individuals as they relate to the public sector). Approval from the Clinical Research Ethics Board was obtained. Additionally, an Information Sharing Agreement was initiated by the user partner, governing the relationship and setting out the obligations of the pharmacists and pharmacies with respect to the University. The user partner and their legal counsel acted as an intermediary between the University and the participating corporations in executing each of these agreements. A final piece of legislation considered was The Health Care (Consent) and Care Facility (Admission) Act, which regulates the consent requirements for the provision of healthcare services.

2.4.1 Legal Review

We obtained legal counsel to review the informed consent and data collection protocols developed by the study team prior to deployment. These ethics approved SOPs governed all activities in the study.

Chapter 3: Genotype Analysis

During the beginning stages of Phase 2 we were given the opportunity to partner with Kailos Genetics to investigate the uses of TRS in preemptive PGx testing. TRS, as opposed to panel-based genotyping, uses NGS with targeted probes to sequence only genes of interest. This has the benefit of finding rare variants while reducing costs to be viable in a commercial setting. Comparing the results of TRS to the approved and validated myDNA LDT offers insight into its utility as a diagnostic aid. Overall turnaround time and support from both services were equivalent. We also found that Kailos returned more genotype information, however that information was less likely to be supported by CPIC/DPWG guidelines as rarer allelic events could be captured. Additionally, investigations into genotype frequency can assure that results are in line with global averages.

Sample collection and genotyping was accomplished in two main batches. Batch one comprised 130 samples, 116 of which passed QC. In batch two 48 samples were collected, 42 of which passed QC. We also received 19 samples as a retest, in total generating 150 myDNA and 37 TRS genetic reports, with 47 failures. Some patient's sputum simply did not provide adequate DNA as re-extraction only continued to produce insufficient or degraded samples with nanodrop scores closely matching. This may be due to producing insufficient amounts of sputum, natural variations in cheek shedding, or medications. Analyzing the results of the genetic analysis we wished to show that TRS produces similar results to a standardized array from which we found a combined error rate of 1.7%. We also investigated population frequencies and found that both TRS and myDNA closely matched other mixed populations. None of the analyses or TRS reports were returned to pharmacists or participants, who received only copies of their myDNA reports.

Furthermore, using only the myDNA samples we investigated the relationship between drug-drug and drug-gene interactions in our patient population. This was done because patient's current medications were not included in the generation of the Kailos/TRS reports; only participant gender. Patient Gender may also impact expression of CYP450 enzymes.[62] Drug-gene interactions have the ability to impact metabolism of the participants' other medications. From our population 53 cases gene-gene interactions were recorded. However, some participants were on multiple compounds capable of attenuating CYP drug metabolism.

3.1 Comparison of Calls

We found 9 total differences in genotype calls between those that underwent both TRS and myDNA genotyping (for a total of 592 SNPS), Table 3.1. Between the two datasets there were 296 comparable genotypes giving a discordance of 1.7%, which suggests an error rate below 1% for either platform. One gene could not be called by TRS. This may have been due to the region being degraded or problems with amplification for the patient. TRS also called two additional alleles that myDNA does not, CYP2D6 *35A and CYP3A4 *8. *35A is a subset of the *2 allele. *2 contains SNPs 2851: c > t and 4181: g > c, while *35A contains the additional SNP 31 g > a. *35A has the same normal metabolizer phenotype.[210,211] As such, the two calls containing *35A can be considered the same as that by myDNA. The CYP3A4 *8 allele has been associated with decreased function of the CYP3A4 protein. Although, as of March 2021, PharmGKB lists this as a level 3 (i.e., low evidence) claim.[121,212] Regardless, this genotype is absent in the myDNA report resulting in a normal metabolizer call. The remaining differences were minor, suggesting a small number of SNP-specific variables for each platform.

Table 3.1 Differences found between genes shared in the Kailos/TRS and myDNA datasets

GENE	TRS Genotype	myDNA Genotype	Comparison
CYP2C19	*XX/*XX	*1/*17	TRS no call
CYP2C19	CYP2C19 *1/*2	*2/*2	different
CYP2C9	*1/*3	*3/*3	different
CYP2D6	*2/*2	*2/*5	different
CYP2D6	*35A/*5	*2/*5	TRS only allele *35A
CYP2D6	*35A/*4	*2/*4	TRS only allele *35A
CYP3A4	*1/*8	*1/*1	TRS only allele *8
SLCO1B1	T/C Het	T/T Wild	different
SLCO1B1	T/C Het	T/T Wild	different

3.2 Population Frequency

3.2.1 Genotype

Next, we compared the frequency of a subset of genotypes that were in both the TRS and myDNA reports. Genotypes were compared to each other and to the population average. Population averages, comprising of mixed populations from Australian, American, and global ethnic data.[152,197,200] Frequencies closely matched those from within the study at both sites, Table

3.2. The averages between myDNA and TRS were similar, showing little variance between the two data types and indicating robust genotyping.

Table 3.2 Sample of a table comparing the frequency of myDNA calls and Kailos/TRS calls to population averages of those genotypes. Full table contains 62 genetic variations. See Appendix - VI.

GENE	myDNA Genotype	TRS Genotype	Phenotype	myDNA Genotype Frequency % n = 150	TRS Genotype Frequency % n = 37	Population Level Frequency %
CYP2C19	*1/*1	*1/*1	Normal metabolizer	35.33	27	39.7
CYP2C19	*1/*17	*1/*17	Rapid metabolizer	33.33	37.8	25.80%
CYP2C19	*1/*2	*1/*2	Intermediate metabolizer	14	18.9	20.70%
CYP2C19	*17/*17	*17/*17	Ultrarapid metabolizer	2.67	2.7	0
CYP2C19	*2/*17	*2/*17	High intermediate metabolizer	8	8.1	6.20%
CYP2C19	*2/*2	*2/*2	Poor metabolizer	6.67	2.7	2.90%
CYP2C19	NA	*XX/*XX	NA	NA	2.7	NA
CYP2C9	*1/*1	*1/*1	Normal metabolizer	69.33	62.2	64.84%
CYP2C9	*1/*2	*1/*2	High intermediate metabolizer	15.33	21.6	20.38%
CYP2C9	*1/*3	*1/*3	Intermediate metabolizer	10	10.8	10.60%

3.2.2 Allele

In addition to patient genotype frequency of alleles found in the study, the population frequency of said alleles was evaluated, Table 3.3. This was done using only genotypes provided by myDNA. Allele frequencies were taken from global data, and for the CYP2D6 alleles, an American cohort.[152,200] Both CYP2C19 and CYP2C9 had the frequency of their *1 alleles calculated out of 100%.

Table 3.3 Allele frequencies from myDNA genotyping and population averages. N = number of alleles per gene in the study.

Gene	Allele	Freq	% Freq alleles n=300	Allele Population Frequency
CYP1A2	*1A	93	31.00	32.71
CYP1A2	*1F	207	69.00	67.29
CYP2C19	*1	177	59.00	63.11
CYP2C19	*17	70	23.33	20.36
CYP2C19	*2	53	17.67	16.53
CYP2C9	*1	246	82.00	86.31
CYP2C9	*2	34	11.33	8.86
CYP2C9	*3	20	6.67	4.83
CYP2D6	*1	120	40.00	37.5
CYP2D6	*10	9	3.00	1.7
CYP2D6	*1X2	1	0.33	0.8
CYP2D6	*2	75	25.00	1.9
CYP2D6	*2XN	2	0.67	0.1
CYP2D6	*3	6	2.00	1.4
CYP2D6	*36	1	0.33	0.15
CYP2D6	*4	45	15.00	17.28
CYP2D6	*41	26	8.67	8.23
CYP2D6	*5	8	2.67	3.4
CYP2D6	*6	3	1.00	1.01
CYP2D6	*9	4	1.33	2.41
CYP3A4	*1	292	97.33	96.79
CYP3A4	*22	8	2.67	3.21
CYP3A5	*1	14	4.67	27.75
CYP3A5	*3	286	95.33	72.25
OPRM1	A	249	83.00	87.85
OPRM1	G	51	17.00	12.15
SLCO1B1	C	43	14.33	11.95
SLCO1B1	T	257	85.67	88.05
VKORC1	A	127	42.33	30.87
VKORC1	G	173	57.67	69.13

As the reference study looked at change of copy number of all CYP2D6 alleles frequencies of copy number changes were added to the single copies' frequency for alleles that were not *2 or *1. Like the genotype frequencies, allele frequencies in our study closely matched those found in mixed populations. Most notably the *2 allele is significantly different in our study. This is likely due to the additional *2 genotypes included in the American study (*2A and *35). When added to *2's frequency it becomes much closer to what is seen in our study and others (20.9%).[152,154,197] Furthermore, the CYP3A5 *3 allele in our population is higher than in the global average. Levels of this gene however are known to be variable in different populations and can reach upwards of 95% in Caucasian populations.[163]

3.3 Drug-Drug/ Drug-Gene Interactions

Two major types of interactions with patients' current medications were recorded by the myDNA reports. The first are interactions between multiple antidepressants if a patient was taking more than one. Some classes of MHCs can have a synergistic effect if taken concurrently, which may be responsible for some ADRs. For example, Serotonin syndrome is a toxic effect of accumulated serotonin in the body and can result in life-threating complications.[213] The second being interactions between the patients' medication and their genes. Medications can act to either induce or inhibit gene function which can in turn affect metabolism of drugs that interact with those gene products. In our efforts we analyzed the frequency at which these interactions appeared in our participants, Table 3.4.

Table 3.4 Frequency of drug-drug/gene interactions. N = the number of prescribed medications recorded.

Type of Interaction	Frequency	% Frequency (n=880)
SEROTONIN TOXICITY	80	9.09
INDUCER	12	1.36
INHIBITOR MODERATE	46	5.23
INHIBITOR STRONG	30	3.41

From our study population we returned 80 cases of serotonin toxicity, however this stems from only 38 unique indications. This reflects the choice of MHCs used as criterion. 12 incidences of gene induction by current medication were recorded. Many more drugs were found to inhibit genes. This may in part be due to the non-specific mechanism of some inhibitors which may simply competitively bind to an enzyme's active site. The inhibitor category is split into

moderate and strong inhibitors. Strong inhibitors of genes need more consideration when doing and adding on other medications that may be metabolized by gene products. Additionally, effects of inducers can stack. Care should be given when dosing or starting new drugs and patients should be monitored when changing medications.

Table 3.5 Frequency of each drug-gene interaction state in relation the impacted genes.

Type of Interaction	Interaction With	Frequency	% Frequency (n=880)
INDUCER	CY1A2	1	0.11
INDUCER	CYP1A2	4	0.45
INHIBITOR MODERATE	CYP1A2	10	1.14
INHIBITOR STRONG	CYP1A2	1	0.11
INDUCER	CYP2C19	2	0.23
INHIBITOR MODERATE	CYP2C19	19	2.16
INDUCER	CYP2C9	2	0.23
INHIBITOR MODERATE	CYP2D6	14	1.59
INHIBITOR STRONG	CYP2D6	29	3.30
INDUCER	CYP3A	3	0.35
INHIBITOR MODERATE	CYP3A	3	0.35

We further broke down the drug-gene interactions by affected genes, Table 3.5. Only one site in the study, which only had one participant pass genotyping and receive a report, recorded no interactions with current medications. The most common interaction was the strong inhibition of CYP2D6, caused by close to 3.3% of drugs recorded in the study. This strong inhibition of CYP2D6 was mostly caused by prescribed Bupropion (15 cases). Fluoxetine, which was a criteria compound, contributed significantly to the phenotype (12 cases), Appendix - VII. In total, 88 drug-gene interactions were uncovered out of 880 prescribed compounds (10%). This represents 54 participants (36%), who were taking an additional 375 medications, approximately 43% of recorded compounds.

Chapter 4: PGx Prescribing Considerations

With a sample size of N =150 we sought to determine the utility of providing PGx testing services to BC. To this end, we genotyped our participants using the myDNA reports and analyzed prescribing considerations for current and future drugs. Current prescribing considerations were the ones the participant was already on. Future drugs included all 93 compounds which myDNA makes dosing consideration for, using CPIC and DPWG guidelines. Reports offered three prescribing considerations: 'usual - normal label use of compound'; 'minor- consider test results, as results may be significant'; and 'major - significant results, medication should be reviewed'. Indications were generated based solely on genotype irrespective of any additional medications the patient may have been taking. Frequencies of these events were also interpreted by study location to determine that PGx testing was advantageous regardless of the region of BC or pharmacy setting.

The challenge that prescribing certain classes of MHCs provides is also discussed here. For enrollment in our study participants were required to be prescribed either an antipsychotic or antidepressant with established dosing guidelines. This choice was motivated in part by funder interests in ensuring effective mental health treatment, but also to ensure we capture a wide array of actionable compounds and diversity in participants. It is still clear however, from the results outlined, that PGx can provide utility in optimizing prescribing of MHCs.

4.1 Prescribing Considerations

4.1.1 Possible Prescribing Considerations

In addition to capturing information for medications that patients were already on, reports generated prescribing guidelines for common medications for which there are established prescribing guidelines. Three participants' reports were generated with errors and didn't include prescribing considerations for the drug acenocoumarol. These were the only errors noted on reports.

Table 4.1 lists a sample of the frequencies of prescribing considerations for each medication tested by myDNA. Some medications such as amitriptyline, clomipramine, and doxepin had

major prescribing considerations in 50% of those tested for this study. However, not all drugs had major indications uncovered (31 compounds). One drug, morphine, was found to have only minor considerations in our patient population (100%). Most compounds however were found to have usual indications, followed by minor and major; 8151, 4621, 1176 indications respectively. Major indications made up 8.4% of recorded possible prescribing considerations. Despite this, 6 compounds (mainly of the PPI drug class) had no usual indications. This may be in part due to the large number of CYP3A5 alleles recovered. Only 1 drug, tramadol, had no minor considerations.

Table 4.1 Frequency of major, minor, and usual prescribing considerations for each of myDNA's 93 compounds. N = number of study participants. Full table contains 279 consideration-drug pairs. For full table see Appendix – VIII.

Consideration	Medication	Frequency	% Frequency (n=150)
major	Acenocoumarol	56	37.33
minor	Acenocoumarol	52	34.67
usual	Acenocoumarol	39	26
major	Amitriptyline	75	50
minor	Amitriptyline	30	20
usual	Amitriptyline	45	30
major	Aripiprazole	6	4
minor	Aripiprazole	57	38

Table 4.2 Frequency of possible considerations by myDNA compound. Full table contains 242 rows, not all drugs had major indications. 3 letters = site code and N = number of participants at the site. For full table see Appendix - IX.

Medication	Genes	Consideration	BCP (n=8)	D59 (n=1)	F31 (n=2)	J02 (n=8)	k74 (n=6)	k76 (n=10)	L65 (n=20)	N24 (n=20)	N43 (n=9)	N83 (n=16)
Acenocoumarol	VKORC1 CYP2C9	major	4	0	0	2	2	4	11	8	4	5
Acenocoumarol	VKORC1 CYP2C9	minor	2	1	0	2	3	4	5	5	4	6
Acenocoumarol	VKORC1 CYP2C9	usual	2	0	2	3	1	2	3	6	1	5
Amitriptyline	CYP2D6 CYP2C19	major	4	1	1	4	3	5	11	10	3	7
Amitriptyline	CYP2D6 CYP2C19	minor	0	0	1	1	1	2	1	4	6	2
Amitriptyline	CYP2D6 CYP2C19	usual	4	0	0	3	2	3	8	6	0	7
Aripiprazole	CYP2D6	major	0	0	0	0	0	1	2	1	1	0
Aripiprazole	CYP2D6	minor	2	1	0	3	3	4	7	9	4	9
Aripiprazole	CYP2D6	usual	6	0	2	5	3	5	11	10	4	7

To visualize study site contribution to drug considerations, frequencies of major, minor, and usual prescribing considerations were tabled by pharmacy, Table 4.2. From this it is apparent that all study sites had at least 1 major dosing indication and some sites had 100% of their patients with a major risk allele present. Major indications made up on average 8% of prescribing considerations per site with the highest at 12.2% and lowest at 3.5%. Minor considerations made up around 34% of the considerations given per site; the highest at 58%. However, this location was comprised of 1 study participant. Usual considerations on average were 58% of the dosing indications. The lowest occurred for the location with one participant (33%) and the highest overall was 72%. This site however also had a small sample size with only two enrolled participants.

The phenotypes of each gene, described as a metabolizer state, present in our population was tallied. Indications for warfarin sensitivity were changed from normal warfarin sensitivity, high warfarin sensitivity, and increased warfarin sensitivity were replaced with, normal metabolizer, poor metabolizer, and reduced metabolizer, respectively. Additionally, not all genes were

recorded by noting all metabolizer states. Notably, close to 91% of participants were poor metabolizers for CYP3A5 and 46% were rapid metabolizers for CYP1A2. 58% of CYP2D6 and 35% of CYP2C19 were normal metabolizers requiring no dosing indications. These were consistent with some population averages for the causative alleles[62,143,147]. In a comparison of all phenotypes 42% of CYP2D6, 65% of CYP2C19, 31% of CYP2C9, 62% of VKORC1, and 27% of SLCO1B1 phenotypes captured were associated with altered drug metabolism.

Table 4.3 Frequency of each phenotype in relation to each gene. Not all genes were classified with all available metabolizer states Full table has 72 entries. See Appendix – X.

Phenotype	Gene	Phenotype Frequency	% Frequency (n =150)
High intermediate metabolizer	CYP1A2	0	0
Intermediate metabolizer	CYP1A2	0	0
Low normal metabolizer	CYP1A2	0	0
Normal metabolizer	CYP1A2	81	54
Poor metabolizer	CYP1A2	0	0
Rapid metabolizer	CYP1A2	69	46
Reduced metabolizer	CYP1A2	0	0
Ultrarapid metabolizer	CYP1A2	0	0
High intermediate metabolizer	CYP2C19	12	8

4.1.2 Current Prescribing Considerations

Frequencies of major, minor, and usual prescribing considerations were also investigated in medications which patients were currently taking, Table 4.4. This table includes medications for which there are no current dosing guidelines, but which patients were taking at the time of the study. These were the majority of prescriptions active during enrollment with 530 compounds (60%). Usual and minor drug considerations made up similar proportions of the active considerations with 176 (20%) and 128 (15%) of prescribed compounds. 46 (5%) triggered major consideration warnings, including drugs with narrow therapeutic windows like warfarin. In total 350 of the drugs patients were currently taking had an active PGx dosing guideline. The highest number of major dosing considerations for any one drug was 12 major indications for

escitalopram, while the largest number of minor and usual considerations were 15 for pantoprazole, and 21 for quetiapine, respectively.

Table 4.4 Consideration for each compound that a patient was actively taking. Some compounds had no consideration. Full table contains 292 rows, see Appendix – XI.

Consideration	Medication	Frequencies
NO	Acetaminophen	25
NO	Acetazolamide	1
NO	Acetylsalicylic acid	1
NO	Adalimumab	1
NO	Adapalene	1
NO	Allopurinol	2
NO	Alprazolam	1
Usual	Amitriptyline	1
Minor	Amitriptyline	1

Table 4.5 Frequencies of consideration for current prescriptions. For full table see Appendix – XII.

Medication	Gene(s)	Consideration	BCP (n=8)	D59 (n=1)	F31 (n=2)	J02 (n=8)	k74 (n=6)	k76 (n=10)	L65 (n=20)	N24 (n=20)	N43 (n=9)	N83 (n=16)
Amitriptyline	CYP2C19 CYP2D6	Major	0	0	0	1	0	1	1	3	0	0
Aripiprazole	CYP2D6	Major	0	0	0	0	0	0	1	0	0	0
Citalopram	CYP2C19	Major	0	0	1	0	0	0	2	2	0	3
Clopidogrel	CYP2C19	Major	0	0	1	0	0	0	0	0	0	0
Escitalopram	CYP2C19	Major	0	0	0	2	0	2	3	1	0	1
Fluoxetine	CYP2C9 CYP2D6	Major	0	0	0	0	0	0	0	0	0	0
Ibuprofen	CYP2C9	Major	0	0	0	0	0	1	0	0	0	0
Imipramine	CYP2C19 CYP2D6	Major	0	0	0	0	0	0	0	0	0	1

Table 4.5, addresses the consideration for drugs the patients are currently on at each study location. Drugs with no considerations were excluded from the table. 5 of the 17 study sites (29.4%) had no major indications in drugs their patients were taking. All study sites had minor indications and one site lacked usual. This was the location that recruited only one patient. On average ~11% of active considerations per site were major indications, with the highest at

anyone location between 22% and 25%. Minor indications made up approximately 40% of considerations of current drugs. One site had 100% of its indications be minor. This site however only had one participant and one listed indication for their active medication. Usual indications comprised on average 49% current drug considerations. Aside from one location, no site had less than 25% of their considerations be from usual indications. The highest at any one site was 71%.

4.2 Current MHCs

Because enrollment relied on an active prescription for an MHC a large portion of the current medications recorded were of this class, Table 4.6. In total, MHCs comprised 22% of all drugs recorded. The most common antidepressant was escitalopram closely followed by citalopram with 18% and 17% of patients respectively prescribed. Quetiapine was the most commonly prescribed antipsychotic in the study, making up close to 3% of the total drugs prescribed and 16% of patients actively taking the compound.

Table 4.6 Frequency of each criteria MHC in comparison to: proportion of all participants in the study; out of the total number of MHCs (N = 195); and out of all drugs prescribed to participants.

Drug	Freq	Out of Study n=150	Out of MHCs n=195	Out of all Drugs n=880
Amitriptyline	12	8.00	6.15	1.36
Aripiprazole	9	6.00	4.62	1.02
Citalopram	26	17.33	13.33	2.95
Duloxetine	10	6.67	5.13	1.14
Escitalopram	27	18.00	13.85	3.07
Fluoxetine	12	8.00	6.15	1.36
Fluvoxamine	1	0.67	0.51	0.11
Imipramine	1	0.67	0.51	0.11
Mirtazapine	12	8.00	6.15	1.36
Moclobemide	2	1.33	1.03	0.23
Nortriptyline	6	4.00	3.08	0.68
Olanzapine	5	3.33	2.56	0.57
Paroxetine	2	1.33	1.03	0.23
Quetiapine	24	16.00	12.31	2.73
Risperidone	4	2.67	2.05	0.46
Sertraline	17	11.33	8.72	1.93
Venlafaxine	23	15.33	11.80	2.61
Vortioxetine	2	1.33	1.03	0.23

195 total MHCs were recorded with some people taking more than one of these medications. As all MHCs had dosing guidelines, all drugs returned dosing considerations. There were 38 major, 62 minor, and 95 usual indications from study criteria drugs, Table 4.7. The majority of major indications were from escitalopram and citalopram. These were seen in ~44% of recorded prescriptions for both. Amitriptyline however, had similar numbers of major considers to both escitalopram and citalopram (10 vs. 12 and 11 respectively), and had major indications in 83% of its prescriptions. The majority of the remaining escitalopram users (37%) had usual considerations. Citalopram considerations were split evenly between usual and minor considerations (7 and 8 respectively). Further the antipsychotic, quetiapine, seemed to be genetically tolerated fairly well as 92% of prescriptions returned usual considerations and no major indications were detected.

Table 4.7 Frequency of prescribing considerations for the MHCs used as criteria drugs for this study.

Drug	Consideration	Freq	Drug	Consideration	Freq	Drug	Consideration	Freq
Amitriptyline	Major	10	Escitalopram	Minor	5	Amitriptyline	Usual	1
Aripiprazole	Major	2	Fluoxetine	Minor	2	Aripiprazole	Usual	5
Citalopram	Major	11	Fluvoxamine	Minor	0	Citalopram	Usual	7
Duloxetine	Major	0	Imipramine	Minor	0	Duloxetine	Usual	4
Escitalopram	Major	12	Mirtazapine	Minor	7	Escitalopram	Usual	10
Fluoxetine	Major	1	Citalopram	Minor	8	Fluoxetine	Usual	9
Fluvoxamine	Major	0	Duloxetine	Minor	6	Fluvoxamine	Usual	1
Imipramine	Major	1	Aripiprazole	Minor	2	Imipramine	Usual	0
Mirtazapine	Major	0	Amitriptyline	Minor	1	Mirtazapine	Usual	5
Moclobemide	Major	0	Vortioxetine	Minor	1	Moclobemide	Usual	0
Nortriptyline	Major	1	Sertraline	Minor	10	Nortriptyline	Usual	3
Olanzapine	Major	0	Venlafaxine	Minor	8	Olanzapine	Usual	2
Paroxetine	Major	0	Moclobemide	Minor	2	Paroxetine	Usual	2
Quetiapine	Major	0	Nortriptyline	Minor	2	Quetiapine	Usual	22
Risperidone	Major	0	Olanzapine	Minor	3	Risperidone	Usual	1
Sertraline	Major	0	Paroxetine	Minor	0	Sertraline	Usual	7
Venlafaxine	Major	0	Quetiapine	Minor	2	Venlafaxine	Usual	15
Vortioxetine	Major	0	Risperidone	Minor	3	Vortioxetine	Usual	1

Chapter 5: Cost-Benefit and Pharmacists as Providers

Pharmacist relations were coordinated through our pharmacist liaison DD and maintained by the main study team, CN and SB. Using community pharmacists allowed us to sample a diverse range of participants, in age, sex, ethnicity, polyphamacy status, and to receive a wide range of opinions. To gauge the scope and scale of community acceptance, a simple two-pronged quantitative, frequency-based analysis of patient and pharmacist attitudes and thoughts was conducted via simple surveys. The study also interpreted medication changes as recorded by the pharmacists. Our results show that there is a modest price increase to the cost of drugs for our patient dataset, mostly due to new drugs being added as well as due to dose increases. This may additionally be offset by future utility that PGx offers. In addition, we looked at the association between prescribing considerations and pharmacy location as well as the frequency of metabolizer states for each gene in the study to further elucidate the advantage of providing PGx services.

The myDNA reports returned to the pharmacists were used to produce the data in the drug cost analysis. The restriction to MHCs was only for the eligibility to participate. Once a participant was enrolled, we reviewed all their drugs and many of the drug therapy changes that were made were for drugs other than MHCs. All drug changes, regardless of therapeutic category, were included in the simple drug cost analysis. In a small number of cases (16), reports could not be returned as some pharmacists had lost contact with study participants. Additionally, some doctors either felt uncomfortable changing prescribing considerations based on the report results or did not think it was necessary for some patients. Despite these caveats, we believe that we demonstrated that there is a need for these services in BC from the interest expressed both by the pharmacist and participants.

5.1 Cost-Benefit Analysis

For medications that patients were currently taking, 92 were found to have at least one minor prescribing consideration, 39 had at least one major consideration, and an additional 139 participants were taking a medication with usual prescribing considerations, Figure 5.1. In comparison to a PGx study examining 3 genes using a whole exome sequencing (WES) data set,

20% of study participants had immediately actionable results, comparable to the 26% that we found with a major prescribing concern.[214]

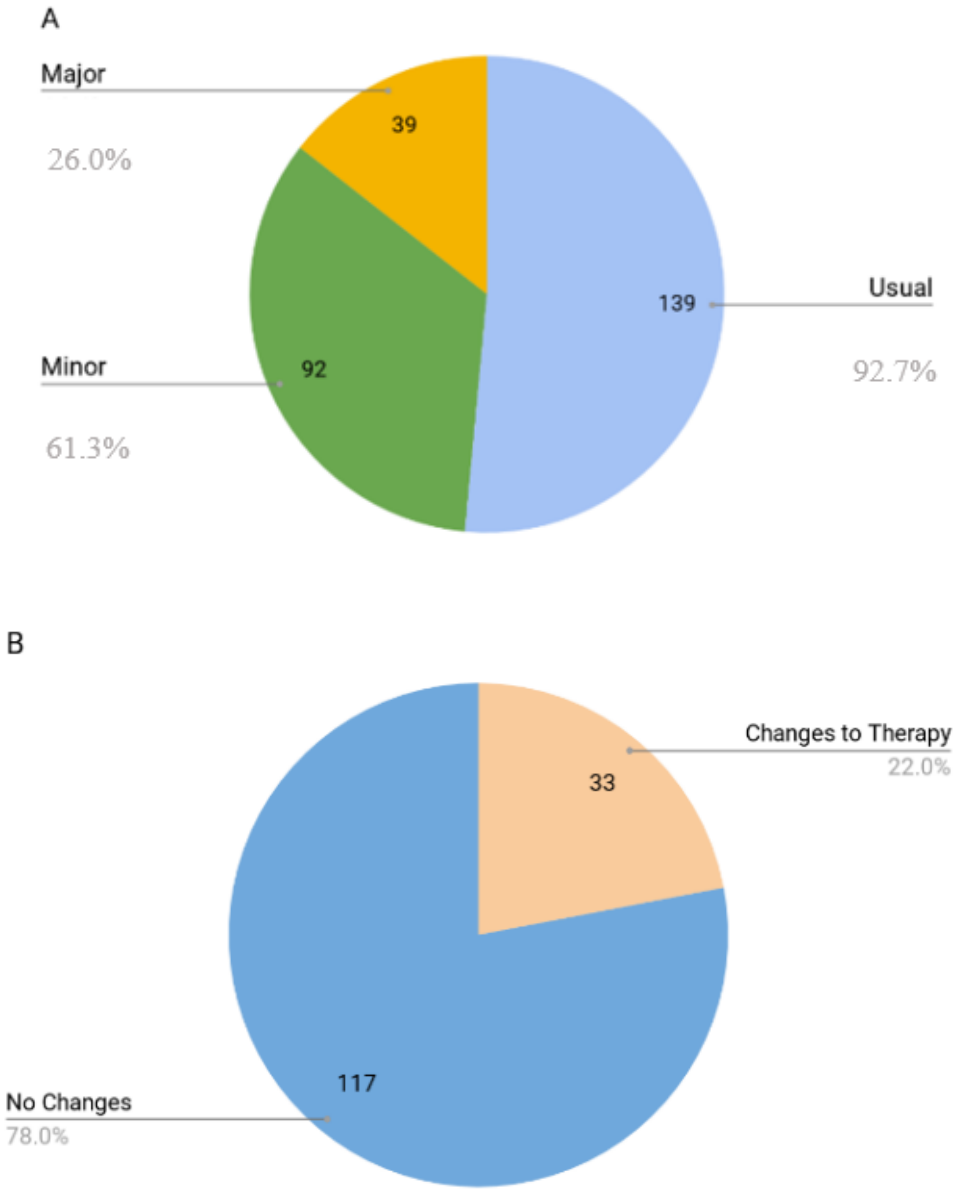

Figure 5.1 (A) Visualization of major, minor, and usual drug considerations discovered, N = 150; (B) Visualization of medication changes in response to the study, N = 150.

Taken together, the aggregate medication changes translated into therapy interventions in 33 patients, representing 22% of all genotyped patients in the project. In addition, the report interpretation with the pharmacist and participant often prompted closer review of patient medications by physicians. There were a total of 81 changes. The changes included dose

increases in 11 patients, dose decreases in 5 patients, new drugs added to the therapy of 20 patients, and 22 patients having drugs discontinued. There were instances of multiple changes for an individual patient, Figure 5.2. Based on this data, we calculate that a year's worth of modified medication therapy for all participants collectively was $797CAD. This represents a per patient cost of $24.15CAD or 3.03% of the annual therapy cost (annual drug cost based on patient specific dosages and net of all changes including discontinued drugs, new drugs added and/or dosage changes) considering only those patients who had a medication change (not including the initial non-recurring testing cost of $199 which was covered by the project budget and should be amortized over the life of each patient). Note that costs in this simple drug cost analysis are all based on annual ongoing treatment costs and are not limited to the actual prescription over the study period. That is to say, the per patient cost of $24.15 represents the average total annual cost increase for each patient's therapy after implementing the changes. It is not restricted to only the cost of each patient's therapy for the study period. Study participants were not followed beyond the consultation with the pharmacist to review results and implement any suggested drug therapy changes. This was a time and budgetary limitation of the study.

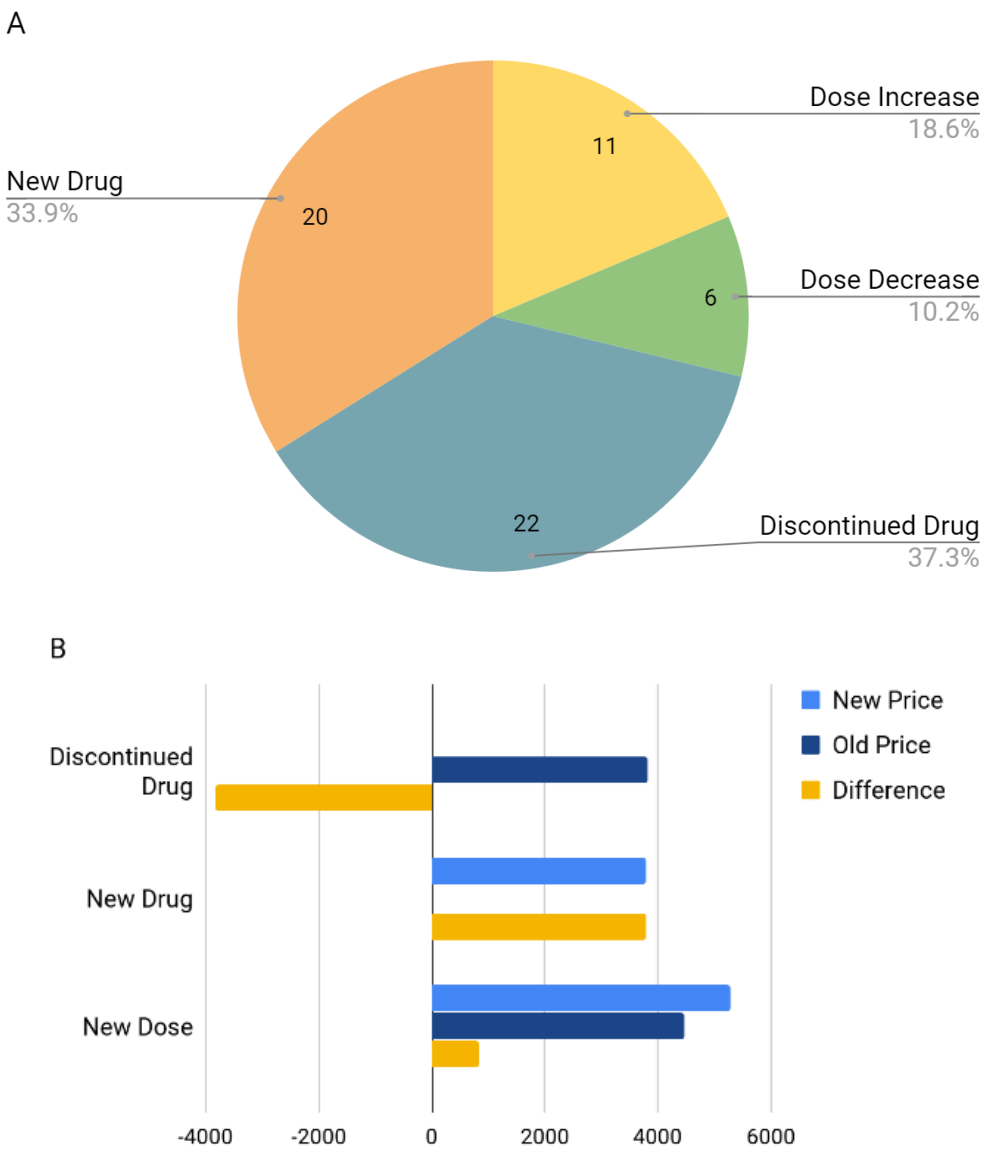

Figure 5.2 (A) Breakdown of therapy changes made by type of change, N = 59; (B) Cost-benefit of drug changes—shows drug cost changes by type of therapy change. Bars represent total cost in CAD.

5.2 Patient Experience

Each participating patient was asked to complete a short seven question survey in which they ranked their response to statements about the project, Figure 2.10. We received 111 patient experience surveys with a response rate of 62%. Some patients were not able to be reached at the end of the study, they had either moved or changed pharmacies. The patients strongly agreed with the seven statements and also agreed that pharmacists are the appropriate providers of

pharmacogenomic services as well as pharmacies being an ideal location to collect samples, Table 5.1.

Table 5.1 Patient experience survey results. All results, 98.2–100% strongly agree/agree, N = 111.

Statement	Strongly Disagree	Disagree	Agree	Strongly Agree	% Agree or Strongly Agree
My pharmacist gave me enough information about the study			25	86	100.0%
I understood the purpose of the study and the terms used by my pharmacist were not overly technical			31	80	100.0%
I was given enough time to ask questions and discuss the study with my pharmacist			17	94	100.0%
I feel comfortable participating in this study			22	89	100.0%
I think the community pharmacy is a good location for genetic testing		1	22	88	99.1%
I am comfortable with the idea of pharmacists using genetic information to help them make drug therapy decisions		1	18	92	99.1%
I would be willing to participate in this type of research again		2	15	94	98.2%
Totals	**0**	**4**	**150**	**623**	

Total # Surveys Completed	111

5.3 Pharmacist Experience

Each participating pharmacist was asked to complete a survey in which they ranked their response to statements about the training and support they received throughout the project. We received responses from 20/21 pharmacists for a response rate of 95%. One pharmacist dropped from the study, and we were unable to contact them.

Table 5.2 Pharmacist experience survey results. 85–100% strongly agree or agree, N = 20.

Statement	# Disagree or Strongly Disagree	# Agree or Strongly Agree	% Agree or Strongly Agree
Overall, I had a positive experience participating in this study	2	19	90.5%
I feel my patients appreciated the opportunity to participate in this study	0	21	100.0%
The materials I received for the study were thorough	1	20	95.2%
The study team responded to my queries in a timely manner	3	18	85.7%
The support from the study team met my needs	2	19	90.5%
The training for participation in this study was adequate and appropriate	1	20	95.2%
Totals	**9**	**117**	

Total # Surveys Completed	21

Pharmacists' opinions were generally very positive as well, Table 5.2. The biggest pharmacists' concern was communication with our research team. This is indicated by the questions "The study team responded to my queries in a timely manner", "The support from the study team met my needs", and "Overall, I had a positive experience participating in this study" which had the least support for pharmacist. This is a fair criticism and likely reflects two constraints of the experimental design; i) because samples were batched, an overly long time (up to six months) between sample collection and report returns was experienced for the samples collected earliest in the project, and ii) the project team strove to maintain an arm's length distance for any prescribing decisions.

Chapter 6: Conclusions and Future Directions

6.1 Current State of PGx

As the technology begins to mature, PGx usage and adoption is becoming more mainstream in countries around the world. The technology and cost of testing are improving as well. As such, we are seeing an increase in NGS or whole genome sequencing WGS/WES being investigated for data collection and testing of PGx samples.[43] WGS and WES, as opposed to the more traditional methods of array- or panel-based genotyping promises less biased results and access to unprecedented amounts of information; i.e. being able to capture an individual's entire coding sequence. In this way direct sequencing is able to detect rare variants that would be missed otherwise by conventional panel-based genotyping methods that detect only the presence or absence of common clinically relevant variants. However, despite that, more than 90% of variants in pharmacogenes are thought to be rare: the variation they add to medication response is not well characterized.[215] Regardless, detecting these individuals would give further power to PGx testing and facilitate research into genotype-phenotype associations. Biases incurred from NGS stem from library preparation methods high repetitiveness, short indels, pseudogenes and regions rich in GC; these challenges can present themselves as a failure to capture the sequence, misalignment while mapping to or assembling the genome, and poor-quality data that is unfit for analysis.[216] For PGx this means missing data or incorrect genotyping. While there are NGS sequencing techniques developed to combat some of these shortfalls, the advent of 3rd and 4th generation technologies promises to further revolutionize the field. These methods can inform on Ems, which can also have an impact on gene expression, translation, and drug metabolism. For example, smoking of tobacco products is known to cause a variety of EMs. Specifically, it can reduce methylation in the promoter region of CYP1A1 and induce expression.[62,217] Detecting and characterizing additional genotype modifications can serve to further empower prescriber decision making. At present, 3rd generation technologies are not accurate enough for use in clinical diagnostics nor are they sufficiently scaleable.[215,218] In addition, the vast majority of a patient's WG/WE sequence is not relevant to any currently available PGx dosing guidelines and the effects of EMs and rare variants are also understudied.[215] This brings into question the utility of capturing or providing such information. If evidence supporting a claim is poorly validated,

supplying that evidence may cause inappropriate prescribing decisions, breaking down the trust between patient and prescriber and both prescriber and patient in PGx utility.[219] Further, the amount of data that is captured and needs to be stored is not trivial. Each human genome can comprise several to hundreds of gigabytes of data depending on the depth of sequencing, level of annotation, mapping, or compression of the file.[220] This needs to be taken into accord when considering WES/WGS to implement a PGx program as storing a large number of patient information will require a dedicated plan.[215] Finally, capturing a patient's entire genome or coding sequence may return off-target or "incidental" findings such as risks of Alzheimer's or certain cancers. Patients may not wish to have this information, or there are fears of coverage denial due to presupposed genetic risks.[221–223] Because of these issues and the costs associated with WGS/WES, targeted approach of gene selection in PGx testing is more commonplace.[215] This has consisted mostly of array-based methods but similarly the drop in sequencing prices allows for TRS of pharmacogenes to be implemented. This reduces issues of file size, serious off-target discoveries, and information relevance while still capturing rare variants and allowing for inclusion of future recommendations in relevant pharmacogenes.[196,215]

Clinical implementation of PGx stands to benefit from the adoption of, or the functionality of a healthcare system's electronic health records (EHR) and clinical decision support (CDS) systems.[23,215,224,225] EHRs allows prescribers and providers to have up to date access to patient medical records. Depending on the healthcare system, EHRs can allow for seamless transition of patient records between institutions and providers.[225] This is important to clinical implementation of PGx where results should be relevant throughout the course of the patient's life; including PGx results in a patient's EHR will provide continued availability of patient specific prescribing considerations.[215,225]

CDS tools in terms of PGx translates patients' genotype or PGx results into prescribing considerations for implementation by prescribers.[215,225,226] These can either be integrated into a patient's EHR or be patient provided; but are crucial for the adoption of PGx as they guide dosing.[215] CDSs are limited by the information and sources they provide as well as the provider's level of understanding of PGx concepts[215]. Currently, there are a variety of different CDS systems utilized in PGx reporting and great benefit could come from standardizing these

systems which may use inconstant sourcing of prescribing methods[23,226]. Additionally, clinicians can feel uncomfortable in utilizing CDS reports if not prescribing in their specialty, or if they feel they are undereducated about PGx topics in general.[43,215,226,227] However, PGx CDS systems can offer ways for patients to engage with their results.[226] They can also potentially be used to alert prescribers to updated prescribing considerations, a feature paramount to the continued utility of PGx.[215,226] Overall, more work needs to be done to standardize PGx technology and in education of prescribers.

6.1.1 Europe

PGx today is reaching more and more people as nations push to develop their own programs. Countries in the European Union (EU) have already started nationwide PGx trials in anticipation of the medical and cost-saving benefits. Since 2004, the Netherlands has been cataloging and made public detailed information on the previous 5 years' dispensed medications and their usage.[122,228] This allows for in depth tracking of the association between the genetics of their populations and drug response. In 2005 they established the DPWG to create clinical PGx dosing guides and encourage the implementation of a PGx program.[122] Today DPWG guidelines are integrated into CDS systems and available to all clinicians and pharmacists; however, most PGx testing done in the Netherlands is for single drug-gene pairs before the start of treatment.[229]
In an effort to further prove the utility of preemptive PGx testing in 2017, members of the EU formed the Ubiquitous Pharmacogenomics Consortium (U-PGx) in an effort to provide clinical documentation and analysis on comprehensive PGx implementation across Europe.[230] To this end, the consortium has started a 3-year clinical trial in 7 EU nations, the Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study. Close to 7000 participants have been enrolled and preemptively tested across 40 markers in 13 pharmacogenes as to DPWG guidelines; data analysis for this project is currently underway and promises to show a reduction in ADRs and a reduction in healthcare costs.[231]

6.1.2 Asia

Nine Southeast Asian countries have formed a collaboration, the Southeast Asian Pharmacogenomics Research Network (SEAPharm). This research partnership aims to share

knowledge and speed the implementation of PGx programs within their respective countries.[232] While focused on meeting the needs of a Southeast Asian population and healthcare system, their collaboration is not limited to member countries and the network further collaborates with other nations in the Middle East and Southern Europe. To further the understanding of unique fluctuation of relevant genotypes within the member countries as well as impact to ADRs and cost-benefit, SEAPharm initiated a study to NGS sequence 100 pharmacogenes within 1500 individuals. This project is currently underway, but of the member nations only Thailand and Singapore have PGx programs implemented at the national level. Additionally, in counties with national PGx policies, they appear to be for drug-gene specific cases. Moreover, specific hospitals and institutions within Thailand and Singapore still face barriers such as doctor education. For a review of SEAPharm and its initiatives see (Chumnumwat et al., 2019)[232].

Japan also conducts its own Pharmacogenomic research and issues its own medication labels. Japan has established a database of 2.5 million SNPs in close to 3000 Japanese patients to assist in PGx research.[233]

6.1.3 USA

The USA has been a hotbed of genomic activity since the inception of the field and solidified with the completion of the human genome project. The USA, through the FDA, issues its own PGx relevant medications labels and issues its own clinical guidelines through CIPC. In the USA, NIH funds two PGx relevant research networks, the Electronic Medical Records and Genomics (eMERGE) and the Implementing Genomics in Practice (IGNITE) networks. These initiatives aim to promote implementation of genomics into clinical practice and research the impact of genomic medicine.[23,234] The lack of a national healthcare policy and disjointed nature of the American insurance system makes it difficult to establish a cohesive PGx policy.[23,225] As such, adoption of PGx practices is done at the level of the individual institutions and clinicians and generally covered by insurance only in specific cases; however, some hospitals have established models for preemptive PGx testing programs such as the Saint Jude PG4KDS program, and research continues to be conducted to prove the utility of preemptive PGx screening.[224,226]

6.1.4 Canada

In Canada, the adoption of PGx and preemptive PGx programs are underway as the country begins to recognize the value of personalized medicine. Canada has a national healthcare system and some specific genetic tests are covered. In addition, Health Canada has issued changes to over 100 medication labels to reflect PGx dosing guidelines.[235] Further, Health Canada has also released guidelines for conducting and submitting PGx research in order to integrate PGx into the drug development approval process.[236,237] The major Canadian consortium conducting research, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is funded provincially and federally and consists of locations across Canada. CPNDS surveils for ADRs across its locations for which it aims to determine the genetic basis and research preventative strategies.[235,238] Based on this work CPNDS also issues clinical PGx dosing guidelines. Despite this, Canada still does not have a national policy for PGx adoption and coverage of tests is often left to marketplace insurance carriers.[239] In a survey of 10 insurance providers, TELUS Health found that all 10 either offered or were in the process of launching some form of PGx testing coverage, Figure 6.1.[240] These highlight programs testing for the effectiveness of MHCs. In addition to increasing coverage by insurers, more and more pharmacies are beginning to offer PGx testing services. RxOME is the collaboration between the British Columbia Pharmacy Association and the myDNA testing service.[241] Together they have provided testing services to

Figure 6.1 has been removed due to copyright restrictions. It was a table showing Canadian Insures' Coverage of PGx testing. All ten surveyed insurers either covered, were investigating, or in the process of implementing PGx testing services. These would be covered as disability benefits, extended health benefits, or preferred pricing option. Table also included partnered testing services if applicable and a brief description of services options. Original source: Telus Health. Pharmacogenomic testing gains foothold in group insurance. Health Benefits Hub. Published November 18, 2020. Accessed March 11, 2021. https://plus.telushealth.co/blogs/health-benefits/en/pharmacogenomic-testing-gains-foothold-in-group-insurance/

Figure 6.1 PGx policies of major Canadian insurers. Thumbs up indicates plans exist; Rocket indicates that a plan is being launched; Paper indicates the investigation of a new plan. Taken from (Telus Health, 2020).[240]

over 70 pharmacy locations in BC and other locations across Canada.[242]

6.2 Impact of Environmental Factors

Environmental factors (EFs) can impact one's ability to metabolize or effectively utilize medications. EFs can either act directly on the drug, the drug's molecular target, or can cause epigenetic changes which affect gene translation and subsequent drug response. Diet is one such example of a consequential EF. For example, some citrus fruits such as grapefruits contain the compound furanocoumarin which is thought to inhibit the CYP3A4 enzyme; disrupting the normal digestion and raising serum levels of dozens of medications.[243] While knowledge about diet may be important when starting new medications, it is already recommended when starting new drugs to stop consumption of grapefruit and similar food items which would disrupt dosing guidelines[244]. Additionally, while there are diets which are known to produce epigenetic changes and impact protein function, not enough is known about how these changes impact drug metabolism and to what extent to guide clinical dosing. A related and emerging field of nutrigenomics aims to potentially elucidate answers to those questions and personalize nutrition.[245]

The use of addictive substances also impacts drug metabolism and should be considered when starting new medications. These may be harder for the patient to give up compared to a dietary change and may prevent patients from effectively taking their medications. Alcohol, for example, may act synergistically with some CNS depressants to increase drowsiness or in some cases even cause death. Further, alcohol is digested by some cytochrome P450 enzymes (mainly CYP2E1) and may either inhibit or induce its function depending on frequency of consumption (moderate consumption may sequester enzymes and prevent digestion of other medications while heavy drinking may induce expression).[246,247] Not enough research has been done on the specific effects of alcohol impacting drug metabolism to inform clinical dosing guidelines. However, it is still important for patients to discuss with their prescriber their level of alcohol consumption.[244,246] Smoking, on the other hand, is known to induce CYP1A1, CYP1A2, CYP2E1, and UGT enzymes and higher doses of medication metabolized by those enzymes may be required.[62,63,126,248] Providing substance usage information may benefit prescriber decision making in patients who drink or smoke regularly. Additionally, research has been done into the

pharmacogenetics of smoking, alcohol, and other substance addiction as well as their cessation drugs.[249–251] While work may be necessary to strengthen the evidence for some drug-gene pairs capturing information on illicit drug, smoking and alcohol consumption on genetic screens may help empower patients to quit.

6.3 Bringing PGx Testing to Canada

Establishment of preemptive PGx services is underway in Canada. Implementation can be accelerated by the adoption of a federal plan for PGx enactment. This could include offering PGx testing services with provincial health coverage; funding more research into the cost-saving benefits in terms of a Canadian population; looking into strategies for sharing data securely across provinces and institutions; as well as educating prescribers. Currently, doctors feel undereducated to be making dosing changes based on PGx guidelines. Between 84% and 98% of healthcare providers believe PGx testing could offer some clinical utility, but only 10% to 14% felt adequality informed with the majority (89%-97%) interested in additional training.[215] Offering educational courses into PGx principles can help bridge the gap between prescribing guidelines and patient medication adjustments. Our study found that offering a relatively simple PGx course was sufficient to give pharmacists the ability to adequately council their patients and improve both their own and their patient's confidence in PGx testing. Encouraging physicians to utilize these resources and to further their understanding into genetic testing may offer an additional way to increase adoption of preemptive PGx.

As many private Canadian insurers are beginning to expand their benefits to include PGx testing, further work can be done to increase access to those benefits including adding a preemptive PGx testing policy to Canada's national healthcare system. A recent review of the economic impacts of PGx testing in 44 studies found 27 % were found to be cost neutral, while an additional 30% were found to be cost effective.[215,252] Additionally, further cost saving benefits can be seen in specific cases of medication indications such as with MHC. A recent model of the cost-benefit of a PGx-guided treatment for depression estimated savings of $3,962 USD annually per patient.[215,253] Results from our study may defer from looking at the actual changes in prescribing due to PGx testing where a major prescribing indication did not always result in a medication change. The study also included impact to indirect economic cost of depression care, which

contributes a huge burden to the health care system.[253] Further, In one study, offering preemptive PGx testing saved an estimated 14,656 single genetic tests from having to be ordered.[215,254] The presence of clinically actionable alleles are high with around 90-99% of the population carrying a high-risk allele. [215,254] Our own study found that ~40% of currently prescribed medications had dosing guidelines with 17% of compounds unrelated to our criteria MHCs. Approximately 20% of all prescribed compounds produced an actionable consideration and close to half of participants had an allele that impacted CYP2D6 metabolism. A policy of offering cost-effective testing services will continue to reap benefits. As the long-term benefits are researched, an increase of action is taken on part of prescribers and testing costs decrease. As such, it may be of economic benefit for Canada to switch to a policy of preemptive PGx testing in certain circumstances such as during other routine genetic screenings.[235]

The expansion of these services could be greatly benefited by including pharmacists in the decision making and testing process. In Canada, the pharmacist is the expert on drug dispensing, efficacy, and in-patient counseling.[18,255] Pharmacies additionally are already equipped to deal with a variety of different payment methods and the pharmacist can help communicate PGx results to perscribers.[18,255] The pharmacist is accessible, making it easier to gain access to preemptive PGx testing. As more and more prescribers become familiar with PGx testing concepts and gain experience with PGx prescribing guidelines and dosing there will hopefully be an increase in utilization of PGx testing services in Canada.

6.4 Conclusions

From the results of our study, we are able to draw several broad conclusions:

1. The public perceives pharmacists/pharmacies as a very appropriate healthcare professional/venue to deliver pharmacogenomic services.
2. Frequencies of alleles, interactions, and clinically actionable results are consistent with other studies published in the scientific literature.
3. Changes in drug therapy based on PGx test results represent an inconsequential change in annual drug therapy costs. While drug therapy changes may result in a small cost increase, it is just as likely that costs may decrease.

4. Any cost increase due to drug therapy changes is likely to be small and is justified on the basis that the patient will be taking the most appropriate drug and dose based on their phenotype.
5. Pharmacogenomic testing is appropriate and affordable for certain patient populations.
6. Pharmacogenomic services offered by pharmacists are ready for broad commercial implementation.

6.4.1 Patient Privacy

Patients were less concerned with privacy and confidentiality issues than we anticipated. Patients generally believed that pharmacists have access to their confidential health information, including their full medical records that exists with their physician. While this is not the case, pharmacists in the project were careful to ensure that patients understood the implications of sharing personal confidential medical information about themselves. Patients showed considerable trust in their pharmacists in handling this information and were pleased with the level of detail included in the project consent form. When this study was launched, there were no legal protections of a patient's genetic information data. This changed in 2016 with the passage of bill S-201, the Genetic Non-Discrimination Act which provides robust, albeit untested, protections against discrimination based on genetic information.[256] In practice, we did not encounter resistance to participation, but additional work will be required to assess the impact of these protections on patient behavior with regard to testing.

6.4.2 Drug Cost

Although the additional yearly per-patient cost is ~$25CAD, PGx testing represents a saving to the community as we maximize the therapeutic efficiency of treatments. In fact, other studies have shown cost saving benefits of PGx testing.[252,253,257,258] While opportunities in PGx are clear; reduction in ADRs, elimination of medication trial and error, and more accurate dosing of prescribed medications, data to support the economic argument of drug cost savings are limited. It is not a stretch to hypothesize and make an effective argument that an additional value of PGx testing is the avoidance of weeks to months of costly trial and error when prescribing multiple

drugs, especially in the mental health realm. Thus, using PGx testing to get a patient on the right drug at the right dose has the potential to generate long-term savings relative to that patient's overall healthcare costs. Furthermore, it could be argued that the wrong drug and/or wrong dose for a patient may contribute to poor adherence, further contributing to unnecessary costs. Using PGx could and probably does contribute to improved adherence, which in turn improves cost effectiveness of therapy. Longer-term economic implications related to reduced physician and urgent care (e.g., emergency room) visits, reduced absenteeism, and improved productivity require further study and analysis.

6.4.3 Selection of MHCs as Inclusion Criteria

In consultation with one of our funders, Green Shield Canada, we decided to focus on mental health drugs. Two out of three people will need to try multiple/different antidepressants until they find one that works for them.[35] While this may not match the amount of medication changes we found (22%), we do not know how long the patient has been taking their psychiatric medication and if they are satisfied with the results. Antidepressant/antipsychotic usage was a criterion for the study, but patients may have had their own personal reasons for choosing to enroll. We also don't know how many different antidepressants they have been on previously. Additionally, they may not be taking them for their major indication, but rather an off-label use. However, it was found that a large number of participants poorly tolerated amitriptyline as well as citalopram and escitalopram. Furthermore ~19% of indications found in MHCs in our study were major.

6.4.4 Pharmacists

We erred on the side of caution in making sure that the pharmacists had a high level of familiarity with PGx (equivalent to a 1st year graduate course), including its potential and its limitations. The quality, quantity, and level of detail of information provided in the individual patient reports generated in this project allowed pharmacists to easily interpret results and make drug therapy recommendations with little to no additional training. In BC, pharmacies are operated as private businesses with the ability to bill the public healthcare system for services. Using pharmacies as study sites required compliance with the privacy regulations specific to

private businesses. In some instances, this was a higher threshold than that required by a public university research project. As the focus of this study was to develop and test a protocol that could be commercialized, we focused on ensuring compliance with the highest standards of privacy and informed consent. The underlying premise was that compliance, if introduced and explained at the outset with a clear rationale and requirements, would mitigate the potential for non-compliance. This was coupled with the idea that standardizing the process from the outset would allow identification of any barriers present in each individual pharmacy practice setting. Participating pharmacists reported that the detailed training resulted in no difficulty in complying with the SOPs developed in Phase 1.

6.5 Study Limitations

While this study did help us broaden our understanding of the utility of offering PGx testing through a pharmacist, it did have some important limitations. One limitation was the relatively small sample size with only 150 enrolled participants. Small sample sizes can make it harder to prove statistically significant findings, can compound effects of outliers, and miss certain potential participant demographics. In addition, the population diversity of BC is more diverse than other regions in Canada with close to 25% of the population belonging to a visible minority.[259] This may mean the results of our study are less generalizable to other provinces. However, because we did not make patients include their ethnicity on our patient information collection form, we missed out on being able to stratify for patient demographics. We also did not collect smoker information which could have impacted dosing decisions.

Additional limitations included the small size of the main study team, which consisted of the principal investigator, pharmacist liaison, and graduate researcher. This increased the amount of time it took us to be able to update all the pharmacist partners as well as expanded the amount of time that the samples took to be processed. Patient physicians' knowledge of PGx guidelines also proved a barrier to updating patient medications as some did not feel comfortable adjusting patient dosing with their current knowledge. The lack of follow up power was a limitation as well. The study could have benefited from an investigation of whether participation improved treatment outcomes or reduced risk of ADRs as this factor is likely to have the greatest economic

impact. However, conducting such an analysis this would require a long term follow up which was beyond the scope of this study.

Finally, capturing only relevant pharmacogenes over a patient's whole genome or exome limited the scope of the study and the full potential of the data. Collecting a patient's full coding sequence would allow for continued updating of dosing guidelines whenever a new pharmacogenomic recommendation is made. Collecting only specific genes limits the number of drugs or disease states that the recommendations can be expanded to and limits the number of recommendations that could be made in this study.

Overall, these limitations do not detract from the conclusions of the study.

6.6 Future Directions

To expand further on this study, researchers could consider long term clinical trials into the impact of PGx testing on ADRs and continue to research impacts on patient wellbeing and medication adherence. Further research into the most appropriate method for clinician adoption of PGx testing is desirable, such as looking closer at the benefits of offering full panel PGx test at the time of a new prescription or genetic screening. More research into the cost-effectiveness, to assuage fears in insurer uptake, is also needed.

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Appendices

Appendix - I. Pharmacist Information and Consent Form – Full Document.

Blacked out spaces contain contact or personal information.

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

British Columbia
Pharmacy Association

PHARMACIST INFORMATION and CONSENT FORM

Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Principal Investigator: [redacted]
Faculty of Pharmaceutical Sciences
The University of British Columbia (UBC)
[redacted]

Co-Investigator: [redacted]
British Columbia Pharmacy Association
Vancouver, BC
[redacted]

Sponsors:
British Columbia Pharmacy Association
Green Shield Canada
Pfizer Canada
Genome BC
The University of British Columbia – Faculty of Pharmaceutical Sciences

Study Contact Numbers: [redacted]

1. INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

The study aims to develop methods to optimize medication efficacy, reduce adverse effects and improve drug treatment outcomes using the individual's genetic information (DNA). You are being invited to participate due to your previous participation or because you have expressed interest in the subject.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary. This consent form will tell you about this study, the purpose of the study, your role in the study, and the possible benefits, risks and discomforts. The goal of the study is to help the researchers obtain new knowledge so as to improve health outcomes from drug therapy and help patients in the future with their drug therapy.

If you wish to participate, you will be asked to sign this form. If you decide to take part in this study, you are still free to withdraw at any time without giving any reasons for your decision. Please review the consent document carefully and sign this consent only if you accept being a participant.

3. WHO IS CONDUCTING THIS STUDY?

This study is conducted by researchers in the Faculty of Pharmaceutical Sciences at the University of British Columbia and the BC Pharmacy Association. Funding for the study has been provided by Green Shield Canada, Pfizer Canada and Genome BC. For further clarity, Green Shield Canada and Pfizer Canada have no role in conducting the study and will not receive any study information other than that which is publicly published after the completion of the study.

4. BRIEF BACKGROUND

Because a person's DNA sequence is unique to them and does not change, a DNA sequence can be repeatedly queried (in a manner similar to a database search) for any drug a patient may be prescribed currently or in the future. Among other uses, in a few instances, it can help determine disease diagnosis and prognosis, and appropriate medication therapy. Very little public awareness exists about the potential value of genomic information, and, in particular, the potential values of using genome data to more effectively manage medication therapy – known as 'pharmacogenomic testing'.

A practical application of genome science, pharmacogenomic testing can help predict the efficacy of medications for individuals. In such testing, individual genomic data is gathered to determine the appropriateness of a particular medication for a patient, and need not focus on disease diagnosis or prognosis. Because medications can be targeted to those who will likely benefit, and avoided by those who will likely not, this, in a few instances, has the potential to improve individual health care outcomes and help governments and other payers manage escalating health care costs. By ensuring patients receive only those medications and dosages known to be effective for them, provincial governments and private insurers, in the future, can avoid the costs of using expensive, yet ultimately ineffective, medications.

The science of how genetic interactions with drug therapy has developed over the past forty years. Like all clinical information, there is a spectrum of evidence for how useful a particular intervention is for a particular patient. For this study, we are using information with a very high level of evidence. Specifically, for the gene variants we require one of the following criteria to be met 1) a gene variant interaction with a drug has been documented in a guideline published by a noted medical society and 2) only variants listed by the United States Food and Drug Administration will be tested.
https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.

The science and application of genetic testing is a rapidly developing field. Because drug recommendation and specific doses are designed to serve the largest population possible, we can predict that every individual participant will identify at least one variant that is relevant for at least one medication they are currently taking or will take in the future. That said, as with any clinical assessment, it is not clear at this time if the benefits of making a drug or dosage change outweigh the risks.

5. WHAT IS THE PURPOSE OF THE STUDY?

The Pharmacogenomic Services in Community Pharmacy project is working with pharmacists throughout BC to recruit up to 200 patients to demonstrate that genomic data can be collected via saliva sample by community pharmacists and to use that data to generate clinically actionable reports to make more informed decision about drug therapy.

6. WHAT DOES THIS STUDY INVOLVE

As a participating pharmacist, the study involves four major components for you as follows:

1) Completing pre-study training including the TCPS2:CORE tutorial and an overview webinar to review project logistics. This is could take you approximately three to four hours.
2) Recruiting participants into the study. Each recruitment may require two meetings of up to 25 minutes each. One meeting to explain the study and consent process and a second meeting to complete the consent and collect the sample and the medical data. You will be restricted to recruiting a maximum of ten participants and you will be paid $125 for each participant recruited.
3) Reviewing reports with each participant recruited (up to 25 minutes per participant)
4) Providing qualitative data in an on-line form

This data will include, but is not limited to the following areas:

i) Were you provided with sufficient training to perform the required tasks; consenting patients, explaining the goals of the study, describing the results to each patient?
ii) Did you understand the science behind pharmacogenomics? Where there any questions that arose from patients that you were not able to answer?
iii) What was your impression of the patient reception to each aspect of the study; information, consenting, return of information?
iv) What aspects of the study would you modify and why?
v) Would you be willing to participate in this type of research again?

7. HOW WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
Your confidentiality will be respected. However, research records or other source records identifying you may be inspected in the presence of the Investigator or his designate by representatives of the British Columbia Pharmacy Association and/or Genome BC and UBC Clinical Research Ethics Board for the purpose of monitoring the research

8. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?
If you have any questions or desire further information about this part of the study before or during participation, you can contact:

Principal Investigator: [redacted]
Co-Investigator:

9. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AND/OR EXPERIENCES AS A SUBJECT DURING THE STUDY?
If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia, Office of Research Ethics at by e-mail at RSIL@ors.ubc.ca or by phone at [redacted]

Taking part in this study is entirely up to you. You have the right to refuse to participate in this study. If you decide to take part, you may choose to pull out of the study at any time without giving a reason and without any negative impact. You are not waiving any of my legal rights as a result of signing this consent form.

Your signature below indicates that you have received a copy of this consent form for your own records. Your signature indicates that you consent to participate in this study.

Pharmacist Consent Form

As part of this study you are required to abide by all aspects of the code of ethics as codified by the College of Pharmacists of BC http://library.bcpharmacists.org/6_Resources/6-1_Provincial_Legislation/5019-Code_of_Ethics_Detailed.pdf

Specifically, as pertains to this study, the following standards are relevant

Standard 2: b) Pharmacists support patients in making informed choices about their care by explaining the benefits and risks associated with medication therapy and c) Pharmacists provide information that is evidence based, relevant, up-to-date and consistent with the standard of care.
Standard 3: d) Registrants act in the best interests of their patients and do not exploit the professional relationship for any personal, physical, emotional, financial, social or sexual gain.
Standard 4: d) Registrants maintain confidentiality in creating, storing, accessing, transferring and disposing of records they control.
Standard 5: c) Registrants inform the patient of the purpose of the study, its source of funding, the risks of harm and benefits, and the nature of their participation including any applicable compensation.

By signing this document, you consent to abide by all sections of the Pharmacists code of ethics and maintain a high level of professionalism throughout the course of this study.
By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties.

Pharmacist Full Name	**Signature**	**Date Signed**

[redacted]		
Full Name of investigator obtaining consent	**Signature**	**Date Signed**

Appendix - II. Script for the Participant Informational Video – Full Document

Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Informational Video Script

First Half – Genomics 101

Our bodies, like all living things, are made up of cells. Inside each cell is something called DNA, which is a molecule that determines whether we're a tree, or a dog, or in our case, a human. DNA, or deoxyribonucleic acid, contains four main molecules, called bases, represented by the letters A, C, T or G. These molecules pair up and string together to form a winding ladder 3 billion bases long, called a **genome**.

If you were compare the DNA of one human to another, of those 3 billion letters, 99.9% are the same. It is then that 0.1% difference that makes each of us unique. The differences in each individuals genome that determine who we are is referred to as our **genotype**.

We all can see that we're different on the outside, but the differences don't stop there. Our genome also can determine how our body responds to different medications. All medications have the potential to cause side effects. These can range from mildly annoying, like a rash or an upset stomach, to severe or life threatening. Little is known about how or why these side effects occur, and it is frustratingly difficult to predict them.

Part of the answer to the puzzle lay in our genes. **Genes** are specialized segments of DNA that provide the instructions for how our bodies develop and function. While every individual has a similar set of 20,000 genes, some have certain gene variants "or flavors" that increase the chances of experiencing certain side effects. In the same way that a number of gene variants combine to specify how tall you are, different gene variants combine to predispose you to side effects.

The results of these gene combinations are called traits, or more technically, **phenotypes**. It is essential to appreciate that phenotype is not completely predetermined by our genetics – Genes are half of the story; the environment is the other half. When we say environment, this means everything besides our genes, the meal you ate in the morning is part of your environment, just as is the drug you took with your meal.

Because environment can vary so dramatically, it is essential to consider both sides of the equation when thinking about drug effects. This is the essence of what we call **pharmacogenomics**.

Second Half – Study 101

Fortunately, we can perform genetic tests to find out what types of genes you have. Until very recently, we tested genes one at a time, at a cost of several hundred dollars per test. Recent advances in technology now allow us to sequence or "read" the DNA of all 20,000 genes in a single test starting from a simple saliva sample. We then compare readings between different people to find matches between gene variants and side effects.

The purpose of our study is to learn more about which gene variants are associated with different responses, or side effects, to medication. You have been provided with a detailed consent form you can follow along with which will expand upon what this study involves.

We are doing these genetic tests on participants who receive care at one of the listed study sites. While you may be able to participate in the study if you meet the listed criteria, we also have to make sure there are no reasons why you shouldn't participate in this study. If you decide to join this study, there will be specific procedures carried out related to collecting your saliva sample, and you will be put into a certain study group. The saliva samples we collect from our participants, and the data we get from them, will be stored in a 'biobank' for many years, which will allow us to perform more studies on your DNA in the future.

By using these methods, we hope to improve our knowledge of how medications work. This type of research will help doctors provide the most effective form of treatment to the people being treated by the medications we're studying. Keep in mind, your privacy is of the utmost importance to us, and we will take all measures to maintain your confidentiality. This is provided in your consent form.

Hopefully this provides you with an understanding of what genetics is, and you would like to help with our research. Please read carefully and make sure you understand the consent form, and ask your pharmacist or our study contact listed any questions you may have.

We thank you for your time and hope you join our research about how to make medications safer and more effective.

At the conclusion of the video, before asking the participant if they have any questions, the pharmacist will read the following statement:

Based on your report, the pharmacist, will do one of the following

(i) Take no action and send a copy of the report to your physician to add to your medical record.

(ii) Make a change to your drug therapy by either changing a dose, discontinuing a medication or making a therapeutic substitution to change a medication. I will initiate

the change and within 24 hours report the details of the change, in writing, to your physician along with a copy of the report.

(iii) Recommend to your physician to either change a dose, discontinue a medication or make a therapeutic substitution to change a medication.

Appendix - III. Participant Information and Consent Form – Full Document

Blacked out spaces contain contact or personal information.

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

AFFIX BARCODE LABEL HERE
(1D Alphanumeric Barcode)
Do not photocopy once barcoded

PARTICIPANT INFORMATION and CONSENT FORM

Pharmacogenomic Services in Community Pharmacy
(H16-02362)

Principal Investigator: [redacted]
Faculty of Pharmaceutical Sciences
The University of British Columbia (UBC)
[redacted]

Co-Investigator: [redacted]h
British Columbia Pharmacy Association
Vancouver, BC
[redacted]

Sponsors:
British Columbia Pharmacy Association
Green Shield Canada
Pfizer Canada
Genome BC
The University of British Columbia – Faculty of Pharmaceutical Sciences

Study Contact Numbers: [redacted]

1. INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

You are being invited to participate in this study because you are undergoing, or have previously undergone, drug therapy with at least one of the drugs listed in the appendix to this document and are familiar with your pharmacist, who has completed research ethics training and enrolled in this study.

The study aims to develop methods to optimize medication efficacy, reduce adverse effects and improve drug treatment outcomes using the individual's genetic information (DNA). Your pharmacist is participating in this study under the BC College of Pharmacists Code of Ethics, Standard 5: Registrants Participate in Ethically Valid Research.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary. You have the right to refuse to participate in the study. Before you decide, it is important for you to understand what the study involves. This consent form will tell you about this study, the purpose of the study, your role in the study, and the possible benefits, risks and discomforts. You also need to know that there are important differences between being in a research study and being cared for by your pharmacist or physician. The goal of the study is to help the researchers obtain new knowledge so as to improve health outcomes from your drug therapy and help patients in the future with their drug therapy. At the same time, the researchers and your pharmacist have a duty of care to all participants and will inform you of any information that may affect your willingness to remain in the study.

If you wish to participate, you will be asked to sign this form. If you decide to take part in this study, you are still free to withdraw at any time without giving any reasons for your decision. Your medical care will not be negatively affected if you choose to withdraw from the study. This consent form describes the procedures (Section 11) that are being carried out for research purposes. Please review the consent document carefully when deciding whether or not you wish to be part of the research and sign this consent only if you accept being a research participant. Everything we plan to do in this research study with your personal information (identifying, demographic and medical information detailed in Section 8), saliva sample, DNA sample extracted from the saliva and your DNA sequence is described in this consent form.

Please take time to read the information provided here carefully and ask questions to the pharmacist who will provide you additional information you need. You will also be provided a video that describes genomics. Please ask for advice if you think you need it.

3. WHO IS CONDUCTING THIS STUDY?

This study is conducted by researchers in the Faculty of Pharmaceutical Sciences at the University of British Columbia and the BC Pharmacy Association. Funding for the study has been provided by Green Shield Canada, Pfizer Canada and Genome BC. For further clarity, Green Shield Canada and Pfizer Canada have no role in conducting the study and will not receive any study information other than that which is publicly published after the completion of the study.

4. BRIEF BACKGROUND

Because a person's DNA sequence is unique to them and does not change in the vast majority of the cells of your body, your DNA sequence can, with your permission, be repeatedly queried (in a manner similar to a database search) for any drug you may be prescribed currently or in the future.

Among other uses, in a few instances, it can help determine disease diagnosis and prognosis, and appropriate medication therapy. Very little public awareness exists about the potential value of genomic information, and, in particular, the potential values of using genome data to more effectively manage medication therapy – known as 'pharmacogenomic testing'.

A practical application of genome science, pharmacogenomic testing can help predict the efficacy of medications for individuals. In such testing, individual genomic data is gathered to determine the appropriateness of a particular medication for a patient, and need not focus on disease diagnosis or prognosis. Because medications can be targeted to those who will likely benefit, and avoided by those who will likely not, this, in a few instances, has the potential to improve individual health care outcomes and help governments and other payers manage escalating health care costs. By ensuring patients receive only those medications and dosages known to be effective for them, provincial governments and private insurers, in the future, can avoid the costs of using expensive, yet ultimately ineffective, medications.

The science of how genetic interactions with drug therapy has developed over the past forty years. Like all clinical information, there is a spectrum of evidence for how useful a particular intervention is for a particular patient. For this study, we are using information with a very high level of evidence. Specifically, for the gene variants we require one of the following criteria to be met 1) A DNA sequence that has been reviewed by medical experts to be relevant to certain drugs and 2) only variants listed by the United States Food and Drug Administration will be tested. https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.

The science and application of genetic testing is a rapidly developing field. Because drug recommendation and specific doses are designed to serve the largest population possible, we can predict that every individual participant will identify at least one variant that is relevant for at least one medication they are currently taking or will take in the future. That said, as with any clinical assessment, it is not clear at this time if the benefits of making a drug or dosage change outweigh the risks.

5. WHAT IS THE PURPOSE OF THE STUDY?

The Pharmacogenomic Services in Community Pharmacy project is working with pharmacists at 20-30 community pharmacies throughout BC to recruit up to 200 patients to demonstrate that genomic data can be collected via saliva sample by community pharmacists and to use that data to generate clinically actionable reports for your pharmacist and physician to use to make more informed decision about your drug therapy. The proposed use of community pharmacies as the point of delivery for this service is unique in Canada. The project aims to demonstrate that delivery of pharmacogenomic services can be done in pharmacy effectively and without compromising patient privacy.

This study will utilize Standard Operating Procedures (SOPs) developed in a previous study for, amongst others, sample collection and transportation to the UBC Sequencing Centre for processing and sequencing. We will also develop a training program for community pharmacists, along with educational materials for patients. The end-product will be analysis of genetic information, generation of a clinically actionable report, validation of the storage and communication of the data. A key component is to ensure you understand both the nature of the data collection process, as well as how this information can – and cannot – be used to address issues of your personal health.

The study will also use genetic information obtained from sequencing your DNA to retrospectively analyze your drug therapy and provide recommendations for possible changes in therapy to optimize effectiveness, and reduce adverse effects. As part of ongoing research by the investigators, your DNA sequence is being used to create a digital database so we can learn more about how differences in our DNA can affect our health and wellness. In other words, the project also aims to develop a registry of DNA sequence information to allow for further research. This is why your DNA sequence will not be destroyed upon completion of the study.

6. WHO CAN PARTICIPATE IN THE STUDY?

You may be able to participate in this study if you:

- Are undergoing drug therapy with at least one of the drugs listed in the appendix to this document
- Understand English or have a competent person translate for you
- Are 19 years or older
- Able to provide the information described in section 8
- Able to consent using the form provided in this package

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

There are no criteria that would exclude you from participating as long as you have been identified by a participating pharmacist as meeting the criteria for the study. If you are willing to provide your saliva sample and identifying, demographic and medical information and meet the criteria above, then you are able to participate.

8. WHAT ARE MY RESPONSIBILITIES?

If you decide to take part in this study, the pharmacist will collect a saliva sample from you as well as the information listed below.

- Identifying Information
    - Name (as it appears on Care Card)
    - Personal Health Number
    - Address (optional)
    - Telephone Number (optional)
    - E-mail (optional)
- Demographic Information
    - Month and year of birth

  - Gender
  - Height (optional)
  - Weight (optional)
  - Ethnic Background (optional)
- Medical Information
  - Current medications including dosage and directions for use
  - Over the counter (OTC) drugs if used
  - Allergies
  - Medical conditions
  - Identified adverse drug events
  - Laboratory test results (optional)

You will also be asked to complete a post-study experiential survey and you may also be asked to participate in a voluntary post-study interview conducted by one of the investigators.

9. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

Benefits to You

The direct benefit to you will be a clinically actionable report that may assist your pharmacist and/or physician in making possible adjustments to your drug therapy to ensure you're a getting the maximum benefit from the drug(s) while minimizing adverse effects. Your DNA sequence is being used to develop a pharmacogenomics database that will contribute to other patients receiving tailored drug therapy based on their DNA sequence.

Benefits to Others

We hope that the information learned from this study can be used in the future to benefit people in British Columbia.

10. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Physical Risks

The only physical action you will be asked to do is provide a saliva sample. This does not involve serious problems for most people.

Social or Emotional Risks

Your insurer or employer may at some time in the future attempt to request access to your genetic information from the DNA sequence stored at UBC. Since the collection and sequencing of this information has been done for the limited purpose of research, the data cannot be disclosed for such requests. UBC will prohibit such disclosures, as maintaining your privacy is one of our main responsibilities.

11. STUDY PROCEDURES

If You Decide to Join This Study: Specific Procedures

If you agree to take part, the following procedures, which are expected to take approximately 25 minutes of your time, will occur:

Specific Procedures (all overseen by a BC pharmacist registered in our study)		
Saliva Sample Collection	**Collect Personal Information (see 8 above)**	**Additional Clinical Information**
Frequency? Once only **How much?** 1 tube (2mL/tube)	Identifying Information Demographic Information Medical Information	If you consent, you may be contacted and invited to participate in additional research at a later date to provide additional or clarifying the Medical Information

We will:

- Take a total of 1 mL of saliva sample (about ½ teaspoon) by asking you to spit into a tube. We will do this one time only and it will take place in the pharmacy.
- Collect your identifying and demographic information as listed in section 8, as provided by you on the Data Collection Form.
- Collect your medical information as listed in section 8, as provided by you on the Data Collection Form.
- Send your saliva sample to the lab at UBC

The UBC Sequencing Centre lab in the Faculty of Pharmaceutical Sciences at UBC will:

- Extract your DNA sample from your saliva sample.
- Separate the approximately 2% portion of your DNA that contains nearly all 20,000 genes and "read" it to identify anomalies and generate your actual personal DNA sequence.
- Perform gene panel sequencing of up to 340 fragments of your DNA to focus on variants that are known to alter the response to medications
- Securely store your DNA sequence at the UBC Sequencing Centre for as long as it remains useful for research purposes for this study or by other researchers.
- Send your de-identified DNA sequence data to myDNA Australia in Melbourne Australia so that they can generate a clinically actionable report that will be sent to your pharmacist and physician (if you agree) to be reviewed with you, potentially resulting in modifications to your drug therapy.

The review of your report with your pharmacist is expected to take an additional 20-25 minutes.

12. WHAT ARE THE ALTERNATIVES TO PARTICIPATION IN THIS PART OF THE STUDY?

The study is not related a new remedy or medication for your healthcare. As such, not participating in this study will have no adverse effect on the health care you receive from your pharmacist, physician(s), or other health care professional.

13. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You can stop participating in the study at any time without giving reasons. If you withdraw your consent, the medical care you receive from your pharmacists, physician(s), or other health care

professional will not change. You do not have to give any explanation for why you wish to withdraw.

There are two types of withdrawals you may choose from:

1. **Withdraw consent for any future activities of this study but allow continued access to information.** This means that you will no longer be contacted or asked to participate in ongoing study activities. The project will continue using the information you already provided and continue to access information in the study database.
2. **Withdraw consent for past and future activities of the study.** This means that you can no longer be contacted and we can no longer access any information about you. All the data and samples already collected about you will be destroyed.

Depending on the type of withdrawal you choose the withdrawal process and deletion of your information, if required, will also be implemented at the pharmacy at which you enrolled.

If you wish to stop participating at any time, please contact the Principal Investigator, [redacted]
Nislow: Telephone:[redacted]
E-mail: [redacted]
Mail: [redacted]

14. CAN I BE ASKED TO LEAVE THE STUDY?

The study investigators may decide to ask you to leave the study if they feel that it is in your best interests. You may be withdrawn from the study, for example, if you no longer meet the study requirements. Again, the medical care you receive from your pharmacist and other health care professionals remains unchanged regardless of whether or not you are a participant in the study. At that time of withdrawal, the Principal Investigator will contact you and explain the steps being undertaken.

15. HOW WILL MY PERSONAL & HEALTH INFORMATION BE PROTECTED?

Applicable Laws: At all times, your personal and health information is protected by *The Personal Information Protection Act, The Freedom of Information and Protection of Privacy Act*, *The Health Professions Act* and its *Bylaws*, *The Health Care(Consent) and Care Facility (Admission) Act,* and *The Pharmacy Operations and Drug Scheduling Act.* These laws lay out the obligations of the pharmacist, the pharmacy and the University of British Columbia with respect to personal and health information.

The pharmacist obtaining your consent is subject to the obligations with respect to the collection, use, disclosure and security of your personal and health information under *The Health Professions Act* and its *Bylaws* and *The Personal Information Protection Act.* They are also trained by the UBC research team in the process of obtaining consent and the confidentiality obligations in the conduct of research study.

The researchers are UBC employees and will use and retain personal and health information under *The Freedom of Information and Protection of Privacy Act* and the policies of UBC and its Research Ethics Board. Your confidentiality will be respected. However, research records or other source records identifying you may be inspected in the presence of the Investigator or his designate by representatives of the British Columbia Pharmacy Association and/or Genome BC and UBC Clinical Research Ethics Board for

the purpose of monitoring the research.
The other sponsors of the study will never have access to your information. UBC may disclose your DNA sequence to other researchers who receive necessary ethical and legal approval.

Coding: You will be assigned a unique Participant Code as a participant in this study (for example, 'Participant ABC-001'). This code will be used instead of your identifying information on all study-related information collected from you, so that your identity as a participant in this study will be kept confidential. Information that identifies you will be known only to the Principal Investigator, his designate and your pharmacist who collected the information at the outset.

The list that matches your name to the unique code that is used on your research-related information (i.e. the 'coding list') will be securely stored and access limited to three individuals at UBC. None of your personal information (section 8) will be sold to anybody or used for commercial purposes and your identity will not be disclosed in any report.

Data Management and Security: Once collected from you after your consent, your personal information (identifying) will be stored in a secure form at the participating pharmacy and transferred securely to the study researchers at UBC Pharmaceutical Sciences. At UBC, storage of this information is subject to the UBC Information Security Standards under Policy #104, Acceptable Use and Security of UBC Electronic Information and Systems. Personal identifying information will be removed and only the Participant Code will be used thereafter. The consent form and your identifying information with the link to your Participant Code will be stored in an encrypted form in a separate password protected file on a different server at UBC. The key file, after coding described above, will be transferred to a separate hard drive which will be kept in a safe within UBC with limited access.

Research using your coded information might someday lead to the development and sale of a medical or genetic test or product. This may be done by a university of hospital, or a commercial company, because sometimes researchers are funded by or work with companies. This means that in the future researchers, including potentially commercial companies, may benefit financially. However, you will not gain any personal financial advantage from this commercialization.

Retention period and sharing of your information: The long-range goal of this study is to develop a DNA sequence database (the registry described in Section 5) that may be used to predict the potential and level of efficacy or degree of adverse events that may occur in an individual depending upon the drug prescribed for a particular disease therapy and the individual's personal gene sequence.

Other researchers might request from the principal investigator the use of your DNA sequence for other projects in the future. The DNA sequence does not link to your identifying, demographic or medical information. Any such access will be subject to the ethical and legal approval.

Destroying your personal information: All of your personal information (identifying, demographic and medical information), including your saliva and DNA sample, will be destroyed no later than December 31, 2020.

Any study related data and/or samples, sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries, (for e.g. the Patriot Act in the United States) dealing with protection of information may not be as strict as in Canada. However,

all study related data and/or samples, that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information and/or samples, to organizations located outside of Canada.

- myDNA Australia

If you have any questions with regards to your collection, use, management or security of your personal information or any other issue before completing the consent process, please ask the pharmacist to clarify. At any later time, should you have more questions or need clarifications please use the contacts in Section 18 and 19.

16. WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

17. IS THERE ANY FINANCIAL GAIN OR COST TO ME TO PARTICIPATE?

Costs

This study will not cost you any money, other than the time it takes for you to participate in the study procedures at the pharmacy collecting your personal information, medication history and saliva sample after obtaining your consent.

18. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this part of the study before or during participation, you can contact:

Co-Investigator: [redacted]

Principal Investigator: [redacted]

19. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AND/OR EXPERIENCES AS A SUBJECT DURING THE STUDY?

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia, Office of Research Ethics at by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

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20. AFTER THE STUDY IS FINISHED

The DNA sequence will be securely stored digitally at UBC for as long as it remains useful for research purposes for this study or by other researchers – this could be for decades. You will not be given the DNA sequence because these results will not benefit you or your family. You will,

however, be given the results of your genetic tests in the form of a clinically actionable report. The general study results using coded data provided by all participants will be published in articles, poster presentations, or talks. These results are expected to be publically available in a few years' time. When your DNA sequence is sent to myDNA Australia to generate your report, it will be linked to your demographic and medical information but not your name.

APPENDIX

Antidepressants	Antipsychotics
Agomelatine	Aripiprazole
Amitriptyline	Clozapine
Citalopram	Haloperidol
Clomipramine	Olanzapine
Dothiepin	Quetiapine
Duloxetine	Risperidone
Escitalopram	Zuclopenthixol
Fluoxetine	
Fluvoxamine	
Imipramine	
Mianserin	
Mirtazapine	
Moclobemide	
Nortriptyline	
Paroxetine	
Sertraline	
Trimipramine	
Venlafaxine	
Vortioxetine	

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Pharmacogenomic Services in Community Pharmacy
Principal Investigator: Dr. Corey Nislow, Associate Professor, UBC

Principal Investigator: [redacted]

Co-Investigator: [redacted]

Participant Consent Form

My pharmacist explained the research project objectives, the benefits and potential harms and discomforts to me and answered the questions posed by me. In addition, I have read and understood the information provided to me by my pharmacist, in writing and presented in a video. I have been able to reflect on the request for information and ask for advice if needed.

I understand that:

- my pharmacist will collect my saliva, identifying information, demographic information and medical information
- the information collected will be kept confidential and secure as described in the participant information section
- my participation is completely voluntary and I can withdraw from the study at any time
- this study may not provide me any direct benefits for participation
- I will receive a copy of this signed consent form for my records
- I may contact the pharmacist or study team at any time to access or correct my personal information
- I will not be provided my DNA sequence however I will be provided genetic test results in a clinically actionable report
- I am not waiving any of my legal rights as a result of signing this consent form

I consent to:

- participate in this study
- the pharmacist identified below collecting my identifying, demographic and medical information from me and sending it to University of British Columbia for use in the research study "Pharmacogenomic Services in Community Pharmacy"
- the pharmacist, on behalf of the study team, taking my saliva sample for use in the study as described in the participant information section
- my saliva sample with my identifying, demographic and medical information to be sent to the University of British Columbia for use in the research study "Pharmacogenomic Services in Community Pharmacy" as described in the participant information section
- my genetic data being sent securely, along with my demographic and medical information in a de-identified manner to myDNA Australia to have a clinically actionable report generated
- the pharmacist reviewing the results of my genetic tests (clinically actionable report) with me

- my DNA sequence information to be securely stored at UBC for as long as it remains useful for research purposes for this study or by other researchers
- my DNA sequence information to be shared with other research groups who have obtained necessary ethical and legal approval
- being contacted to participate in additional research to providing additional medical information or clarifying information provided

Participant 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**

Appendix - IV. R Code – Annotated

Copy of R code used to preform data analysis and create study tables.

Community PGX R Code

Samantha Breaux

September 19, 2019 - March 12, 2021

Packages Required

Packages + function need to run the code in this file

```
library(data.table)
library(tidyverse)
library(plyr)
library(reshape2)
library(compare)
library(rowr)
library(stringr)

# renames column based on column index not
# name
rename_col_by_position <- function(df, position,
    new_name) {
    new_name <- enquo(new_name)
    new_name <- quo_name(new_name)
    select(df, `:=`(!!new_name, !!quo(names(df)[[position]])),
        everything())
}

firstup <- function(x) {
    substr(x, 1, 1) <- toupper(substr(x, 1, 1))
    x
}
```

Load Data

Loading in and tiding all inital data sets

Output Files:

- tidy_mydna.csv = Tidy myDNA genotype data
- tidykailos.csv = Tidy kailos genotype data
- allmydrugdata.csv = Tidy myDNA drug/phenotype data

```
# change working directory to that with myDNA
# CSVs
setwd("C:/Users/Sam/Documents/pgx/mydna")
getwd()
# load in snp data and genotype data: rename
# some columns to match those in mydna CSVs
```

```
snpdat <- read.csv("C:/Users/Sam/Documents/pgx/mydna snps - Sheet1.csv")
mydata <- read.csv("C:/Users/Sam/Documents/pgx/mygenotypes.csv") %>%
    rename(c(gene = "GENE", genotype = "GENOTYPE"))


# load in and bind all myDNA genotype CSVs
# into one file. remove trailing spaces

files <- list.files()
temp <- lapply(files, fread, sep = ",")
data <- rbindlist(temp) %>% mutate_if(is.character,
    str_trim)

# make CSV of all myDNA patient genotype
# information
write_csv(data, "C:/Users/Sam/Documents/pgx/results/tidy_mydna.csv")

# load in kailos data and remove any trailing
# spaces
kdata <- read.csv("C:/Users/Sam/Documents/pgx/allkailos4.csv")

kd <- kdata %>% mutate_if(is.factor, as.character) %>%
    mutate_if(is.character, str_trim)

# tidy data: create gene column, replace nulls
# with NA and then remove na rows, rename
# columns to match
m <- melt(kd, id.vars = "ID", measure.vars = 2:39) %>%
    mutate_all(~replace(., . == "", NA)) %>% na.omit() %>%
    rename(c(variable = "GENE", value = "kailos_call"))

# output tidy data as a cSV
write.csv(m, "C:/Users/Sam/Documents/pgx/results/tidykailos.csv")

# load in my DNA patient drug response data,
# bind into one data frame and remove any
# trailing spaces
setwd("C:/Users/Sam/Documents/pgx/myDNA_drugs_CLEAN2")
files2 <- list.files()
temp2 <- lapply(files2, fread, sep = ",")
data2 <- as.data.frame(rbindlist(temp2, use.names = TRUE)) %>%
    mutate_if(is.character, str_trim)

# create pharmacy ID column
sites <- separate(data2, ID, into = c("site",
    "xxx"), sep = "-", remove = F) %>% select(-xxx)

# output tidy data as csv
write.csv(sites, "C:/Users/Sam/documents/pgx/results/allmydrugdata.csv")
```

Frequency of myDNA Calls

Calculating the frequency of myDNA calls

Output Files:

- mydna_freq.csv = Number of times each myDNA genotype was called

```
# split dataframe into seperate data frames
# based on gene
xx <- split(data, data$GENE, drop = F)

# create function to get genotype frequencies
genotype_freqs <- function(df) {
    v <- table(df$GENOTYPE) %>% as.data.frame() %>%
        rename(c(Var1 = "GENOTYPE")) %>% mutate(myDNA_call_freq_percent = Freq/150 *
        100) %>% merge(df, by = "GENOTYPE")
}

# get genotype frequncies and bind back into
# one data frame
data_F <- lapply(xx, genotype_freqs) %>% rbindlist() %>%
    rename(c(Freq = "myDNA_call_freq"))

# return only unique rows
data_Freq <- data_F %>% select(-ID, -`PREDICTED FUNCTION`) %>%
    unique()

# merge with population data
frequencies <- merge(mydata, data_Freq, by = c("GENE",
    "GENOTYPE"))

# round to 2 digits
frequencies <- format(frequencies, digits = 2)

# create csv of mydna gene freqs
write_csv(frequencies, "C:/Users/Sam/Documents/pgx/results/myDNA_freq.csv")
```

Frequency of Kailos Calls

Output Files:

- kailos_call.csv = Number of times all kailos snps were called

```
# get unique kailos genotype frequencies and
# round table

lol <- table(m$kailos_call) %>% as.data.frame() %>%
    rename(c(Var1 = "kailos_call")) %>% mutate(`kailos_Genotype_Freqency_%` = Freq/37 *
    100) %>% rename(c(Freq = "kailos_Genotype_Freqency")) %>%
    merge(m, by = "kailos_call") %>% select(-ID) %>%
    unique() %>% format(digits = 2)

# output kailos genotype frequncies as a csv
write.csv(lol, "C:/Users/Sam/Documents/pgx/results/kailos_freq.csv")
```

```
# remove rs codes that dont exist in the myDNA
# data set
toMatch <- c("rs9923231", "rs762551", "rs4149056",
    "CYP2D6", "CYP2C19", "CYP3A4", "CYP3A5", "CYP2C9")
k_calls_only <- filter(m, grepl(paste(toMatch,
    collapse = "|"), kailos_call))

# get frequncy of only those genes that exist
# in both data sets
kailosco_freq <- table(k_calls_only$kailos_call) %>%
    as.data.frame() %>% rename(c(Var1 = "kailos_call")) %>%
    mutate(`kailos_Genotype_Freqency_%` = Freq/37 *
        100) %>% rename(c(Freq = "kailos_Genotype_Freqency")) %>%
    merge(m, by = "kailos_call") %>% select(-ID) %>%
    unique() %>% format(digits = 2)
```

Comparison of Kailos and myDNA Genotype Calls

t60-163 and t60-169 failed mydna genotyping. - passed kailos

- Both were retested and t60-169 passed (t60-163 did not)
- Changed sample name in kailos file to t60-169-RT so they could be compared

L65-294 and L65-295 were Swapped and L65-293 = L65-296

- Changed names to reflect this in the kailos data file
- L65-293 = L65-296
- L65-294 = L65-295
- L65-295 = L65-294

35a called Only in Kailos reports

- Has normal metaboliser status
- Subset of *2 allele (2851 c>t, 4181 g>c VS. 2851 c>t, 4181 g>c AND 31 g>A)

Output Files:

- different_genotype.csv = Table of samples whose genotype calls did not match between data sets
- my_vs_kailosgenotypes.csv = Comparison of all myDNA and kailos calls

```
# introduce patient ids back into genotype
# freq data
mydata_geno <- merge(mydata, data, by = c("GENE",
    "GENOTYPE"))

# merge in kailos data
my_v_k <- merge(k_calls_only, mydata_geno, by = c("GENE",
    "ID"), all = T)

# remove myDNA genes that are not found in the
# kailos data det
mmm <- my_v_k[!is.na(my_v_k$kailos_call.x), ] %>%
    select(-GENOTYPE, -population.level, -phenotype,
        -"PREDICTED FUNCTION") %>% rename(c(kailos_call.x = "kailos_call",
```

```
    kailos_call.y = "myDNA_call"))

# create column to hightlight different gene
# calls between data sets (x = same)
mmm$compare <- ifelse(mmm$kailos == mmm$myDNA,
    "x", ifelse(mmm$kailos != mmm$myDNA, "different",
        "a"))

# create data frame of only differing gene
# calls
diffrentsamples <- filter(mmm, compare == "different")

# output myDNA v. Kalios comparison table and
# table of samples that differ between data
# sets
write.csv(diffrentsamples, "C:/Users/Sam/Documents/pgx/results/different_genotypes.csv")
write.csv(mmm, "C:/Users/Sam/Documents/pgx/results/my_vs_kaliosgenotypes.csv")
```

myDNA vs Kailos Genotype Freqencies Compared With Population Level

Genotype frequencies For CYP2D6, CYP2C19, CYP2C9 and VKORC1

- Taken from myDNA paper
- (doi: 10.1007/s00702-018-1922-0)
- Two cyp2d6 alleles tested for(29 and 36) were not mentioned at all in study. one person was found to have a *36 (1/36) genotype ** Used frequency from this paper (doi: 10.3389/fphar.2018.00305) and matched to 1/14b genotype which had the same snp freq

Genotype frequencies for SLCO1B1, CYP1A2, CYP3A4, CYP3A5, and OPRM1

- Calculated from SNP frequency in hardy winberg equlibrium
- SNP frequency found from ncbi.nlm.nih.gov (us national library of medicine snp database) spec frequncy is the global frequency recorded by the genome aggregation database (gnomeAD)

Output Files:

- my_vs_kailos_freq_pop = kailos vs my dna genotype frequencies

```
# merge kailos freq into myDNA freq table
mykailos <- join(frequencies, lol, by = "kailos_call",
    match = "all")

# remove last colunmn (duplicate)
mykailos <- mykailos[c(1:9)]

# output frequency comparison as csv
write.csv(mykailos, "C:/Users/Sam/Documents/pgx/results/my_vs_kailos_freq_pop.csv")
```

Drug vs Phenotype frequencies

Remove/Replace warfin columns

- Normal warfarin sensitivity = Normal metaboliser

- High warfarin sensitivity = Poor metaboliser
- Increased warfarin sensitivity = Reduced metaboliser

Output Files:

- myFUNCTION_drug_freq.csv = frequncy of each predicted phenotype
- drug_pheno.csv = number of times each phenotype was called for each drug based on gene

```
# get unique drug gene information, rename
# colum to match
drugs <- sites[c("MEDICATION", "GENE(S)\rINVOLVED")] %>%
    unique() %>% rename_col_by_position(2, GENE)

# couldnt get the genes to correctly sepreate
# into individual rows so outputed data as csv
# and edited by hand. hashed line so it
# wouldnt overwrite good drug file
# write.csv(drugs,
# 'C:/Users/Sam/Documents/pgx/drugs.csv')

# read back in good drug file
drugs <- read.csv("C:/Users/Sam/Documents/pgx/drugs.csv")


# get frequency of each perdicted metabolism
# function
mydrugs <- table(data$`PREDICTED FUNCTION`) %>%
    as.data.frame() %>% rename(c(Var1 = "PREDICTED FUNCTION")) %>%
    mutate(per_fun_freq = Freq/150 * 100) %>%
    rename(c(Freq = "Phenotype_freq")) %>% merge(data,
    by = "PREDICTED FUNCTION") %>% select(-ID,
    -GENOTYPE) %>% unique()

# merge in drug data
function_freq_drug <- merge(mydrugs, drugs, by = "GENE")

# output frequency of perdicted phenotype/drug
# table as csv
write.csv(function_freq_drug, "C:/Users/Sam/Documents/pgx/results/myFUNCTION_drug_freq.csv")

# get cleaner function/ phenotype data
pheno_data <- mydata_geno %>% select(phenotype,
    "PREDICTED FUNCTION")

# merge in phenotype information and remove
# trailing spaces
fun_pheno <- merge(function_freq_drug, pheno_data,
    by = "PREDICTED FUNCTION") %>% unique()
fun_pheno <- fun_pheno %>% mutate_if(is.factor,
    as.character) %>% mutate_if(is.character,
    str_trim)

# number of times each drug per gene is
# impacted by each phenotype
cast_pheno <- dcast(fun_pheno, MEDICATION + GENE ~
```

```
    phenotype, fun.aggregate = sum, value.var = "Phenotype_freq")
# output file as csv
write.csv(cast_pheno, "C:/Users/Sam/Documents/pgx/drug_pheno.csv")
```

Number of Drug Considerations Per Study Site

Output Files:

- site_consideration.csv = frequency of each pharmacogentic consideration for each study site and medication

```
# get frequency of each pharmacogentic
# consideration for each study site and
# medication
conc_freq <- as.data.frame(table(sites$site, sites$CONSIDERATION,
    sites$MEDICATION)) %>% rename(c(Var1 = "site",
    Var2 = "CONSIDERATION", Var3 = "MEDICATION")) %>%
    merge(sites, by = c("site", "CONSIDERATION",
        "MEDICATION")) %>% rename(c(`GENE(S)\rINVOLVED` = "GENEs"))

# cast site column and use frequency column to
# fill
cast_site <- dcast(conc_freq, MEDICATION + GENEs +
    CONSIDERATION ~ site, fun.aggregate = mean,
    value.var = "Freq") %>% rename(c(BCP = "BCP (n=8)",
    D59 = "D59 (n=1)", F31 = "F31 (n=2)", J02 = "J02 (n=8)",
    K74 = "k74 (n=6)", K76 = "k76 (n=10)", L65 = "L65 (n=20)",
    N24 = "N24 (n=20)", N43 = "N43 (n=9)", N83 = "N83 (n=16)",
    S73 = "S73 (n=5)", S81 = "S81 (n=4)", S94 = "S94 (n=3)",
    T37 = "T37 (n=9)", T60 = "T60 (n=9)", W19 = "W19 (n=10)",
    X73 = "X73 (n=10)"))

# change NAN values to 0
cast_site[is.na(cast_site)] <- 0
# output as a csv
write.csv(cast_site, "C:/Users/Sam/documents/pgx/results/site_consideration.csv")
```

Missing drug

From here on is me investigating (in a round about way) the missing drug, acenocoumarol, in the three patients J02-131, L65-291, and N24-325

```
lo <- split(sites, sites$ID)


drugcat <- as.data.frame(lo$`BCP-011`$`DRUG CATEGORY`,
    lo$`BCP-011`$MEDICATION) %>% rownames_to_column() %>%
    rename_col_by_position(1, "MEDICATION") %>%
    rename_col_by_position(2, `DRUG CATEGORY`)

sites <- sites %>% select(-"DRUG CATEGORY") %>%
    merge(drugcat)
```

```
drugc <- split(sites, sites$`DRUG CATEGORY`)
majorAC <- split(drugc$Anticoagulants, drugc$Anticoagulants$CONSIDERATION)
view(majorAC$major)
med <- split(majorAC$usual, majorAC$usual$MEDICATION)


m <- "drug"
normal <- as.data.frame(lo$`BCP-011`$MEDICATION) %>%
    rename_col_by_position(1, drug)

j02131 <- as.data.frame(lo$`J02-131`$MEDICATION) %>%
    rename_col_by_position(1, drug)
l65291 <- as.data.frame(lo$`L65-291`$MEDICATION) %>%
    rename_col_by_position(1, drug)
l65292 <- as.data.frame(lo$`L65-292`$MEDICATION) %>%
    rename_col_by_position(1, drug)
n24325 <- as.data.frame(lo$`N24-325`$MEDICATION) %>%
    rename_col_by_position(1, drug)

dif131 <- anti_join(normal, j02131)
dif291 <- anti_join(normal, l65291)
dif325 <- anti_join(normal, n24325)
```

Current Medication

Changed all insulins to just insulin ### Output Files:

- site_consideration.csv - considerations per drug per site

```
setwd("C:/Users/Sam/Documents/pgx/myDNA_PATIENT_DRUGS")
getwd()
files3 <- list.files("C:/Users/Sam/Documents/pgx/myDNA_PATIENT_DRUGS")
temp3 <- lapply(files3, fread, sep = ",")
data3 <- as.data.frame(rbindlist(temp3, use.names = TRUE)) %>%
    mutate_if(is.character, str_trim) %>% rename(c(MEDICATION = "MEDS"))
data3$MEDS <- firstup(data3$MEDS)
data3$CONSIDERATION <- word(data3$`PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST`,
    1)
data3$MEDICATION <- gsub("\\([^()]*\\)", "", data3$MEDS)
data3$MEDICATION <- gsub("\\([^()]*\\)", "", data3$MEDICATION)

patient_drugs <- separate(data3, ID, into = c("site",
    "xxx"), sep = "-", remove = F) %>% select(-xxx)

cons_freq <- as.data.frame(table(patient_drugs$site,
    patient_drugs$CONSIDERATION, patient_drugs$MEDICATION)) %>%
    rename(c(Var1 = "site", Var2 = "CONSIDERATION",
        Var3 = "MEDICATION")) %>% merge(patient_drugs,
    by = c("site", "CONSIDERATION", "MEDICATION")) %>%
    rename(c(`GENE(S)` = "GENEs"))

cast_sites <- dcast(cons_freq, MEDICATION + GENEs +
    CONSIDERATION ~ site, fun.aggregate = mean,
    value.var = "Freq")
```

```
library(splitstackshape)
df2 <- cSplit(df1, "Item.Code", sep = "/", direction = "long")
```

Thesis Analysis

Additional analysis completed for thesis

- Allele frequency
  - Population frequency from genome aggregation database or doi: 10.3389/fphar.2018.00305
- MHCs frequency and frquency of considerations
- Number of considerations per meds (potential meds)

Output Files:

- drugs_patients_with_intrxn.csv - Drugs that patients who experinced a reaction are currently taking
- drug_gene_Inhibition_freq.csv - Frequency of each drug per interaction state
- Criteria_meds.csv - Frequency of MCHs
- criteria_considerations.csv - Frequency of dosing considerations per MCH
- critera_metabolism.csv - Frequency of metaboliZer state per MCH
- mydna_alleles.csv - Table of myDNA alleles
- mydna_alleles_freqs.csv - Frequency of alleles

```
# patient interaction data
inter_s <- read.csv("interaction_samples2.csv")
# patient genotype data
DNA_geno <- read.csv("tidy_myDNA.csv")
# patient current medications
all_p_drugs <- read.csv("patient_drugs.csv")

# recover all sites in study
all_sites <- separate(DNA_geno, ID, into = c("site",
    "xxx"), sep = "-", remove = F)
a_S <- as.data.frame(unique(all_sites$site))

# sites where patient experienced an
# interaction
sites <- as.data.frame(unique(inter_s$site))

# frequency of each drug per interaction state
# (not including serotonin sickness)
drug_gene_interactions <- inter_s[!grepl("SEROTONIN",
    inter_s$interaction_TYPE), ]
drug_indi <- as.data.frame(table(drug_gene_interactions$MEDICATION,
    drug_gene_interactions$interaction_TYPE))
drug_indi[drug_indi == 0] <- NA
dr_gn <- drug_indi[!is.na(drug_indi$Freq), ]
x <- sum(dr_gn$Freq)

# frequency of each drug per gene per
# interaction state (not including serotonin
# sickness)
drug_indi_gene <- as.data.frame(table(drug_gene_interactions$MEDICATION,
```

```
    drug_gene_interactions$interaction_TYPE, drug_gene_interactions$interaction_with))
drug_indi_gene[drug_indi_gene == 0] <- NA
dr_gn_gene <- drug_indi_gene[!is.na(drug_indi_gene$Freq),
    ]
write.csv(dr_gn_gene, "C:/Users/Sam/Downloads/thesis_data/drug_gene_Inhibition_freq.csv")
y <- sum(dr_gn_gene$Freq)

# unique patients with recoreded drug-gene
# interactions
unique_patients <- unique(drug_gene_interactions$ID)
# drugs that patients who experinced a
# reaction are currently taking
pd <- all_p_drugs[all_p_drugs$ID %in% unique_patients,
    ]
write.csv(pd, "C:/Users/Sam/Downloads/thesis_data/drugs_patients_with_intrxn")
# number of drugs with CPIC considerations
consid <- pd[!grepl("NO", pd$CONSIDERATION), ]
```

```
# patient drugs
PD <- read.csv("C:/Users/Sam/Downloads/patient_drugs.csv")

# inclusion drugs

PID <- c("Agomelatine", "Amitriptyline", "Citalopram",
    "Clomipramine", "Dothiepin", "Duloxetine",
    "Escitalopram", "Fluoxetine", "Fluvoxamine",
    "Imipramine", "Mianserin", "Mirtazapine",
    "Moclobemide", "Aripiprazole", "Clozapine",
    "Haloperidol", "Olanzapine", "Quetiapine",
    "Risperidone", "Zuclopenthixol", "Nortriptyline",
    "Paroxetine", "Sertraline", "Trimipramine",
    "Venlafaxine", "Vortioxetine")
library(tidyverse)
library(tidyr)


# get only MHC data
PD_NT <- PD %>% mutate_if(is.character, str_trim)
PDID_NT <- PD_NT %>% subset(MEDICATION %in% PID)


patient_I <- PD %>% select(ID) %>% unique()

all_pateints <- merge(patient_I, PDID_NT, all = T)


# frequncy of MHCs vs study vs all drugs
patients_on <- table(all_pateints$MEDICATION) %>%
    as.data.frame() %>% mutate(`Study_percent n=150` = Freq/150 *
    100) %>% mutate(`criteria_drug_percent n=195` = Freq/195 *
    100) %>% mutate(`out_all_drugs_on n=880` = Freq/880 *
    100)
write_csv(patients_on, "C:/Users/Sam/Documents/pgx/results/Criteria_meds.csv")
```

```
# dosing considerations per MHC
critera_considerations <- as.data.frame(table(all_pateints$MEDICATION,
    all_pateints$CONSIDERATION))
write_csv(critera_considerations, "C:/Users/Sam/Documents/pgx/results/criteria_considerations.csv")

# metabolizer state per MHC
mydata <- read.csv("C:/Users/Sam/Documents/pgx/mygenotypes.csv") %>%
    rename(c(gene = "GENE", genotype = "GENOTYPE"))

PD_rel <- all_pateints %>% select("ID", "GENE.S.",
    "MEDICATION") %>% rename(c(GENE.S. = "GENE")) %>%
    separate_rows("GENE")
PHENO <- mydata_geno %>% select(GENE, phenotype,
    ID)

patient_pheno <- merge(PD_rel, PHENO, by = c("GENE",
    "ID"))
critera_metabolism <- as.data.frame(table(patient_pheno$MEDICATION,
    patient_pheno$phenotype))
write_csv(critera_metabolism, "C:/Users/Sam/Documents/pgx/results/critera_metabolism.csv")
```

```
data <- mydata
# genotype data seperate CYP alleles
alleles <- data %>% separate_rows("GENOTYPE",
    sep = "/") %>% mutate_if(is.character, str_trim)

# only CYP alleles
allelesE <- alleles[alleles$GENE != "OPRM1", ]
allelesf <- allelesE[allelesE$GENE != "VKORC1",
    ]
allelesg <- allelesf[allelesf$GENE != "SLCO1B1",
    ]

# sepreate VKORC1 OPRM1 SLCO1B1
a <- c("VKORC1", "OPRM1", "SLCO1B1")
aa <- alleles[alleles$GENE %in% a, ] %>% mutate_if(is.character,
    str_trim)
ax <- aa %>% separate_rows("GENOTYPE", sep = "")
aaa <- ax[ax$GENOTYPE != "", ]

# combine
all_alleles <- rbind(allelesg, aaa)
write_csv(all_alleles, "C:/Users/Sam/Documents/pgx/results/mydna_alleles.csv")

# alelle frequency
allele_freq <- as.data.frame(table(all_alleles$GENE,
    all_alleles$GENOTYPE))

AF <- allele_freq[allele_freq$Freq != "0", ] %>%
    mutate(`Freq alleles per gene n=300` = Freq/300 *
        100)
write_csv(AF, "C:/Users/Sam/Documents/pgx/results/mydna_alleles_freqs.csv")
```

Appendix - V. myDNA Sample Report – Full Document

Actual report returned for a participant in the study. Personal or contact information has been blacked-out.

6 December 2018

[redacted]

Dear [redacted]

Please find attached your patient's myDNA report.

Patient Full Name: Patient S81-252
Patient Address: [redacted]
DOB: [redacted]
Reference ID: [redacted]
Patient Phone Number: [redacted]

This myDNA medication pharmacogenomic test was ordered by your patient and they nominated you to receive a copy of their results.

The myDNA medication test is a pharmacogenomic test which looks at common genetic variants in a number of genes with likely clinical significance and potential to enhance safe and effective prescribing of a range of medications. The information provided by the test is mainly around drug metabolism and how genotype-predicted changes influence plasma concentrations, and clinical effects (both therapeutic and adverse). The reports prepared by the myDNA clinical team, provide suggestions on medication selection, dose modification and other clinically relevant information. This information is based on the published literature, as well as peer-reviewed pharmacogenomic guidelines where available.

This report is not sent directly to the patient. The results and report are delivered to the patient by a registered healthcare professional, who is either 1) a requesting doctor, 2) a requesting community pharmacist or 3) the patient's self-nominated doctor if the test was conducted with a self-administered kit. Following the delivery of the results by the relevant healthcare professional, the patient is given access to a secure online portal at www.mydna.life/explore where they can view their report and receive simple explanations of the results.

As pharmacogenomics is a relatively new area of medicine which clinicians are incorporating into their practice, our service believes it is vital to provide timely support. Therefore, we have a clinical team available by phone to answer any questions you may have about this report, including interpretation and clinical utility, or about pharmacogenomics in general. The clinical team can be reached on 1-844-472-7896.

Kind Regards,

A/Prof Les Sheffield
Medical Director
MyDNA Life

ABOUT THIS REPORT

Overview

This report provides clinically relevant information on what the patient's genetic results predict about their response to a number of medications covered by this report.

The information concerns drug metabolism and plasma concentrations (drug exposure), as well as the potential for altered clinical effects.

Based on the available information found in the published literature, each medication has been assigned a category according to the likely clinical significance of each gene-drug interaction.

The three categories are:

- Major – significant result that may require altering this medication
- Minor – result should be considered as may affect medication response
- Usual – usual prescribing considerations apply

For many medications covered in this report, international, peer reviewed prescribing guidelines are available and these are included in our report.

The two major guidelines are those of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Royal Dutch Pharmacists Association – Pharmacogenetics Working Group (DPWG).

Report breakdown

The report consists of the following sections:

- Report Summary – identifies which of the patient's listed medications have pharmacogenomic information relevant to the genes tested, with an indication of the clinical importance of this information (i.e. "Major", "Minor" or "Usual" prescribing considerations).
- Genetic Test Results Overview – genotype result for the eight gene test (i.e. six genes encoding CYP450 metabolising enzymes relevant to a large number of medications, *VKORC1* which relates to warfarin sensitivity and *SLCO1B1* which relates to statin induced myopathy).
- Current Medications – details of the interaction between the patient's genetic results and their medication, based on the current scientific literature, as well as clinical recommendations, many sourced from peer-reviewed, published guidelines.
- Potential Drug Interactions – identifies which of the patient's listed medications can significantly inhibit or induce CYP enzymes, as they may modify the genotype-predicted enzyme function.
- Future Medications – lists medications that the patient is not currently taking that have potentially clinically significant prescribing considerations based on the patient's genetic test results (also classified as having "Major", "Minor" or "Usual" prescribing considerations).

As part of our clinical service, we have a team of clinical experts available to answer any questions you may have about this report or about pharmacogenomics in general.

If you have any such queries, please call our clinical team on 1-844-472-7896.

myDNA
Medication

Personalised Medication Report

for ***Patient S81-252***

Name: [redacted]
Address: [redacted]

DOB: [redacted]
myDNA ID:
Pathology No:

Collected: 27-Oct-2018
Received: 30-Nov-2018
Reported: 6-Dec-2018

Doctor: [redacted]
Copy to:

Clinical Notes:

Genetic interpretation by:
myDNA
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
Pantoprazole	*CYP2C19*	Minor – result should be considered as may affect medication response
Fluoxetine	*CYP2C9* *CYP2D6*	Usual prescribing considerations apply
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST		
oestrogen (Premarin Tablets), lamotrigine, trazadone		

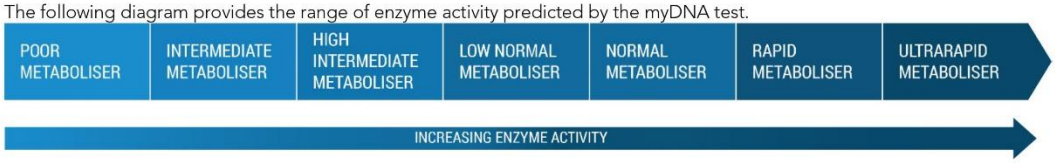
LEGEND: Major prescribing considerations Minor prescribing considerations Usual prescribing considerations

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

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PHENOTYPE	GENE	GENOTYPE	PHENOTYPE
CYP2D6	*1/*2	Normal metaboliser	*CYP3A4*	*1/*1	Normal metaboliser
CYP2C19	*1/*17	Rapid metaboliser	*CYP3A5*	*3/*3	Poor metaboliser
CYP2C9	*1/*1	Normal metaboliser	*SLCO1B1*	TT	Normal Transporter Function
VKORC1	GG	Normal VKORC1 enzyme level	*OPRM1*	AA	Higher opioid sensitivity
CYP1A2	*1A/*1F	Normal metaboliser			

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.



1-844-472-7896 · www.mydna.life

CURRENT MEDICATIONS

PERSONALISED INTERPRETATION AND RECOMMENDATIONS		
MEDICATION	**INTERPRETATION**	**RECOMMENDATION**
Pantoprazole	*CYP2C19* - Rapid metaboliser: This genotype predicts slightly increased metabolism of pantoprazole which has been linked to an incomplete clinical response in conditions such as oesophagitis and H. pylori.	If response is inadequate, consider 1) a preference for esomeprazole or rabeprazole, 2) increasing the dose, and 3) using divided dosing (i.e. at least twice daily) even of the same overall daily dose.
Fluoxetine	*CYP2D6* - Normal metaboliser *CYP2C9* - Normal metaboliser: The metabolism of fluoxetine is complex due to the involvement of several CYP enzymes (especially CYP2D6 and CYP2C9), the formation of active metabolites and the inhibition of CYP2D6 by fluoxetine and its metabolites. The CYP2D6 genotype predicts normal fluoxetine exposure and normal formation of the active S-norfluoxetine metabolite. The CYP2C9 genotype predicts normal metabolism via this pathway. However, fluoxetine and its metabolites can strongly inhibit CYP2D6 function, converting the phenotype to an intermediate or poor metaboliser which can last for up to 9 weeks after cessation of fluoxetine (this is particularly relevant if commencing a drug extensively metabolised by CYP2D6 during this time). This CYP2D6 inhibition is dose and duration of therapy dependent and could potentially lead to late onset adverse effects on a previously tolerated fluoxetine dose.	Standard dosing and prescribing measures apply. If adverse effects are a concern, consider an alternative antidepressant for which normal metabolism is predicted.

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
Fluoxetine	CYP2C19	CYP2D6	

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
Antidepressants - SSRIs	Citalopram	*CYP2C19*	Reduced / inadequate response	*CPIC*[1]
	Escitalopram	*CYP2C19*	Reduced / inadequate response	*CPIC*[1]
Antidepressants - tricyclic antidepressants	Amitriptyline	*CYP2D6* *CYP2C19*	Reduced / inadequate response	*CPIC*[2]
	Clomipramine	*CYP2D6* *CYP2C19*	Reduced / inadequate response	*CPIC*[2]
	Doxepin	*CYP2D6* *CYP2C19*	Reduced / inadequate response	*CPIC*[2]
	Imipramine	*CYP2D6* *CYP2C19*	Reduced / inadequate response	*CPIC*[2]
Antifungals - Azoles	Voriconazole	*CYP2C19*	Reduced / inadequate response	*CPIC*[3]

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antidepressants - other	Moclobemide	*CYP2C19*	Reduced / inadequate response	-
Antidepressants - SSRIs	Sertraline	*CYP2C19*	Reduced / inadequate response	*CPIC*[1]
Antidiabetics	Gliclazide	*CYP2C9* *CYP2C19*	Reduced / inadequate response	-
Antiplatelet drugs	Clopidogrel	*CYP2C19*	Adverse effects	*CPIC*[4]
Benzodiazepines	Clobazam	*CYP2C19*	Reduced / inadequate response	-
	Diazepam	*CYP2C19*	Reduced / inadequate response	-
Miscellaneous	Cyclophosphamide	*CYP2C19*	Increased therapeutic and/or adverse effects	-
	Naltrexone	*OPRM1*	Associated with reduced response to naltrexone	
	Proguanil	*CYP2C19*	Altered response	-
Opioid Analgesics	Morphine	*OPRM1*	Associated with increased therapeutic and/or adverse effects to morphine	-
Proton pump inhibitors	Dexlansoprazole	*CYP2C19*	Reduced / inadequate response	-
	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	-

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
ADHD - miscellaneous agents	Atomoxetine	*CYP2D6*	No altered effect predicted by genotype	-

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Angiotensin receptor blockers	Irbesartan	*CYP2C9*	No altered effect predicted by genotype	-
	Losartan	*CYP2C9*	No altered effect predicted by genotype	-
Antiarrhythmics	Flecainide	*CYP2D6*	No altered effect predicted by genotype	-
	Propafenone	*CYP2D6*	No altered effect predicted by genotype	-
Anticholinergics (genitourinary)	Darifenacin	*CYP2D6*	No altered effect predicted by genotype	-
	Fesoterodine	*CYP2D6*	No altered effect predicted by genotype	-
	Tolterodine	*CYP2D6*	No altered effect predicted by genotype	-
Anticholinesterases	Donepezil	*CYP2D6*	No altered effect predicted by genotype	-
	Galantamine	*CYP2D6*	No altered effect predicted by genotype	-
Anticoagulants	Acenocoumarol	*VKORC1* *CYP2C9*	Normal acenocoumarol sensitivity	
	Warfarin	*VKORC1* *CYP2C9*	Normal warfarin sensitivity	*FDA*[5]
Antidepressants - other	Mirtazapine	*CYP2D6* *CYP1A2*	No altered effect predicted by genotype	-
	Vortioxetine	*CYP2D6*	No altered effect predicted by genotype	-
Antidepressants - serotonin noradrenaline reuptake inhibitors	Duloxetine	*CYP2D6* *CYP1A2*	No altered effect predicted by genotype	-
	Venlafaxine	*CYP2D6*	No altered effect predicted by genotype	*DPWG*[6]
Antidepressants - SSRIs	Fluoxetine	*CYP2D6* *CYP2C9*	No altered effect predicted by genotype	-
	Fluvoxamine	*CYP2D6* *CYP1A2*	No altered effect predicted by genotype	*CPIC*[1]
	Paroxetine	*CYP2D6*	No altered effect predicted by genotype	*CPIC*[1]
Antidepressants - tricyclic antidepressants	Desipramine	*CYP2D6*	No altered effect predicted by genotype	*CPIC*[2]
	Nortriptyline	*CYP2D6*	No altered effect predicted by genotype	*CPIC*[2]
Antidiabetics	Glimepiride	*CYP2C9*	No altered effect predicted by genotype	-
	Glyburide	*CYP2C9*	No altered effect predicted by genotype	-
Antiemetics	Metoclopramide	*CYP2D6*	No altered effect predicted by genotype	-
	Ondansetron	*CYP2D6*	No altered effect predicted by genotype	*CPIC*[7]
Antiepileptics	Phenytoin	*CYP2C9*	No altered effect predicted by genotype	*CPIC*[8]
Antihistamines	Chlorpheniramine	*CYP2D6*	No altered effect predicted by genotype	-
	Dexchlorpheniramine	*CYP2D6*	No altered effect predicted by genotype	-

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
	Promethazine	*CYP2D6*	No altered effect predicted by genotype	-
Antipsychotics	Aripiprazole	*CYP2D6*	No altered effect predicted by genotype	-
	Brexpiprazole	*CYP2D6*	No altered effect predicted by genotype	-
	Chlorpromazine	*CYP2D6*	No altered effect predicted by genotype	-
	Clozapine	*CYP1A2*	No altered effect predicted by genotype	-
	Haloperidol	*CYP2D6*	No altered effect predicted by genotype	-
	Olanzapine	*CYP1A2*	No altered effect predicted by genotype	-
	Pimozide	*CYP2D6*	No altered effect predicted by genotype	
	Quetiapine	*CYP3A4*	No altered effect predicted by genotype	-
	Risperidone	*CYP2D6*	No altered effect predicted by genotype	-
	Zuclopenthixol	*CYP2D6*	No altered effect predicted by genotype	-
Antitussives	Dextromethorphan	*CYP2D6*	No altered effect predicted by genotype	-
Beta blockers	Carvedilol	*CYP2D6*	No altered effect predicted by genotype	-
	Metoprolol	*CYP2D6*	No altered effect predicted by genotype	-
	Nebivolol	*CYP2D6*	No altered effect predicted by genotype	-
	Propranolol	*CYP2D6* *CYP1A2*	No altered effect predicted by genotype	-
Calcineurin inhibitors	Tacrolimus	*CYP3A5*	No altered effect predicted by genotype	*CPIC*[9]
Glaucoma - ocular preparations	Timolol	*CYP2D6*	No altered effect predicted by genotype	-
Hypnotics	Melatonin	*CYP1A2*	No altered effect predicted by genotype	-
Immunomodulators and antineoplastics	Tamoxifen	*CYP2D6*	No altered effect predicted by genotype	*CPIC*[10]
Miscellaneous	Atazanavir	*CYP3A5*	No altered effect predicted by genotype	-
	Eliglustat	*CYP2D6*	No altered effect predicted by genotype	*TGA*[11]
Neurological drugs	Tetrabenazine	*CYP2D6*	No altered effect predicted by genotype	*FDA*[12]
NSAIDs	Celecoxib	*CYP2C9*	No altered effect predicted by genotype	-
	Diclofenac	*CYP2C9*	No altered effect predicted by genotype	-
	Flurbiprofen	*CYP2C9*	No altered effect predicted by genotype	-
	Ibuprofen	*CYP2C9*	No altered effect predicted by genotype	-

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
	Indomethacin	*CYP2C9*	No altered effect predicted by genotype	-
	Mefenamic Acid	*CYP2C9*	No altered effect predicted by genotype	-
	Meloxicam	*CYP2C9*	No altered effect predicted by genotype	-
	Piroxicam	*CYP2C9*	No altered effect predicted by genotype	-
Opioid Analgesics	Codeine	*CYP2D6* *OPRM1*	Associated with increased sensitivity to codeine	*CPIC*[13]
	Hydrocodone	*CYP2D6*	No altered effect predicted by genotype	
	Oxycodone	*CYP2D6*	No altered effect predicted by genotype	-
	Tramadol	*CYP2D6*	No altered effect predicted by genotype	-
Psychostimulants	Dextroamphetamine	*CYP2D6*	No altered effect predicted by genotype	-
	Lisdexamfetamine	*CYP2D6*	No altered effect predicted by genotype	-
Statins	Atorvastatin	*SLCO1B1* *CYP3A4*	No altered effect predicted by genotype	-
	Fluvastatin	*SLCO1B1* *CYP2C9*	No altered effect predicted by genotype	-
	Pravastatin	*SLCO1B1*	No altered effect predicted by genotype	-
	Rosuvastatin	*SLCO1B1*	No altered effect predicted by genotype	-
	Simvastatin	*SLCO1B1* *CYP3A4*	No altered effect predicted by genotype	*CPIC*[14]

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

PHARMACOGENOMIC INTERPRETATION

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
CYP2D6	*1/*2	*CYP2D6* - 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 CYP2D6, drug exposure and clinical effects may be expected to lie within the normal range.

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
CYP2C19	*1/*17	*CYP2C19* - Rapid metaboliser Due to the presence of one normal function allele and one increased function allele, this individual is predicted to have a rapid metaboliser phenotype. For a drug extensively metabolised by CYP2C19, drug exposure and clinical effects may either be slightly decreased (for an active drug) or slightly increased (for a prodrug). This individual is at risk of therapeutic failure (active drug) or adverse effects (prodrug).
CYP2C9	*1/*1	*CYP2C9* - 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 CYP2C9, drug exposure and clinical effects may be expected to lie within the normal range.
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	*1A/*1F	*CYP1A2* - Normal metaboliser Due to the presence of only one copy of the *1F allele, this individual is predicted to have a normal metaboliser phenotype. Normal metabolism of CYP1A2 substrate drugs is predicted. Furthermore, metabolism is not expected to be increased by exposure to inducers such as tobacco smoking and certain dietary components and drugs.
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	TT	*SLCO1B1* - Normal Transporter Function The decreased function *5 allele is not present and this individual is predicted to have normal function of the *SLCO1B1* encoded transporter. The transporter is important for the clearance of certain drugs, including simvastatin.
OPRM1	AA	*OPRM1* - Higher opioid sensitivity The AA genotype contains two normal alleles for the OPRM1 gene which encodes the mu opioid receptor. Whilst the evidence around OPRM1 genetic variation continues to develop, it appears that this result is associated with increased sensitivity to certain opioids (in particular, morphine) compared to those with the variant allele (G). These findings are supported by a number of cohort studies and at least two meta-analyses[15,16] however, this is not shown in all studies. For naltrexone in the management of alcohol use disorder, some studies have shown an association of this result with a reduced response compared to those with the variant allele. 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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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 myDNA and its affiliates 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

For all health practitioner enquiries please contact myDNA clinical support

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Appendix - VI. Genotype Frequencies – Full Table

Full table comparing the frequency of myDNA calls and TRS calls to population averages of those genotype

GENE	myDNA Genotype	TRS Genotype	Phenotype	myDNA Genotype Frequency	TRS Genotype Frequency	myDNA Genotype Frequency % N = 150	TRS Genotype Frequency %, N = 37	population level
CYP2C19	*1/*1	CYP2C19 *1/*1	Normal metabolizer	53	10	35.33	27	39.7
CYP2C19	*1/*17	CYP2C19 *1/*17	Rapid metabolizer	50	14	33.33	37.8	25.80%
CYP2C19	*1/*2	CYP2C19 *1/*2	Intermediate metabolizer	21	7	14	18.9	20.70%
CYP2C19	*17/*17	CYP2C19 *17/*17	Ultrarapid metabolizer	4	1	2.67	2.7	0
CYP2C19	*2/*17	CYP2C19 *2/*17	High intermediate metabolizer	12	3	8	8.1	6.20%
CYP2C19	*2/*2	CYP2C19 *2/*2	Poor metabolizer	10	1	6.67	2.7	2.90%
CYP2C19	NA	CYP2C19 *XX/*XX	NA	NA	1	NA	2.7	NA
CYP2C9	*1/*1	CYP2C9 *1/*1	Normal metabolizer	104	23	69.33	62.2	64.84%
CYP2C9	*1/*2	CYP2C9 *1/*2	High intermediate metabolizer	23	8	15.33	21.6	20.38%
CYP2C9	*1/*3	CYP2C9 *1/*3	Intermediate metabolizer	15	4	10	10.8	10.60%
CYP2C9	*2/*2	CYP2C9 *2/*2	Poor metabolizer	4	1	2.67	2.7	1.65%
CYP2C9	*2/*3	CYP2C9 *2/*3	Poor metabolizer	3	1	2	2.7	1.87%
CYP2C9	*3/*3	CYP2C9 *3/*3	Poor metabolizer	1	NA	0.67	NA	0.67%
CYP2D6	*1/*1	CYP2D6 *1/*1	Normal metabolizer	23	4	15.33	10.8	14.37%
CYP2D6	*1/*10	CYP2D6 *1/*10	Normal metabolizer	3	NA	2	NA	2.02%
CYP2D6	*1/*1 × 2	CYP2D6 *1/*1 × 2	Ultrarapid metabolizer	1	NA	0.67	NA	0.54%
CYP2D6	*1/*2	CYP2D6 *1/*2	Normal metabolizer	32	9	21.33	24.3	14.76%
CYP2D6	*1/*2 × 3	CYP2D6 *1/*2	Ultrarapid	1	NA	0.67	NA	0.89%

		× 3	metabolizer					
CYP2D6	*1/*3	CYP2D6 *1/*3	Low normal metabolizer	2	1	1.33	2.7	1.24%
CYP2D6	*1/*36	CYP2D6 *1/*36	Low normal metabolizer	1	NA	0.67	NA	0.04%
CYP2D6	*1/*4	CYP2D6 *1/*4	Low normal metabolizer	17	3	11.33	8.1	13.79%
CYP2D6	*1/*41	CYP2D6 *1/*41	Normal metabolizer	12	2	8	5.4	7.93%
CYP2D6	*1/*5	CYP2D6 *1/*5	Low normal metabolizer	3	1	2	2.7	2.22%
CYP2D6	*1/*6	CYP2D6 *1/*6	Low normal metabolizer	1	NA	0.67	NA	0.46%
CYP2D6	*1/*9	CYP2D6 *1/*9	Normal metabolizer	1	1	0.67	2.7	1.70%
CYP2D6	*10/*10	CYP2D6 *10/*10	Intermediate metabolizer	1	NA	0.67	NA	0.92%
CYP2D6	*2/*10	CYP2D6 *2/*10	Normal metabolizer	2	1	1.33	2.7	0.91%
CYP2D6	*2/*2	CYP2D6 *2/*2	Normal metabolizer	9	3	6	8.1	5.09%
CYP2D6	*2/*2 × 2	CYP2D6 *2/*2 × 2	Ultrarapid metabolizer	1	NA	0.67	NA	0.02%
CYP2D6	*2/*3	CYP2D6 *2/*3	Low normal metabolizer	1	NA	0.67	NA	0.67%
CYP2D6	*2/*4	CYP2D6 *2/*4	Low normal metabolizer	11	1	7.33	2.7	7.23%
CYP2D6	*2/*41	CYP2D6 *2/*41	Normal metabolizer	5	1	3.33	2.7	4.46%
CYP2D6	*2/*5	CYP2D6 *2/*5	Low normal metabolizer	4	1	2.67	2.7	1.24%
CYP2D6	*2/*6	CYP2D6 *2/*6	Low normal metabolizer	1	1	0.67	2.7	0.41%
CYP2D6	*3/*3	CYP2D6 *3/*3	Poor metabolizer	1	NA	0.67	NA	0.02%
CYP2D6	*3/*41	CYP2D6 *3/*41	Intermediate metabolizer	1	NA	0.67	NA	0.33%
CYP2D6	NA	CYP2D6 *35/*5	NA	NA	1	NA	2.7	NA
CYP2D6	*4/*10	CYP2D6 *4/*10	Intermediate metabolizer	2	NA	1.33	NA	0.70%
CYP2D6	NA	CYP2D6 *4/*35A	NA	NA	1	NA	2.7	NA
CYP2D6	*4/*4	CYP2D6 *4/*4	Poor metabolizer	4	3	2.67	8.1	3.42%

CYP2D6	*4/*41	CYP2D6 *4/*41	Intermediate metabolizer	5	2	3.33	5.4	3.59%
CYP2D6	*4/*6	CYP2D6 *4/*6	Poor metabolizer	1	NA	0.67	NA	0.28%
CYP2D6	*4/*9	CYP2D6 *4/*9	Intermediate metabolizer	1	NA	0.67	NA	0.76%
CYP2D6	*5/*41	CYP2D6 *5/*41	Intermediate metabolizer	1	NA	0.67	NA	0.48%
CYP2D6	*9/*41	CYP2D6 *9/*41	Intermediate metabolizer	2	1	1.33	2.7	0.50%
CYP3A4	*1/*1	CYP3A4 *1/*1	Normal metabolizer	141	33	94	89.2	93.70%
CYP3A4	*1/*22	CYP3A4 *1/*22	Normal metabolizer	8	3	5.33	8.1	6.20%
CYP3A4	NA	CYP3A4 *1/*8	NA	NA	1	NA	2.7	0
CYP3A5	*1/*3	CYP3A5 *1/*3	Low normal metabolizer	14	1	9.33	2.7	38.80%
CYP3A5	*3/*3	CYP3A5 *3/*3	Poor metabolizer	136	36	90.67	97.3	54.30%
OPRM1	AA	NA	Normal metabolizer	107	NA	71.33	NA	77.10%
OPRM1	AG	NA	Low normal metabolizer	35	NA	23.33	NA	21.40%
OPRM1	GG	NA	Reduced metabolizer	8	NA	5.33	NA	1.50%
SLCO1B1	CC	rs4149056:C/C Hom	Reduced metabolizer	3	NA	2	NA	1.80%
SLCO1B1	TC	rs4149056:T/C Het	Low normal metabolizer	37	10	24.67	27	23.10%
SLCO1B1	TT	rs4149056:T/T Wild	Normal metabolizer	110	27	73.33	73	75.20%
CYP1A2	*1F/*1F	rs762551:A/A Hom	Rapid metabolizer	69	12	46	32.4	45%
CYP1A2	*1A/*1F	rs762551:C/A Het	Normal metabolizer	69	23	46	62.2	44.20%
CYP1A2	*1A/*1A	rs762551:C/C Wild	Normal metabolizer	12	2	8	5.4	10.80%
VKORC1	GG	rs9923231:C/C Wild	Normal warfarin sensitivity	57	15	38	40.5	35.80%
VKORC1	AG	rs9923231:C/T Het	Increased warfarin sensitivity	59	13	39.33	35.1	47.90%
VKORC1	AA	rs9923231:T/T Hom	High warfarin sensitivity	34	9	22.67	24.3	16.30%

Appendix - VII. Interaction Frequency

Frequency of each interaction type per medication. Ethinyloestradiol is broken into its different prescriptions however, it totals 6 interactions.

Drug	Type of Interaction	Gene	Freq
Montelukast	INDUCER	CY1A2	1
Mometasone	INDUCER	CYP1A2	1
Montelukast	INDUCER	CYP1A2	2
Omeprazole	INDUCER	CYP1A2	1
Desogestrel / ethinyloestradiol	INHIBITOR MODERATE	CYP1A2	2
Drospirenone / ethinyloestradiol	INHIBITOR MODERATE	CYP1A2	2
Ethinylestradiol / levonorgestrel	INHIBITOR MODERATE	CYP1A2	5
Ethinyloestradiol / norethisterone	INHIBITOR MODERATE	CYP1A2	1
Ciprofloxacin	INHIBITOR STRONG	CYP1A2	1
Carbamazepine	INDUCER	CYP2C19	2
Esomeprazole	INHIBITOR MODERATE	CYP2C19	4
Fluoxetine	INHIBITOR MODERATE	CYP2C19	12
Moclobemide	INHIBITOR MODERATE	CYP2C19	2
Omeprazole	INHIBITOR MODERATE	CYP2C19	1
Carbamazepine	INDUCER	CYP2C9	2
Doxepin	INHIBITOR MODERATE	CYP2D6	1
Duloxetine	INHIBITOR MODERATE	CYP2D6	9
Eletriptan	INHIBITOR MODERATE	CYP2D6	1
Flecainide	INHIBITOR MODERATE	CYP2D6	1
Moclobemide	INHIBITOR MODERATE	CYP2D6	2

Drug	Type of Interaction	Gene	Freq
Fluoxetine	INHIBITOR STRONG	CYP2D6	12
Paroxetine	INHIBITOR STRONG	CYP2D6	2
Carbamazepine	INDUCER	CYP3A	2
Modafinil	INDUCER	CYP3A	1
Ciprofloxacin	INHIBITOR MODERATE	CYP3A	1
Cyclosporin	INHIBITOR MODERATE	CYP3A	1
Diltiazem	INHIBITOR MODERATE	CYP3A	1

Appendix - VIII. Indications of Possible Medications – Full Table

Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150
major	Atazanavir	0	0.00	minor	Tramadol	0	0.00	usual	Dexlansoprazole	0	0.00
major	Atorvastatin	0	0.00	minor	Pravastatin	1	0.67	usual	Esomeprazole	0	0.00
major	Carvedilol	0	0.00	minor	Rosuvastatin	1	0.67	usual	Lansoprazole	0	0.00
major	Chlorpheniramine	0	0.00	minor	Tacrolimus	1	0.67	usual	Morphine	0	0.00
major	Chlorpromazine	0	0.00	minor	Phenytoin	2	1.33	usual	Omeprazole	0	0.00
major	Clozapine	0	0.00	minor	Codeine	3	2.00	usual	Pantoprazole	0	0.00
major	Cyclophosphamide	0	0.00	minor	Simvastatin	6	4.00	usual	Rabeprazole	11	7.33
major	Darifenacin	0	0.00	minor	Quetiapine	9	6.00	usual	Acenocoumarol	39	26.00
major	Dexchlorpheniramine	0	0.00	minor	Hydrocodone	10	6.67	usual	Warfarin	39	26.00
major	Dextroamphetamine	0	0.00	minor	Timolol	13	8.67	usual	Gliclazide	40	26.67
major	Diclofenac	0	0.00	minor	Fluvoxamine	14	9.33	usual	Naltrexone	42	28.00
major	Donepezil	0	0.00	minor	Atazanavir	15	10.00	usual	Amitriptyline	45	30.00
major	Fesoterodine	0	0.00	minor	Fluvastatin	16	10.67	usual	Clomipramine	45	30.00
major	Galantamine	0	0.00	minor	Losartan	17	11.33	usual	Doxepin	45	30.00
major	Indomethacin	0	0.00	minor	Tolterodine	17	11.33	usual	Imipramine	45	30.00
major	Irbesartan	0	0.00	minor	Vortioxetine	17	11.33	usual	Citalopram	53	35.33
major	Lisdexamfetamine	0	0.00	minor	Oxycodone	19	12.67	usual	Clobazam	53	35.33
major	Mefenamic Acid	0	0.00	minor	Carvedilol	22	14.67	usual	Clopidogrel	53	35.33
major	Melatonin	0	0.00	minor	Dextroamphetamine	22	14.67	usual	Cyclophosphamide	53	35.33
major	Metoclopramide	0	0.00	minor	Lisdexamfetamine	22	14.67	usual	Diazepam	53	35.33
major	Morphine	0	0.00	minor	Nebivolol	22	14.67	usual	Escitalopram	53	35.33
major	Naltrexone	0	0.00	minor	Chlorpromazine	23	15.33	usual	Moclobemide	53	35.33
major	Nebivolol	0	0.00	minor	Darifenacin	23	15.33	usual	Proguanil	53	35.33
major	Olanzapine	0	0.00	minor	Donepezil	23	15.33	usual	Sertraline	53	35.33
major	Pravastatin	0	0.00	minor	Fesoterodine	23	15.33	usual	Voriconazole	53	35.33
major	Proguanil	0	0.00	minor	Galantamine	23	15.33	usual	Duloxetine	66	44.00
major	Promethazine	0	0.00	minor	Metoclopramide	23	15.33	usual	Mirtazapine	66	44.00
major	Propranolol	0	0.00	minor	Promethazine	23	15.33	usual	Propranolol	69	46.00
major	Quetiapine	0	0.00	minor	Diclofenac	24	16.00	usual	Clozapine	80	53.33

Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150
major	Rabeprazole	0	0.00	minor	Indomethacin	24	16.00	usual	Melatonin	80	53.33
major	Rosuvastatin	0	0.00	minor	Mefenamic Acid	24	16.00	usual	Olanzapine	80	53.33
major	Gliclazide	1	0.67	minor	Amitriptyline	30	20.00	usual	Aripiprazole	87	58.00
major	Duloxetine	2	1.33	minor	Clomipramine	30	20.00	usual	Atomoxetine	87	58.00
major	Mirtazapine	2	1.33	minor	Doxepin	30	20.00	usual	Brexpiprazole	87	58.00
major	Moclobemide	2	1.33	minor	Imipramine	30	20.00	usual	Chlorpheniramine	87	58.00
major	Oxycodone	3	2.00	minor	Citalopram	32	21.33	usual	Desipramine	87	58.00
major	Dexlansoprazole	4	2.67	minor	Escitalopram	32	21.33	usual	Dexchlorpheniramine	87	58.00
major	Esomeprazole	4	2.67	minor	Voriconazole	33	22.00	usual	Dextromethorphan	87	58.00
major	Lansoprazole	4	2.67	minor	Celecoxib	39	26.00	usual	Eliglustat	87	58.00
major	Omeprazole	4	2.67	minor	Fluoxetine	39	26.00	usual	Flecainide	87	58.00
major	Pantoprazole	4	2.67	minor	Flurbiprofen	39	26.00	usual	Haloperidol	87	58.00
major	Aripiprazole	6	4.00	minor	Ibuprofen	39	26.00	usual	Metoprolol	87	58.00
major	Atomoxetine	6	4.00	minor	Meloxicam	39	26.00	usual	Nortriptyline	87	58.00
major	Brexpiprazole	6	4.00	minor	Piroxicam	39	26.00	usual	Ondansetron	87	58.00
major	Dextromethorphan	6	4.00	minor	Glimepiride	40	26.67	usual	Paroxetine	87	58.00
major	Fluoxetine	6	4.00	minor	Glyburide	40	26.67	usual	Pimozide	87	58.00
major	Haloperidol	6	4.00	minor	Metoprolol	41	27.33	usual	Propafenone	87	58.00
major	Pimozide	6	4.00	minor	Desipramine	44	29.33	usual	Risperidone	87	58.00
major	Risperidone	6	4.00	minor	Flecainide	44	29.33	usual	Tamoxifen	87	58.00
major	Tetrabenazine	6	4.00	minor	Nortriptyline	44	29.33	usual	Tetrabenazine	87	58.00
major	Timolol	6	4.00	minor	Propafenone	44	29.33	usual	Venlafaxine	87	58.00
major	Tolterodine	6	4.00	minor	Tamoxifen	44	29.33	usual	Zuclopenthixol	87	58.00
major	Vortioxetine	6	4.00	minor	Atorvastatin	46	30.67	usual	Glimepiride	102	68.00
major	Zuclopenthixol	6	4.00	minor	Irbesartan	48	32.00	usual	Glyburide	102	68.00
major	Celecoxib	8	5.33	minor	Acenocoumarol	52	34.67	usual	Irbesartan	102	68.00
major	Flurbiprofen	8	5.33	minor	Warfarin	52	34.67	usual	Phenytoin	102	68.00
major	Fluvastatin	8	5.33	minor	Clopidogrel	54	36.00	usual	Celecoxib	103	68.67
major	Glimepiride	8	5.33	minor	Eliglustat	54	36.00	usual	Flurbiprofen	103	68.67
major	Glyburide	8	5.33	minor	Ondansetron	54	36.00	usual	Ibuprofen	103	68.67
major	Ibuprofen	8	5.33	minor	Paroxetine	54	36.00	usual	Meloxicam	103	68.67

Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150
major	Losartan	8	5.33	minor	Venlafaxine	54	36.00	usual	Piroxicam	103	68.67
major	Meloxicam	8	5.33	minor	Aripiprazole	57	38.00	usual	Atorvastatin	104	69.33
major	Piroxicam	8	5.33	minor	Atomoxetine	57	38.00	usual	Simvastatin	104	69.33
major	Eliglustat	9	6.00	minor	Brexpiprazole	57	38.00	usual	Fluoxetine	105	70.00
major	Fluvoxamine	9	6.00	minor	Dextromethorphan	57	38.00	usual	Losartan	125	83.33
major	Hydrocodone	9	6.00	minor	Haloperidol	57	38.00	usual	Diclofenac	126	84.00
major	Ondansetron	9	6.00	minor	Pimozide	57	38.00	usual	Fluvastatin	126	84.00
major	Paroxetine	9	6.00	minor	Risperidone	57	38.00	usual	Indomethacin	126	84.00
major	Venlafaxine	9	6.00	minor	Tetrabenazine	57	38.00	usual	Mefenamic Acid	126	84.00
major	Clobazam	10	6.67	minor	Zuclopenthixol	57	38.00	usual	Chlorpromazine	127	84.67
major	Diazepam	10	6.67	minor	Chlorpheniramine	63	42.00	usual	Darifenacin	127	84.67
major	Sertraline	11	7.33	minor	Dexchlorpheniramine	63	42.00	usual	Donepezil	127	84.67
major	Tacrolimus	14	9.33	minor	Clozapine	70	46.67	usual	Fesoterodine	127	84.67
major	Codeine	19	12.67	minor	Melatonin	70	46.67	usual	Fluvoxamine	127	84.67
major	Desipramine	19	12.67	minor	Olanzapine	70	46.67	usual	Galantamine	127	84.67
major	Flecainide	19	12.67	minor	Propranolol	81	54.00	usual	Metoclopramide	127	84.67
major	Nortriptyline	19	12.67	minor	Duloxetine	82	54.67	usual	Promethazine	127	84.67
major	Propafenone	19	12.67	minor	Mirtazapine	82	54.67	usual	Tolterodine	127	84.67
major	Tamoxifen	19	12.67	minor	Sertraline	86	57.33	usual	Vortioxetine	127	84.67
major	Metoprolol	22	14.67	minor	Clobazam	87	58.00	usual	Carvedilol	128	85.33
major	Tramadol	22	14.67	minor	Diazepam	87	58.00	usual	Codeine	128	85.33
major	Simvastatin	40	26.67	minor	Moclobemide	95	63.33	usual	Dextroamphetamine	128	85.33
major	Clopidogrel	43	28.67	minor	Cyclophosphamide	97	64.67	usual	Lisdexamfetamine	128	85.33
major	Phenytoin	46	30.67	minor	Proguanil	97	64.67	usual	Nebivolol	128	85.33
major	Acenocoumarol	56	37.33	minor	Naltrexone	108	72.00	usual	Oxycodone	128	85.33
major	Warfarin	59	39.33	minor	Gliclazide	109	72.67	usual	Tramadol	128	85.33
major	Voriconazole	64	42.67	minor	Rabeprazole	139	92.67	usual	Hydrocodone	131	87.33
major	Citalopram	65	43.33	minor	Dexlansoprazole	146	97.33	usual	Timolol	131	87.33
major	Escitalopram	65	43.33	minor	Esomeprazole	146	97.33	usual	Atazanavir	135	90.00
major	Amitriptyline	75	50.00	minor	Lansoprazole	146	97.33	usual	Tacrolimus	135	90.00
major	Clomipramine	75	50.00	minor	Omeprazole	146	97.33	usual	Quetiapine	141	94.00

Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150	Cons	Drug	Freq	% n=150
major	Doxepin	75	50.00	minor	Pantoprazole	146	97.33	usual	Pravastatin	149	99.33
major	Imipramine	75	50.00	minor	Morphine	150	100.0 0	usual	Rosuvastatin	149	99.3 3

Appendix - IX. Possible Drug Considerations Per Site – Full Table

Consideration per site of 93 drugs with dosing guidelines. 3 letters = site code and N = number of participants at the site. Total = total number of considerations per site. Cons = dosing consideration/indication.

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Gliclazide	major	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Duloxetine	major	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Mirtazapine	major	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Moclobemide	major	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Oxycodone	major	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0
Dexlansoprazole	major	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	1	0
Esomeprazole	major	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	1	0
Lansoprazole	major	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	1	0
Omeprazole	major	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	1	0
Pantoprazole	major	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	1	0
Aripiprazole	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Atomoxetine	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Brexpiprazole	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Dextromethorphan	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Fluoxetine	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Haloperidol	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Pimozide	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Risperidone	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Tetrabenazine	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Timolol	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Tolterodine	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Vortioxetine	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Zuclopenthixol	major	0	0	0	0	0	1	2	1	1	0	0	0	0	1	0	0	0
Celecoxib	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Flurbiprofen	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Fluvastatin	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Glimepiride	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Glyburide	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Ibuprofen	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Losartan	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Meloxicam	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Piroxicam	major	2	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	1
Eliglustat	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Fluvoxamine	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Hydrocodone	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Ondansetron	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Paroxetine	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Venlafaxine	major	0	0	0	1	0	2	2	1	1	0	0	0	0	2	0	0	0
Clobazam	major	1	0	1	0	0	0	1	1	1	0	0	0	1	0	1	3	0
Diazepam	major	1	0	1	0	0	0	1	1	1	0	0	0	1	0	1	3	0
Sertraline	major	2	0	1	0	0	0	1	1	1	0	0	0	1	0	1	3	0
Tacrolimus	major	1	0	0	0	1	0	1	2	1	3	0	1	0	1	0	2	1
Codeine	major	0	0	0	1	2	2	5	3	1	1	0	0	0	3	0	1	0
Desipramine	major	0	0	0	1	2	2	5	3	1	1	0	0	0	3	0	1	0
Flecainide	major	1	0	0	0	2	1	5	3	1	1	0	0	0	2	0	2	1
Nortriptyline	major	0	0	0	1	2	2	5	3	1	1	0	0	0	3	0	1	0
Propafenone	major	1	0	0	0	2	1	5	3	1	1	0	0	0	2	0	2	1
Tamoxifen	major	1	0	0	0	2	1	5	3	1	1	0	0	0	2	0	2	1
Metoprolol	major	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Tramadol	major	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Simvastatin	major	1	1	1	4	3	1	7	4	2	5	1	0	1	2	1	5	1
Clopidogrel	major	2	0	2	1	1	2	4	5	7	2	1	1	2	1	2	5	5
Phenytoin	major	3	1	0	4	2	2	7	6	1	3	2	2	1	2	4	3	3
Acenocoumarol	major	4	0	0	2	2	4	11	8	4	5	2	1	1	1	4	5	2
Warfarin	major	4	0	0	3	2	4	12	9	4	5	2	1	1	1	4	5	2
Voriconazole	major	3	1	1	4	1	4	7	10	3	7	3	1	1	4	6	5	3
Citalopram	major	4	1	1	4	1	4	7	10	3	7	3	1	1	4	6	5	3
Escitalopram	major	4	1	1	4	1	4	7	10	3	7	3	1	1	4	6	5	3
Amitriptyline	major	4	1	1	4	3	5	11	10	3	7	3	1	1	6	6	6	3

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Clomipramine	major	4	1	1	4	3	5	11	10	3	7	3	1	1	6	6	6	3
Doxepin	major	4	1	1	4	3	5	11	10	3	7	3	1	1	6	6	6	3
Imipramine	major	4	1	1	4	3	5	11	10	3	7	3	1	1	6	6	6	3
Pravastatin	minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Rosuvastatin	minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Tacrolimus	minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Phenytoin	minor	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Codeine	minor	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Simvastatin	minor	0	0	0	1	0	0	0	0	1	0	0	1	0	2	0	0	1
Quetiapine	minor	0	0	0	1	1	0	0	0	1	1	0	1	0	3	0	0	1
Hydrocodone	minor	0	0	0	0	2	0	3	2	0	1	0	0	0	1	0	1	0
Timolol	minor	1	0	0	0	2	0	3	2	0	1	0	0	0	1	0	2	1
Fluvoxamine	minor	1	0	0	0	2	0	3	2	1	1	0	0	0	1	0	2	1
Atazanavir	minor	1	0	0	0	1	0	1	2	1	4	0	1	0	1	0	2	1
Fluvastatin	minor	0	0	0	2	1	1	3	2	0	3	1	1	0	0	1	1	0
Losartan	minor	0	0	0	2	1	1	3	2	1	3	1	1	0	0	1	1	0
Tolterodine	minor	1	0	0	1	2	1	3	2	1	1	0	0	0	2	0	2	1
Vortioxetine	minor	1	0	0	1	2	1	3	2	1	1	0	0	0	2	0	2	1
Oxycodone	minor	1	0	0	0	2	1	5	3	1	1	0	0	0	2	0	2	1
Carvedilol	minor	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Dextroamphetamine	minor	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Lisdexamfetamine	minor	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Nebivolol	minor	1	0	0	1	2	2	5	3	1	1	0	0	0	3	0	2	1
Chlorpromazine	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Darifenacin	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Donepezil	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Fesoterodine	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Galantamine	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Metoclopramide	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Promethazine	minor	1	0	0	1	2	2	5	3	2	1	0	0	0	3	0	2	1
Diclofenac	minor	2	0	0	2	1	2	3	3	0	4	1	1	0	1	1	2	1
Indomethacin	minor	2	0	0	2	1	2	3	3	0	4	1	1	0	1	1	2	1

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Mefenamic Acid	minor	2	0	0	2	1	2	3	3	0	4	1	1	0	1	1	2	1
Amitriptyline	minor	0	0	1	1	1	2	1	4	6	2	1	1	1	1	1	2	5
Clomipramine	minor	0	0	1	1	1	2	1	4	6	2	1	1	1	1	1	2	5
Doxepin	minor	0	0	1	1	1	2	1	4	6	2	1	1	1	1	1	2	5
Imipramine	minor	0	0	1	1	1	2	1	4	6	2	1	1	1	1	1	2	5
Citalopram	minor	0	0	1	1	1	2	3	4	6	2	1	1	1	1	1	2	5
Escitalopram	minor	0	0	1	1	1	2	3	4	6	2	1	1	1	1	1	2	5
Voriconazole	minor	1	0	1	1	1	2	3	4	6	2	1	1	1	1	1	2	5
Celecoxib	minor	1	1	0	4	2	1	7	5	1	3	2	2	1	1	4	2	2
Fluoxetine	minor	3	0	0	3	3	3	5	5	1	4	1	1	0	3	1	4	2
Flurbiprofen	minor	1	1	0	4	2	1	7	5	1	3	2	2	1	1	4	2	2
Ibuprofen	minor	1	1	0	4	2	1	7	5	1	3	2	2	1	1	4	2	2
Meloxicam	minor	1	1	0	4	2	1	7	5	1	3	2	2	1	1	4	2	2
Piroxicam	minor	1	1	0	4	2	1	7	5	1	3	2	2	1	1	4	2	2
Glimepiride	minor	1	1	0	4	2	1	7	5	2	3	2	2	1	1	4	2	2
Glyburide	minor	1	1	0	4	2	1	7	5	2	3	2	2	1	1	4	2	2
Metoprolol	minor	1	1	0	2	1	3	4	7	4	8	1	1	1	2	2	2	1
Desipramine	minor	2	1	0	2	1	3	4	7	4	8	1	1	1	2	2	3	2
Flecainide	minor	1	1	0	3	1	4	4	7	4	8	1	1	1	3	2	2	1
Nortriptyline	minor	2	1	0	2	1	3	4	7	4	8	1	1	1	2	2	3	2
Propafenone	minor	1	1	0	3	1	4	4	7	4	8	1	1	1	3	2	2	1
Tamoxifen	minor	1	1	0	3	1	4	4	7	4	8	1	1	1	3	2	2	1
Atorvastatin	minor	1	1	1	5	3	1	7	4	3	5	1	1	1	4	1	5	2
Irbesartan	minor	3	1	0	4	2	2	7	6	2	4	2	2	1	2	4	3	3
Acenocoumarol	minor	2	1	0	2	3	4	5	5	4	6	2	2	1	6	4	1	4
Warfarin	minor	2	1	0	2	3	4	5	5	4	6	2	2	1	6	4	1	4
Clopidogrel	minor	2	1	0	4	1	4	6	9	2	7	3	1	0	4	5	2	3
Eliglustat	minor	2	1	0	2	3	3	7	9	4	9	1	1	1	3	2	4	2
Ondansetron	minor	2	1	0	2	3	3	7	9	4	9	1	1	1	3	2	4	2
Paroxetine	minor	2	1	0	2	3	3	7	9	4	9	1	1	1	3	2	4	2
Venlafaxine	minor	2	1	0	2	3	3	7	9	4	9	1	1	1	3	2	4	2
Aripiprazole	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Atomoxetine	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Brexpiprazole	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Dextromethorphan	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Haloperidol	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Pimozide	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Risperidone	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Tetrabenazine	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Zuclopenthixol	minor	2	1	0	3	3	4	7	9	4	9	1	1	1	4	2	4	2
Chlorpheniramine	minor	2	1	0	3	3	5	9	10	5	9	1	1	1	5	2	4	2
Dexchlorpheniramine	minor	2	1	0	3	3	5	9	10	5	9	1	1	1	5	2	4	2
Clozapine	minor	5	1	1	3	3	6	7	8	4	9	2	2	3	4	4	4	4
Melatonin	minor	5	1	1	3	3	6	7	8	4	9	2	2	3	4	4	4	4
Olanzapine	minor	5	1	1	3	3	6	7	8	4	9	2	2	3	4	4	4	4
Propranolol	minor	6	1	1	3	3	7	9	10	5	9	2	2	3	6	4	5	5
Duloxetine	minor	5	1	1	4	3	8	9	10	6	9	2	2	3	5	4	5	5
Mirtazapine	minor	5	1	1	4	3	8	9	10	6	9	2	2	3	5	4	5	5
Sertraline	minor	2	1	1	5	2	6	9	13	8	9	4	2	1	5	6	4	8
Clobazam	minor	3	1	1	5	2	6	9	13	8	9	4	2	1	5	6	4	8
Diazepam	minor	3	1	1	5	2	6	9	13	8	9	4	2	1	5	6	4	8
Moclobemide	minor	3	1	2	5	2	6	10	13	9	9	4	2	2	5	7	7	8
Cyclophosphamide	minor	4	1	2	5	2	6	10	14	9	9	4	2	2	5	7	7	8
Proguanil	minor	4	1	2	5	2	6	10	14	9	9	4	2	2	5	7	7	8
Naltrexone	minor	7	1	1	6	5	8	14	18	3	9	1	3	1	7	8	9	7
Gliclazide	minor	6	1	1	7	3	7	14	16	6	10	4	3	3	7	7	7	7
Rabeprazole	minor	8	1	2	8	5	10	20	19	6	16	4	3	3	9	8	9	8
Dexlansoprazole	minor	8	1	2	8	6	10	20	18	9	15	5	4	3	9	9	9	10
Esomeprazole	minor	8	1	2	8	6	10	20	18	9	15	5	4	3	9	9	9	10
Lansoprazole	minor	8	1	2	8	6	10	20	18	9	15	5	4	3	9	9	9	10
Omeprazole	minor	8	1	2	8	6	10	20	18	9	15	5	4	3	9	9	9	10
Pantoprazole	minor	8	1	2	8	6	10	20	18	9	15	5	4	3	9	9	9	10
Morphine	minor	8	1	2	8	6	10	20	20	9	16	5	4	3	9	9	10	10
Rabeprazole	usual	0	0	0	0	1	0	0	1	3	0	1	1	0	0	1	1	2

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Acenocoumarol	usual	2	0	2	3	1	2	3	6	1	5	1	1	1	2	1	4	4
Warfarin	usual	2	0	2	3	1	2	3	6	1	5	1	1	1	2	1	4	4
Gliclazide	usual	1	0	1	1	3	3	6	4	3	6	1	1	0	2	2	3	3
Naltrexone	usual	1	0	1	2	1	2	6	2	6	7	4	1	2	2	1	1	3
Amitriptyline	usual	4	0	0	3	2	3	8	6	0	7	1	2	1	2	2	2	2
Clomipramine	usual	4	0	0	3	2	3	8	6	0	7	1	2	1	2	2	2	2
Doxepin	usual	4	0	0	3	2	3	8	6	0	7	1	2	1	2	2	2	2
Imipramine	usual	4	0	0	3	2	3	8	6	0	7	1	2	1	2	2	2	2
Citalopram	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Clobazam	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Clopidogrel	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Cyclophosphamide	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Diazepam	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Escitalopram	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Moclobemide	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Proguanil	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Sertraline	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Voriconazole	usual	4	0	0	3	4	4	10	6	0	7	1	2	1	4	2	3	2
Duloxetine	usual	2	0	1	4	3	2	11	10	3	7	3	2	0	3	5	5	5
Mirtazapine	usual	2	0	1	4	3	2	11	10	3	7	3	2	0	3	5	5	5
Propranolol	usual	2	0	1	5	3	3	11	10	4	7	3	2	0	3	5	5	5
Clozapine	usual	3	0	1	5	3	4	13	12	5	7	3	2	0	5	5	6	6
Melatonin	usual	3	0	1	5	3	4	13	12	5	7	3	2	0	5	5	6	6
Olanzapine	usual	3	0	1	5	3	4	13	12	5	7	3	2	0	5	5	6	6
Aripiprazole	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Atomoxetine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Brexpiprazole	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Chlorpheniramine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Desipramine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Dexchlorpheniramine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Dextromethorphan	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Eliglustat	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Flecainide	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Haloperidol	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Metoprolol	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Nortriptyline	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Ondansetron	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Paroxetine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Pimozide	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Propafenone	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Risperidone	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Tamoxifen	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Tetrabenazine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Venlafaxine	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Zuclopenthixol	usual	6	0	2	5	3	5	11	10	4	7	4	3	2	4	7	6	8
Glimepiride	usual	5	0	2	4	4	8	13	14	7	12	3	2	2	7	5	7	7
Glyburide	usual	5	0	2	4	4	8	13	14	7	12	3	2	2	7	5	7	7
Irbesartan	usual	5	0	2	4	4	8	13	14	7	12	3	2	2	7	5	7	7
Phenytoin	usual	5	0	2	4	4	8	13	14	7	12	3	2	2	7	5	7	7
Celecoxib	usual	5	0	2	4	4	8	13	14	8	12	3	2	2	7	5	7	7
Flurbiprofen	usual	5	0	2	4	4	8	13	14	8	12	3	2	2	7	5	7	7
Ibuprofen	usual	5	0	2	4	4	8	13	14	8	12	3	2	2	7	5	7	7
Meloxicam	usual	5	0	2	4	4	8	13	14	8	12	3	2	2	7	5	7	7
Piroxicam	usual	5	0	2	4	4	8	13	14	8	12	3	2	2	7	5	7	7
Atorvastatin	usual	7	0	1	3	3	9	13	16	6	11	4	3	2	5	8	5	8
Simvastatin	usual	7	0	1	3	3	9	13	16	6	11	4	3	2	5	8	5	8
Fluoxetine	usual	5	1	2	5	3	6	13	14	7	12	4	3	3	5	8	6	8
Losartan	usual	6	1	2	6	5	8	17	17	8	12	4	3	3	8	8	8	9
Diclofenac	usual	6	1	2	6	5	8	17	17	9	12	4	3	3	8	8	8	9
Fluvastatin	usual	6	1	2	6	5	8	17	17	9	12	4	3	3	8	8	8	9
Indomethacin	usual	6	1	2	6	5	8	17	17	9	12	4	3	3	8	8	8	9
Mefenamic Acid	usual	6	1	2	6	5	8	17	17	9	12	4	3	3	8	8	8	9
Chlorpromazine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Darifenacin	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Donepezil	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Fesoterodine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Fluvoxamine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Galantamine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Metoclopramide	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Promethazine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Tolterodine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Vortioxetine	usual	7	1	2	7	4	8	15	17	7	15	5	4	3	6	9	8	9
Carvedilol	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Codeine	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Dextroamphetamine	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Lisdexamfetamine	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Nebivolol	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Oxycodone	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Tramadol	usual	7	1	2	7	4	8	15	17	8	15	5	4	3	6	9	8	9
Hydrocodone	usual	8	1	2	7	4	8	15	17	8	15	5	4	3	6	9	9	10
Timolol	usual	7	1	2	8	4	9	15	17	8	15	5	4	3	7	9	8	9
Atazanavir	usual	7	1	2	8	5	10	19	18	8	12	5	3	3	8	9	8	9
Tacrolimus	usual	7	1	2	8	5	10	19	18	8	12	5	3	3	8	9	8	9
Quetiapine	usual	8	1	2	7	5	10	20	20	8	15	5	3	3	6	9	10	9
Pravastatin	usual	8	1	2	8	6	10	20	20	9	15	5	4	3	9	9	10	10
Rosuvastatin	usual	8	1	2	8	6	10	20	20	9	15	5	4	3	9	9	10	10
	Totals	744	93	186	743	558	930	1859	1859	837	1488	465	372	279	837	837	930	930

Appendix - X. Gene – Phenotype Frequency – Full Table

Indications for Warfarin sensitivity, normal warfarin sensitivity, high warfarin sensitivity, and increased warfarin sensitivity were replaced with, normal metabolizer, poor metabolizer, and reduced metabolizer respectively. Additionally, not all genes were recorded with noting all metabolizer states.

Phenotype	Gene	Freq	% Freq N =150	Phenotype	Gene	Freq	% Freq, N =150
High intermediate metaboliser	CYP1A2	0	0.00	Poor metaboliser	CYP3A4	0	0.00
Intermediate metaboliser	CYP1A2	0	0.00	Rapid metaboliser	CYP3A4	0	0.00
Low normal metaboliser	CYP1A2	0	0.00	Reduced metaboliser	CYP3A4	0	0.00
Normal metaboliser	CYP1A2	81	54.00	Ultrarapid metaboliser	CYP3A4	0	0.00
Poor metaboliser	CYP1A2	0	0.00	High intermediate metaboliser	CYP3A5	0	0.00
Rapid metaboliser	CYP1A2	69	46.00	Intermediate metaboliser	CYP3A5	0	0.00
Reduced metaboliser	CYP1A2	0	0.00	Low normal metaboliser	CYP3A5	14	9.33
Ultrarapid metaboliser	CYP1A2	0	0.00	Normal metaboliser	CYP3A5	0	0.00
High intermediate metaboliser	CYP2C19	12	8.00	Poor metaboliser	CYP3A5	136	90.67
Intermediate metaboliser	CYP2C19	21	14.00	Rapid metaboliser	CYP3A5	0	0.00
Low normal metaboliser	CYP2C19	0	0.00	Reduced metaboliser	CYP3A5	0	0.00
Normal metaboliser	CYP2C19	53	35.33	Ultrarapid metaboliser	CYP3A5	0	0.00
Poor metaboliser	CYP2C19	10	6.67	High intermediate metaboliser	OPRM1	0	0.00
Rapid metaboliser	CYP2C19	50	33.33	Intermediate metaboliser	OPRM1	0	0.00
Reduced metaboliser	CYP2C19	0	0.00	Low normal metaboliser	OPRM1	35	23.33
Ultrarapid metaboliser	CYP2C19	4	2.67	Normal metaboliser	OPRM1	107	71.33
High intermediate metaboliser	CYP2C9	23	15.33	Poor metaboliser	OPRM1	0	0.00
Intermediate metaboliser	CYP2C9	15	10.00	Rapid metaboliser	OPRM1	0	0.00
Low normal metaboliser	CYP2C9	0	0.00	Reduced metaboliser	OPRM1	8	5.33
Normal metaboliser	CYP2C9	104	69.33	Ultrarapid metaboliser	OPRM1	0	0.00
Poor metaboliser	CYP2C9	8	5.33	High intermediate metaboliser	SLCO1B1	0	0.00
Rapid metaboliser	CYP2C9	0	0.00	Intermediate metaboliser	SLCO1B1	0	0.00
Reduced metaboliser	CYP2C9	0	0.00	Low normal metaboliser	SLCO1B1	37	24.67
Ultrarapid metaboliser	CYP2C9	0	0.00	Normal metaboliser	SLCO1B1	110	73.33
High intermediate metaboliser	CYP2D6	0	0.00	Poor metaboliser	SLCO1B1	0	0.00
Intermediate metaboliser	CYP2D6	13	8.67	Rapid metaboliser	SLCO1B1	0	0.00
Low normal metaboliser	CYP2D6	41	27.33	Reduced metaboliser	SLCO1B1	3	2.00

Phenotype	Gene	Freq	% Freq N =150	Phenotype	Gene	Freq	% Freq, N =150
Normal metaboliser	CYP2D6	87	58.00	Ultrarapid metaboliser	SLCO1B1	0	0.00
Poor metaboliser	CYP2D6	6	4.00	High intermediate metaboliser	VKORC1	0	0.00
Rapid metaboliser	CYP2D6	0	0.00	Intermediate metaboliser	VKORC1	0	0.00
Reduced metaboliser	CYP2D6	0	0.00	Low normal metaboliser	VKORC1	0	0.00
Ultrarapid metaboliser	CYP2D6	3	2.00	Normal metaboliser	VKORC1	57	38.00
High intermediate metaboliser	CYP3A4	0	0.00	Poor metaboliser	VKORC1	34	22.67
Intermediate metaboliser	CYP3A4	0	0.00	Rapid metaboliser	VKORC1	0	0.00
Low normal metaboliser	CYP3A4	0	0.00	Reduced metaboliser	VKORC1	59	39.33
Normal metaboliser	CYP3A4	149	99.33	Ultrarapid metaboliser	VKORC1	0	0.00

Appendix - XI. Consideration Per Current Medication – Full Table

Cons = dosing consideration/indication.

CONS	Drug	Freq	CONS	Drug	Freq	CONS	Drug	Freq
NO	Acetaminophen	15	Minor	EscitalopramV	1	NO	Nifedipine	2
NO	Acetaminophen	10	Minor	Esomeprazole	3	NO	Nitrofurantoin	1
NO	Acetazolamide	1	Minor	Esomeprazole	1	NO	Nitrofurantoin	1
NO	Acetylsalicylic acid	1	NO	Estradiol	3	Usual	Nortriptyline	3
NO	Adalimumab	1	NO	Ethinylestradiol / levonorgestrel	4	Minor	Nortriptyline	2
NO	Adapalene	1	NO	Ethinyloestradiol / levonorgestrel	1	Major	Nortriptyline	1
NO	Allopurinol	2	NO	Ethinyloestradiol / norethisterone	1	NO	Nystatin	1
NO	Alprazolam	1	NO	Ezetimibe	2	NO	Oestradiol	3
Usual	Amitriptyline	1	NO	Fenofibrate	1	NO	Oestriol	1
Minor	Amitriptyline	1	NO	Finasteride	1	NO	Oestrogen	5
Major	Amitriptyline	10	Usual	Flecainide	1	Usual	Olanzapine	2
NO	Amlodipine	13	NO	Fluorometholone	1	Minor	Olanzapine	3
NO	Amoxicillin	1	Usual	Fluoxetine	9	NO	Olopatadine	3
NO	Amphetamine	3	Minor	Fluoxetine	2	Minor	Omeprazole	1
NO	Amylase / betaine hydrochloride / papain	1	Major	Fluoxetine	1	Usual	Ondansetron	1
NO	Anastrozole	1	NO	Fluticasone	6	Minor	Ondansetron	1
NO	Andesartan	1	NO	Fluticasone	4	NO	Orlistat	1
Usual	Aripiprazole	2	Usual	Fluvoxamine	1	NO	Oxazepam	2
Minor	Aripiprazole	1	NO	Folic acid	6	NO	Oxcarbazepine	1
Usual	Aripiprazole	3	NO	Furosemide	5	Minor	Oxycodone	1
Minor	Aripiprazole	1	NO	Gabapentin	15	Usual	Oxycodone	1
Major	Aripiprazole	2	Usual	Glibenclamide	1	NO	Pancreatic extract bp	1
NO	Aspirin	4	Minor	Glibenclamide	1	Minor	Pantoprazole	15
NO	Aspirin	3	Usual	Gliclazide	1	Minor	Pantoprazole	3
NO	Atenolol	1	Minor	Gliclazide	2	Major	Pantoprazole	1
Usual	Atorvastatin	5	Usual	Gliclazide	1	Usual	Paroxetine	2
Minor	Atorvastatin	5	NO	Glucosamine	1	NO	Perindopril	1

CONS	Drug	Freq	CONS	Drug	Freq	CONS	Drug	Freq
NO	Azathioprine	2	NO	Golimumab	2	Minor	Pimozide	1
NO	Azelastine	1	NO	Hydrochlorothiazide	6	NO	Potassium chloride	1
NO	Azithromycin	1	NO	Hydrochlorothiazide, aspirin	1	NO	Prazosin	3
NO	Baclofen	1	NO	Hydrocortisone	3	NO	Prednisone	5
NO	Beclomethasone dipropionate	2	NO	Hydrocortisone sodium succinate	1	NO	Pregabalin	3
NO	Betamethasone dipropionate	2	NO	Hydromorphone hydrochloride	2	NO	Progesterone	3
NO	Betamethasone valerate	2	NO	Hydromorphone hydrochloride	1	Usual	Propranolol	2
NO	Bisoprolol	4	NO	Hydroxychloroquine	3	Minor	Propranolol	2
NO	Bisoprolol	1	NO	Hydroxyzine hydrochloride	1	NO	Pseudoephedrine	1
NO	Bisoprolol,	1	NO	Hydroxyzine hydrochloride	1	Usual	Quetiapine	21
NO	Brimonidine	1	NO	Ibandronate sodium	1	Minor	Quetiapine	2
NO	Brinzolamide	1	Usual	Ibuprofen	9	Usual	Quetiapine	1
NO	Budesonide	2	Minor	Ibuprofen	4	Minor	Rabeprazole	9
NO	Budesonide / eformoterol fumarate dihydrate	7	Major	Ibuprofen	1	NO	Ramipril	15
NO	Buprenorphine	1	Minor	Ibuprofen	2	NO	Ranitidine	7
NO	Buprenorphine hydrochloride / naloxone	1	Major	Imipramine	1	NO	Risedronate	1
NO	Bupropion	15	NO	Indapamide	1	Usual	Risperidone	1
NO	Buspirone	4	NO	Infliximab	1	Minor	Risperidone	2
NO	Caffeine	6	NO	Insulin	9	Minor	Risperidone	1
NO	Calcium carbonate	3	NO	Ipratropium	1	NO	Rituximab	1
NO	Calcium carbonate / potassium bicarbonate / sodium alginate	1	Usual	Irbesartan	2	NO	Rivaroxaban	1
NO	Candesartan	2	NO	Ketorolac trometamol	2	NO	Rivaroxaban	1
NO	Carbamazepine	2	NO	Lamotrigine	7	NO	Rizatriptan benzoate	1
NO	Carbidopa / entacapone / levodopa	1	NO	Lamotrigine	1	Usual	Rosuvastatin	13
Usual	Celecoxib	1	Minor	Lansoprazole	1	NO	Salbutamol	7
NO	Cephalexin	1	Major	Lansoprazole	1	NO	Salbutamol	4

CONS	Drug	Freq	CONS	Drug	Freq	CONS	Drug	Freq
NO	Cetirizine	3	NO	Latanoprost	2	NO	Salmeterol	1
Usual	Chlorpromazine	1	NO	Letrozole	1	NO	Sennosides a and b	1
NO	Ciprofloxacin	1	NO	Levetiracetam	1	Usual	Sertraline	6
Usual	Citalopram	7	NO	Levonorgestrel	1	Minor	Sertraline	9
Minor	Citalopram	8	NO	Levothyroxine sodium	13	Usual	Sertraline	1
Major	Citalopram	11	NO	Liothyronine	2	Minor	Sertraline	1
NO	Clindamycin	1	Minor	Lisdexamfetamine	1	NO	Sildenafil	1
NO	Clobetasol propionate	2	NO	Lithium	2	NO	Sodium fusidate	1
NO	Clonazepam	11	NO	Loratadine	3	NO	Somatropin	1
NO	Clonazepam	1	NO	Lorazepam	14	NO	Spironolactone	4
NO	Clonidine	2	NO	Lorazepam	3	NO	Sulfasalazine	1
Minor	Clopidogrel	3	Usual	Losartan	1	NO	Sulfasalazine	1
Major	Clopidogrel	2	NO	Lurasidone	1	NO	Sumatriptan	3
Usual	Codeine	1	NO	Medroxyprogesterone	1	Usual	Tacrolimus	3
Usual	Codeine	8	NO	Medroxyprogesterone	1	NO	Tadalafil	1
NO	Cyclosporin	1	Usual	Melatonin	6	NO	Tamsulosin	5
NO	Cyproterone	1	Minor	Melatonin	4	NO	Telmisartan	1
NO	Dabigatran	1	Usual	Meloxicam	2	NO	Temazepam	1
NO	Denosumab	2	NO	Meperidine hydrochloride	1	NO	Testosterone	4
NO	Desogestrel / ethinyloestradiol	2	NO	Mesalazine	2	NO	Thyroxine	5
NO	Desvenlafaxine	1	NO	Metformin	6	NO	Thyroxine,	1
NO	Desvenlafaxine	1	NO	Metformin	3	Usual	Timolol	1
Usual	Dexamphetamine	1	NO	Metformin / sitagliptin	1	NO	Tiotropium	1
Usual	Dextroamphetamine	2	NO	Methadone	2	NO	Topiramate	3
Minor	Dextroamphetamine	1	NO	Methocarbamol	5	Major	Tramadol	1
Usual	Diazepam	1	NO	Methotrexate	4	Usual	Tramadol	1
Usual	Diclofenac	8	NO	Methylphenidate	1	NO	Travoprost	1
Usual	Diclofenac	4	Usual	Metoprolol	4	NO	Travoprost	1
Minor	Diclofenac	1	Major	Metoprolol	1	NO	Trazadone	22
NO	Diltiazem	1	NO	Metronidazole	2	NO	Trimethoprim	1
NO	Dimenhydrinate	3	NO	Minoxidil	1	NO	Trimipramine,	1

CONS	Drug	Freq	CONS	Drug	Freq	CONS	Drug	Freq
NO	Domperidone	2	Usual	Mirtazapine	5	NO	Ursodiol	1
Usual	Doxepin	1	Minor	Mirtazapine	7	NO	Valaciclovir	2
NO	Drospirenone / ethinyloestradiol	2	Minor	Moclobemide	2	NO	Valproate	5
Usual	Duloxetine	3	NO	Modafinil	1	NO	Valsartan	3
Minor	Duloxetine	3	NO	Mometasone	2	NO	Varenicline	2
Usual	Duloxetine	1	NO	Mometasone	2	Usual	Venlafaxine	15
Minor	Duloxetine	3	NO	Montelukast	3	Minor	Venlafaxine	8
NO	Dutasteride	1	NO	Montelukast	1	Usual	Vortioxetine	1
NO	Dutasteride / tamsulosin	1	NO	Mycophenolate	2	Minor	Vortioxetine	1
NO	Eletriptan	2	Usual	Naltrexone	1	Major	Warfarin	1
Usual	Escitalopram	10	Minor	Naltrexone	1	NO	Ziprasidone	1
Minor	Escitalopram	4	NO	Naproxen	7	NO	Zolmitriptan	2
Major	Escitalopram	12	NO	Nifedipine	2	NO	Zolpidem	1
						NO	Zopiclone	19

Appendix - XII. Indication of Current Prescriptions by Site – Full Table

3 letters = site code and N = number of participants at the site. Total = total number of considerations per site. Cons = dosing consideration/indication.

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Acetaminophen	NO	1	0	0	0	0	0	1	1	2	0	0	0	1	3	2	3	1
Acetaminophen	NO	0	0	0	0	0	0	2	2	1	0	0	2	0	0	2	0	1
Acetazolamide	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Acetylsalicylic acid	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Adalimumab	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Adapalene	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Allopurinol	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Alprazolam	NO	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Amitriptyline	Major	0	0	0	1	0	1	1	3	0	0	0	0	0	1	0	1	2
Amitriptyline	Minor	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Amitriptyline	Usual	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Amlodipine	NO	0	0	0	2	1	1	2	0	1	2	0	1	0	0	2	0	1
Amoxicillin	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Amphetamine	NO	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
Amylase / betaine hydrochloride / papain	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Anastrozole	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Andesartan	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Aripiprazole	Minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Aripiprazole	Usual	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Aripiprazole	Major	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
Aripiprazole	Minor	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aripiprazole	Usual	0	0	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0
Aspirin	NO	0	0	0	0	0	2	0	0	0	0	0	0	0	0	2	0	0
Aspirin	NO	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1
Atenolol	NO	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Atorvastatin	Minor	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	1
Atorvastatin	Usual	0	0	0	1	0	1	0	1	1	1	0	0	0	0	0	0	0
Azathioprine	NO	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Azelastine	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Azithromycin	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Baclofen	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Beclomethasone dipropionate	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Betamethasone dipropionate	NO	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
Betamethasone valerate	NO	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Bisoprolol	NO	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	2
Bisoprolol	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Bisoprolol,	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Brimonidine	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Brinzolamide	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Budesonide	NO	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Budesonide / eformoterol fumarate dihydrate	NO	0	0	0	0	0	0	0	3	0	2	1	0	0	1	0	0	0
Buprenorphine	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Buprenorphine hydrochloride / naloxone	NO	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Bupropion	NO	1	0	0	3	0	3	3	1	0	0	0	0	0	1	1	2	0
Buspirone	NO	1	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0
Caffeine	NO	0	0	0	0	0	0	2	2	0	0	0	1	0	0	1	0	0
Calcium carbonate	NO	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Calcium carbonate / potassium bicarbonate / sodium alginate	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Candesartan	NO	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Carbamazepine	NO	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Carbidopa / entacapone / levodopa	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Celecoxib	Usual	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Cephalexin	NO	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Cetirizine	NO	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0
Chlorpromazine	Usual	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Ciprofloxacin	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Citalopram	Major	0	0	1	0	0	0	2	2	0	3	1	0	0	0	0	2	0
Citalopram	Minor	0	0	0	0	1	0	1	1	0	0	0	0	1	1	1	1	1
Citalopram	Usual	0	0	0	1	0	1	1	1	0	1	0	0	1	0	0	1	0
Clindamycin	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Clobetasol propionate	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Clonazepam	NO	1	0	0	1	0	0	1	1	1	2	1	1	1	0	1	0	0
Clonazepam	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Clonidine	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Clopidogrel	Major	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Clopidogrel	Minor	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0
Codeine	Usual	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Codeine	Usual	0	0	0	0	0	0	2	2	0	0	0	1	0	0	2	0	1
Cyclosporin	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cyproterone	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dabigatran	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Denosumab	NO	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Desogestrel / ethinyloestradiol	NO	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0
Desvenlafaxine	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Desvenlafaxine	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Dexamphetamine	Usual	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Dextroamphetamine	Minor	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dextroamphetamine	Usual	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Diazepam	Usual	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Diclofenac	Usual	0	0	0	0	0	0	1	2	0	1	0	1	0	0	2	0	1
Diclofenac	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Diclofenac	Usual	0	0	0	0	0	0	0	2	0	0	0	0	0	1	0	1	0
Diltiazem	NO	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Dimenhydrinate	NO	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0
Domperidone	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Doxepin	Usual	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Drospirenone / ethinyloestradiol	NO	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Duloxetine	Minor	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Duloxetine	Usual	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
Duloxetine	Minor	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0
Duloxetine	Usual	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Dutasteride	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Dutasteride / tamsulosin	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Eletriptan	NO	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Escitalopram	Major	0	0	0	2	0	2	3	1	0	1	1	0	0	0	2	0	0
Escitalopram	Minor	0	0	1	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Escitalopram	Usual	0	0	0	0	2	1	2	1	0	2	0	0	0	1	0	1	0
EscitalopramV	Minor	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Esomeprazole	Minor	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0
Esomeprazole	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Estradiol	NO	0	0	0	0	0	0	2	0	0	1	0	0	0	0	0	0	0
Ethinylestradiol / levonorgestrel	NO	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	1
Ethinyloestradiol / levonorgestrel	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Ethinyloestradiol / norethisterone	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Ezetimibe	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
Fenofibrate	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Finasteride	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Flecainide	Usual	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Fluorometholone	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Fluoxetine	Major	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Fluoxetine	Minor	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Fluoxetine	Usual	0	0	1	0	0	0	1	1	0	0	0	1	1	0	2	1	1
Fluticasone	NO	0	0	0	0	0	1	0	1	0	2	0	1	0	0	0	1	0
Fluticasone	NO	1	0	0	0	0	0	0	2	0	1	0	0	0	0	0	0	0
Fluvoxamine	Usual	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Folic acid	NO	0	0	0	0	0	2	1	0	0	1	0	0	0	0	1	1	0
Furosemide	NO	0	0	0	1	0	1	0	0	0	2	0	0	0	0	0	0	1
Gabapentin	NO	0	0	0	1	0	2	2	3	0	1	0	1	0	4	1	0	0
Glibenclamide	Minor	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Glibenclamide	Usual	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Gliclazide	Minor	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Gliclazide	Usual	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Gliclazide	Usual	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Glucosamine	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Golimumab	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
Hydrochlorothiazide	NO	0	0	0	1	0	2	1	1	0	0	0	0	0	0	1	0	0
Hydrochlorothiazide, aspirin	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Hydrocortisone	NO	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0
Hydrocortisone sodium succinate	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Hydromorphone hydrochloride	NO	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Hydromorphone hydrochloride	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Hydroxychloroquine	NO	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0
Hydroxyzine hydrochloride	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Hydroxyzine hydrochloride	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Ibandronate sodium	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Ibuprofen	Major	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Ibuprofen	Minor	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1	0
Ibuprofen	Usual	0	0	1	0	0	0	1	4	1	1	0	0	0	1	0	0	0
Ibuprofen	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
Imipramine	Major	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Indapamide	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Infliximab	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Insulin	NO	0	0	0	0	0	2	1	3	0	1	0	0	0	0	0	0	2
Ipratropium	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Irbesartan	Usual	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
Ketorolac trometamol	NO	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0
Lamotrigine	NO	1	0	0	0	1	0	1	1	0	1	0	1	0	1	0	0	0
Lamotrigine	NO	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Lansoprazole	Major	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Lansoprazole	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Latanoprost	NO	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Letrozole	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Levetiracetam	NO	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Levonorgestrel	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Levothyroxine sodium	NO	0	0	0	0	0	3	1	3	1	1	0	0	0	0	2	0	2
Liothyronine	NO	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Lisdexamfetamine	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Lithium	NO	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Loratadine	NO	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0
Lorazepam	NO	1	0	0	0	3	2	2	0	1	2	1	0	0	0	0	1	1
Lorazepam	NO	0	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0
Losartan	Usual	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Lurasidone	NO	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Medroxyprogesterone	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Medroxyprogesterone	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Melatonin	Minor	0	0	0	0	0	0	1	2	0	0	1	0	0	0	0	0	0
Melatonin	Usual	0	0	0	1	0	0	1	0	1	0	0	0	0	2	1	0	0
Meloxicam	Usual	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Meperidine hydrochloride	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Mesalazine	NO	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Metformin	NO	0	0	0	0	0	1	1	2	1	0	1	0	0	0	0	0	0
Metformin	NO	0	0	0	2	0	0	0	0	0	1	0	0	0	0	0	0	0
Metformin / sitagliptin	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Methadone	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Methocarbamol	NO	0	0	0	0	0	0	0	1	0	1	0	0	0	2	0	1	0
Methotrexate	NO	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	0
Methylphenidate	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Metoprolol	Major	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Metoprolol	Usual	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	1
Metronidazole	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Minoxidil	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Mirtazapine	Minor	2	0	0	0	0	1	0	1	1	0	0	1	1	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Mirtazapine	Usual	0	0	0	0	1	0	1	0	1	1	0	0	0	0	1	0	0
Moclobemide	Minor	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Modafinil	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Mometasone	NO	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0
Mometasone	NO	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Montelukast	NO	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0
Montelukast	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Mycophenolate	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
Naltrexone	Minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Naltrexone	Usual	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Naproxen	NO	0	0	0	0	0	0	1	0	1	0	0	1	0	0	0	1	3
Nifedipine	NO	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Nifedipine	NO	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Nitrofurantoin	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nitrofurantoin	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Nortriptyline	Major	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Nortriptyline	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Nortriptyline	Usual	0	0	0	0	0	0	2	0	0	0	0	1	0	0	0	0	0
Nystatin	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Oestradiol	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
Oestriol	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Oestrogen	NO	1	0	0	0	0	0	0	1	0	0	0	2	0	0	0	1	0
Olanzapine	Minor	0	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0
Olanzapine	Usual	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Olopatadine	NO	0	0	0	0	0	0	1	0	0	2	0	0	0	0	0	0	0
Omeprazole	Minor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Ondansetron	Minor	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Ondansetron	Usual	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Orlistat	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Oxazepam	NO	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Oxcarbazepine	NO	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Oxycodone	Minor	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Oxycodone	Usual	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Pancreatic extract bp	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Pantoprazole	Minor	0	0	0	1	2	1	1	4	0	1	2	1	0	1	0	1	0
Pantoprazole	Major	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Pantoprazole	Minor	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0
Paroxetine	Usual	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Perindopril	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Pimozide	Minor	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Potassium chloride	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Prazosin	NO	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Prednisone	NO	0	0	0	0	0	1	1	1	0	0	0	0	0	0	2	0	0
Pregabalin	NO	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0
Progesterone	NO	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
Propranolol	Minor	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
Propranolol	Usual	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Pseudoephedrine	NO	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Quetiapine	Minor	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Quetiapine	Usual	1	0	0	3	2	0	3	2	2	3	1	1	1	1	0	1	0
Quetiapine	Usual	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Rabeprazole	Minor	0	0	1	0	0	1	1	3	0	0	0	0	0	0	2	0	1
Ramipril	NO	0	0	2	2	1	0	2	1	0	1	0	1	0	0	2	0	3
Ranitidine	NO	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	1	3
Risedronate	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Risperidone	Minor	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Risperidone	Usual	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Risperidone	Minor	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Rituximab	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Rivaroxaban	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Rivaroxaban	NO	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Rizatriptan benzoate	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Rosuvastatin	Usual	0	0	1	2	1	1	1	2	0	0	0	1	1	0	1	1	1
Salbutamol	NO	0	0	0	0	0	1	0	0	0	3	0	1	0	1	0	0	1

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Salbutamol	NO	0	0	0	0	0	0	0	2	0	0	0	0	0	1	1	0	0
Salmeterol	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Sennosides a and b	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Sertraline	Minor	0	0	0	0	1	1	1	0	0	0	0	1	0	2	2	1	0
Sertraline	Usual	1	0	0	0	0	1	2	0	0	0	0	1	0	0	1	0	0
Sertraline	Minor	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Sertraline	Usual	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Sildenafil	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Sodium fusidate	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Somatropin	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Spironolactone	NO	0	0	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0
Sulfasalazine	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Sulfasalazine	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Sumatriptan	NO	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Tacrolimus	Usual	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
Tadalafil	NO	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tamsulosin	NO	0	0	0	0	0	1	0	2	1	1	0	0	0	0	0	0	0
Telmisartan	NO	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Temazepam	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Testosterone	NO	0	0	0	0	0	0	2	1	0	0	0	0	0	0	1	0	0
Thyroxine	NO	0	0	0	2	0	0	1	0	0	1	0	0	0	0	1	0	0
Thyroxine,	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Timolol	Usual	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Tiotropium	NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Topiramate	NO	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
Tramadol	Major	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Tramadol	Usual	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Travoprost	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Travoprost	NO	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Trazadone	NO	2	0	0	1	0	0	7	3	0	2	0	1	0	1	4	0	1
Trimethoprim	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Trimipramine,	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

Drug	Cons	BCP n=8	D59 n=1	F31 n=2	J02 n=8	k74 n=6	k76 n=10	L65 n=20	N24 n=20	N43 n=9	N83 n=16	S73 n=5	S81 n=4	S94 n=3	T37 n=9	T60 n=9	W19 n=10	X73 n=10
Ursodiol	NO	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Valaciclovir	NO	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
Valproate	NO	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0	0	0
Valsartan	NO	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
Varenicline	NO	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Venlafaxine	Minor	0	0	0	1	0	1	2	1	0	1	0	0	0	1	0	0	1
Venlafaxine	Usual	2	0	0	0	1	0	1	2	3	1	0	0	0	2	0	1	2
Vortioxetine	Minor	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Vortioxetine	Usual	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Warfarin	Major	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Ziprasidone	NO	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Zolmitriptan	NO	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Zolpidem	NO	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Zopiclone	NO	0	0	0	1	2	0	2	2	3	1	1	3	0	2	0	2	0