Initiation of New Medication with an Actionable Pharmacogenetics-Based Prescribing Guideline in Discharged Hospital Patients in Finland

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OBJECTIVES. Purpose of this retrospective, register-based pharmacoepidemiologic study was to analyse post-discharge purchases of drugs with an actionable pharmacogenetics-based prescribing guideline with a patient cohort consisting of Finnish hospital patients.

MATERIALS. Altogether 33 eligible actionable drugs were identified from prescribing guidelines compiled by the Clinical Pharmacogenetics Implementation Consortium. Hospital admission data, drug purchase data, and mortality data were utilized from 1.42 million eligible patients.

METHODS. Each patient was followed from the first hospital admission to either surgical or internal medicine unit until the end of year 2016 or until death. Statistical analyses were descriptive on prevalence and incidence of drug purchases of individual drugs and related genes. Impact in Finnish population was studied by combining Finnish phenotype frequencies with drug incidence data. Differences in post-discharge drug purchases between the units was studied with Cox proportional-hazards model.

RESULTS. Genes related to study drugs consisted of five drug-metabolizing CYP-genes, four other pharmacokinetic genes, one gene encoding a pharmacological drug target and three HLA-alleles altering to susceptibility to adverse effects. Most frequently purchased drugs in 2-year follow-up included common analgesics, proton pump inhibitors, cardiovascular drugs and a selective serotonin reuptake inhibitor. In 2-year follow-up, 60% of the patients purchased at least one drug, and drug purchases of 22% of the patients were associated to ≥ 2 different genes.

DISCUSSION. Results provide significant new information of drug initiations in hospital discharged patients, which can be utilized in targeting pre-emptive pharmacogenetics testing to prevent drug adverse effects and rehospitalization. However, more studies are required on cost-effectiveness of pharmacogenetic testing.

Keywords: pharmacogenetics, pharmacoepidemiology, prescribing guideline

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1. Introduction

1.1 Defining pharmacogenetics

Primarily, pharmacogenetics (PGt) is a research area that studies how variations in individual genotype affect drug response, metabolism and risk for adverse drug effects (Niemi, 2016). After establishment in the end of the 1950's, pharmacogenetics has relatively recently become a more popular research area aiming to improve individual drug therapy by utilizing human genomic data. Advancements in gene cloning and techniques in DNA genotyping and sequencing have accelerated understanding of the interplay between genetics and individual drug response (Daly, 2017; Lunenburg et al., 2020).

To be precise with the study area terminology, the ICH guideline E15 defines pharmacogenetics (PGt) as a subset of pharmacogenomics, which studies the variations in DNA sequence related to drug response. Pharmacogenomics (PGx) studies the variations in DNA and RNA characteristics related to drug response. (https://database.ich.org/sites/default/files/E15_Guideline.pdf) Both terms and the abbreviation PGx are often used interchangeably. (Daly, 2017) Pharmacogene is a term referring to pharmacogenetically relevant genes, which can code drug transporters, drug metabolizing enzymes or drug targets. Particular human leukocyte antigen (HLA) alleles in major histocompatibility complex are also pharmacogenes. (https://www.pharmgkb.org/page/typesOfPgx; https://www.pharmvar.org/)

High variation has been found in drug response between individuals, and according to Zhou et al, (2017) it is estimated that 40-70% of patients experience adverse drug reactions (ADR) or lack of efficacy of their medication. Genetic polymorphisms are estimated to cause 15-30% of variations in drug response (Zhou et al., 2017), and pharmacogenetics has been recognised to be a potential tool in personalized medicine. However, it is to be noted that there are also other factors affecting the drug response. Several intrinsic and extrinsic factors have an impact on individual drug metabolism and response, as well as the risk for adverse drug effects. All patient-specific factors should be considered when prescribing a drug. (Raunio and Huupponen, 2018; Niemi, 2016) The main factors affecting drug response are described in the Figure 1 below.

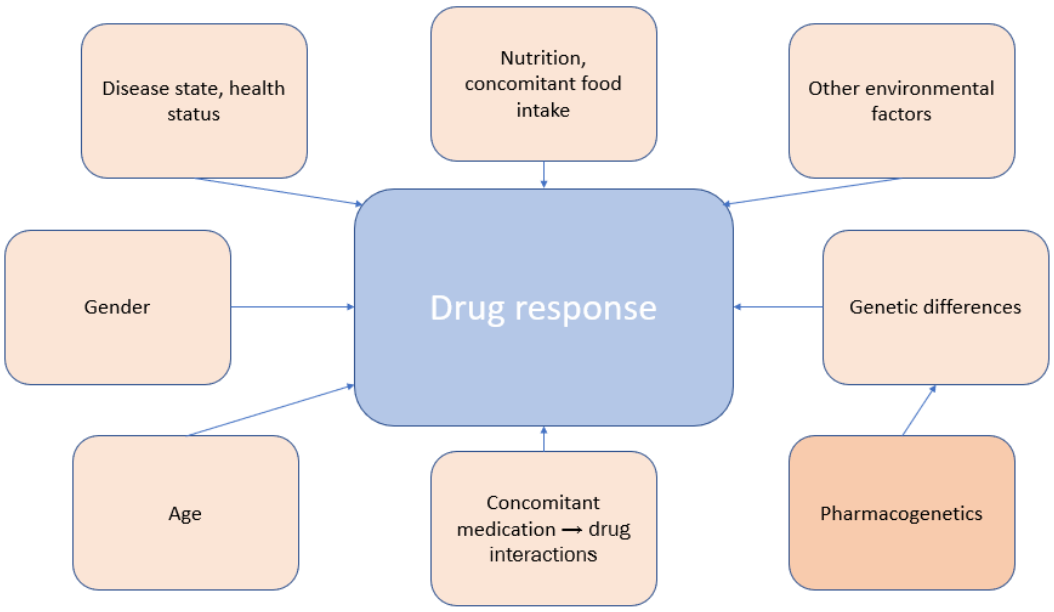

Figure 1. Factors affecting drug response

Of the factors affecting drug response (Figure 1), genes affecting the drug response remain unchangeable during the lifetime, which support consideration of pharmacogenetic testing results in prescribing situations. However, it is to be noted that although the pharmacogenetic test result is permanent, the interpretation might change due to increased knowledge of the allele functions. Other factors represented in the Figure 1 are prone to change during the lifetime and their impact to pharmacotherapy must be evaluated repeatedly.

1.2 Pharmacogenetic testing

Pharmacogenetics is primarily utilized in personalized medicine to determine an appropriate drug dose, to identify patients predicted to have a low or no response to a drug and to recognize individuals at risk for serious drug-induced toxicities (Daly, 2017; Alshabeeb et al., 2019). Testing the allelic variation of relevant pharmacogenes can be either reactive ("as needed") or pre-emptive. (Mukerjee et al., 2018) The impact of genetics in unexplained adverse drug reactions can be analysed with reactive testing. (Lunenburg et al., 2020) Reactive genetic testing is also required before initiating certain pharmacotherapies due to genetic predisposition to a risk for serious adverse drug reactions, such as testing the possible dihydropyrimidine dehydrogenase (DPD) deficiency before initiating fluorouracil treatment. (https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal) Pre-emptive tests are ordered

so that results are available for the future, and can be utilized for the rest of the patient's life. (Mukerjee et al., 2018) The advantage of pre-emptive pharmacogenetic testing is the available test results at the point of prescribing, which facilitates selection of a drug and determining the most likely suitable dose. (Lunenburg et al., 2020; Mukerjee et al., 2018)

In the pharmacogenetic testing, variations in gene regulatory regions or coding regions can be detected. Variations in regulatory regions of the gene affect the level of expression, while variations in the coding region affect the gene function, which both might lead to altered drug exposure, high concentration of toxic metabolites, altered interactions with drug targets or idiosyncratic drug toxicity due to activation of the immune system. (Mukerjee et al., 2018)

In choosing a relevant pharmacogenetic assay, sensitivity and specificity of the test should be evaluated in addition to the target population, possible earlier conducted genotyping, technical requirements and costs. (Mukerjee et al., 2018) Several approaches can be utilized in pharmacogenetic testing, in which either preselected variants are probed with well-defined drug-gene interactions or a panel of well-studied pharmacokinetic and pharmacodynamic markers of relevant drug metabolizing enzymes, drug transporters, receptors and various other genes associated to drug response is chosen. (Mukerjee et al., 2018) Most importantly, the assay chosen should detect variants, which are common in the population to be genotyped. For example, high variation in allele frequencies associated with anticoagulant warfarin response has been detected between different ethnicities. (Mukerjee et al., 2018; Kimmel et al., 2013; Limdi et al., 2015; Wadelius et al., 2009) Patients of Caucasian origin carry reduced function alleles *CYP2C9*2* and *CYP2C9*3* more often than African-Americans. Carriers of these alleles have an increased risk for bleeding due to warfarin therapy and they require lower warfarin doses. However, other reduced function alleles *CYP2C9*5, *6*, *8* and **11* are more common in African-Americans. Ethnic differences were observed in various studies on warfarin dosing algorithms and ethnicity influences to warfarin dosing, which have led to current recommendation of utilizing warfarin dosing algorithms stratified by race. (Kimmel et al., 2013; Limdi et al., 2015; Johnson et al., 2017; Wadelius et al., 2009) Moreover, a broad implementation of pharmacogenetics requires strategies also for detecting and interpreting rare variants. (McInnes et al., 2020) However, technical requirements and exact genotyping assay composition are outside the scope of this study.

Although some dose adjustments based on PGx test results are justified even after drug initiation, it is recognised that testing a patient already exposed to a possible drug-gene interaction is not that beneficial, which strongly supports pre-emptive testing to be conducted before initiating drugs with known drug-gene interaction risk. Pharmacogenetic testing has a possibility to became a valuable

tool when optimizing prescribing, dose determination and patient monitoring. (Westergaard et al., 2020; Lunenburg et al., 2020)

1.3 Relevant pharmacogenes

In general, pharmacogenes, genes affecting the drug response represent four different types of genes, which are illustrated in the Figure 2 below.

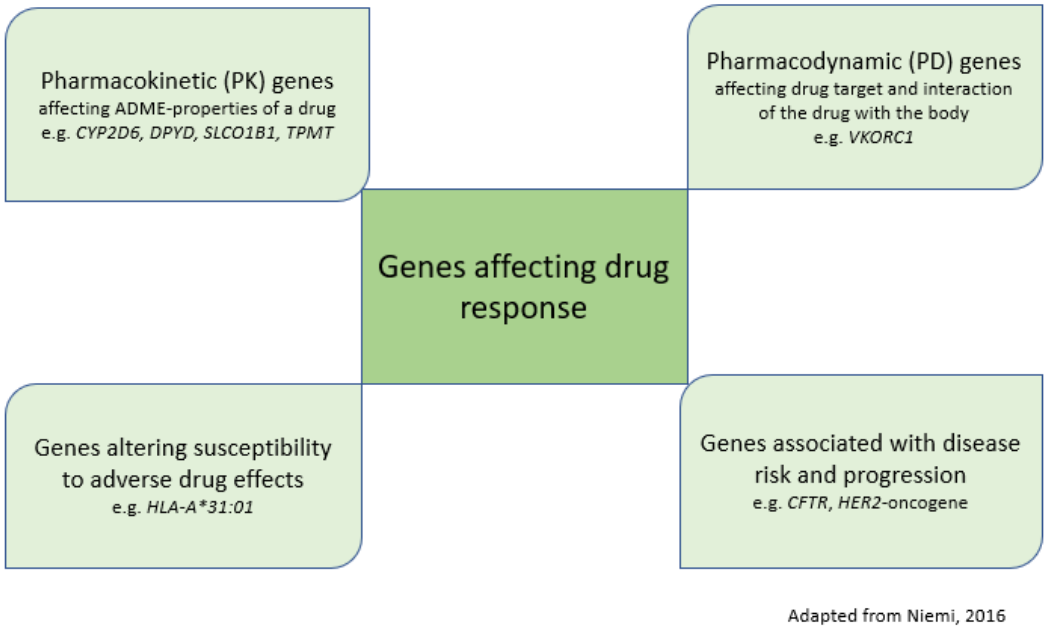

Figure 2. Genes affecting drug response

Pharmacokinetic genes encode proteins that affect the absorption, distribution, metabolism and excretion of the drugs. These cell membrane transport proteins and enzymes catalyse the drug metabolism phases I and II occurring mainly in liver. Pharmacodynamic genes encode receptors and other proteins targeted by drugs, and affect the interaction of the drug with the body. Genes altering the patient to a greater risk for adverse drug reaction are usually related to immunological reactions. Generally, these adverse effects are rare but when occurring, even fatal, and are not dependent on pharmacologic response or the drug dose. Genes such as *HER2* and *CFTR* associated with the disease risk and progression are outside of the scope of this study. In general, they are important factors e.g., in drug selection for a cancer patient. (Niemi, 2016)

It has been showed in a study combining electronic medical records with exome sequencing results of hospitalized patients that the number of pharmacogenetic variants correlates with the mean length of hospital stay. The more the patients had actionable pharmacogenetic variants present in

their genome, the longer was the hospital period. (Finkelstein et al., 2020) Comprehensive and routinely conducted PGx test panels would potentially reduce health care costs by decreasing drug-related adverse events, insufficient treatment responses and re-hospitalization of the polypharmacy patients. (Westergaard et al., 2020; Lunenburg et al., 2020).

Even up to 95% of the population is thought to have at least one clinically relevant pharmacogenetic variant in their genome (van der Wouden, C. H. et al., 2017; Tarkiainen et al., 2021), which is defined as an actionable genotype in pharmacogenetic terminology. An actionable genotype refers to a patient's unique genotype associated with increased risk of lack of efficacy or adverse drug reactions. A patient having an actionable genotype might require either dose increase or decrease of a drug or the drug in question should be avoided. (https://cpicpgx.org/)

In the context of drug metabolism, the variant alleles have a functional status ranging from no function to increased function, which impacts the associated phenotype ranging from ultrarapid metabolizer (UM) to poor metabolizer (PM). Other distinctive phenotypes are rapid metabolizer (RM), normal metabolizer (NM, previously known as extensive metabolizer, EM) and intermediate metabolizer (IM). The functional status is determined by scoring the metabolic activity of the alleles. (Tornio and Backman, 2018; Westergaard et al., 2020) Polymorphism occurring in phase I drug metabolizing enzymes has been recognised to increase the risk for ADRs. (Zhou et al., 2017) Genotype associated with a phenotype of poor metabolizer generally leads to insufficient drug metabolism due to lack of metabolizing enzyme, which increases the drug concentration and altering the patient to ADRs more likely. In case the patient has rapid or ultrarapid metabolizer phenotype, the drug concentration might not reach the therapeutic level leading to insufficient treatment response (Tarkiainen et al., 2021).

For pharmacodynamic genes, phenotypes range from increased activity to poor activity based on allele functional status. For genes associated with high risk for adverse drug reactions, phenotypes of positive or negative are used in which a patient is either a homozygous or heterozygous allele positive or any copies of the allele is not detected. (Caudle et al., 2017)

A star (*) allele nomenclature has been agreed to define the different variants of the genes. A database managed by the Pharmacogene Variation Consortium (PharmVar) includes the identified variants of the Cytochrome P450-genes and some other relevant pharmacogenes (https://www.pharmvar.org/)

In pharmacogenetic literature and test reporting the use of terms has been variable and a need for standardized, consistent PGx terms has been recognized. One standardization project was conducted by the Clinical Pharmacogenetics Implementation Consortium (CPIC) among

pharmacogenetic experts and final terms were published in 2016. The terms agreed in the project are listed in the Table 1 with their respective functional definitions and genetic definitions. The CPIC recommends the terms to be widely used in all areas of pharmacogenetics, including the clinical decision support systems, PGx laboratory testing results and the prescribing recommendations. The name of the associated gene should be added to all terms to describe the association between the genotype and phenotype (e.g., *CYP2C19* Normal metabolizer, *SLCO1B1* Increased function, *HLA-B* allele positive) (Caudle et al., 2017) All possible phenotypes cannot be found in every CYP-enzymes due to the nature of the function of identified alleles, e.g., phenotypes identified for *CYP2C9* are normal, intermediate and poor but no alleles leading to *CYP2C9* ultrarapid or rapid metabolism is known.

Table 1. The final terms agreed in the term standardization project by CPIC for allele functional status and phenotypes

TERM/GENE CATEGORY	FINAL TERM	FUNCTIONAL DEFINITION	GENETIC DEFINITION
ALLELE FUNCTIONAL STATUS: ALL GENES	Increased function	Function greater than normal function	N/A
	Normal function	Fully functional/wild-type	N/A
	Decreased function	Function less than normal function	N/A
	No function	Non-functional	N/A
	Unknown function	No literature describing function or the allele is novel	N/A
	Uncertain function	Literature supporting function is conflicting or weak	N/A
PHENOTYPE: DRUG-METABOLIZING ENZYMES (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultrarapid metabolizer (UM)	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than 2 normal function alleles
	Rapid metabolizer (RM)	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles

	Normal metabolizer (NM)	Fully functional enzyme activity	Combinations of normal function and decreased function alleles
	Intermediate metabolizer (IM)	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles
	Poor metabolizer (PM)	Little to no enzyme activity	Combination of no function alleles and/ or decreased function alleles
PHENOTYPE: TRANSPORTERS (SLCO1B1)	Increased function	Increased transporter function compared to normal function.	One or more increased function alleles
	Normal function	Fully functional transporter function	Combinations of normal function and/ or decreased function alleles
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles
	Poor function	Little to no transporter function	Combination of no function alleles and/ or decreased function alleles
PHENOTYPE: HIGH-RISK GENOTYPE STATUS (HLA-A, HLA-B)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele
	Negative	High-risk allele not detected	No copies of high-risk allele

The table has been partly adapted from Caudle et al., 2017. N/A = not applicable

In translating genotype into a predicted phenotype, the Activity Score (AS) system can be utilized. Introduced by Gaedigk et al., in 2008, the AS system has become widely accepted and used in pharmacogenetics. Originally developed to describe the metabolic phenotype of CYP2D6, the AS is a quantitative value, which is based on the sum of the allele activity scores. The system gives each allele a value 0, 0.5 or 1, based on allele function activity. Value 0 refers to no function, and value 1 to normal function, while value 0.5 stands for decreased function. It is to be noticed that value 0.5 does not stand for 50% reduction in allele activity but a decreased functionality somewhere between no function and full function. In case the allele has two or more copies, the allele value (0, 0.5 or 1) is multiplied by the number of gene copies resulting in an AS value possible higher than 2. (Gaedigk et al., 2008; Gaedigk et al., 2018) In addition to *CYP2D6*, the AS system is used in allele scoring of genes *CYP2C9* and *DPYD*. The AS system is constantly updating, as

new information of allele functional status is gained and possible new alleles are found. (https://cpicpgx.org/)

A drug-drug-gene interaction might lead to phenoconversion, a phenomenon in which a person with a NM or RM phenotype turns to PM due to concomitant medication altering the metabolizing status. Mismatches in genotype to phenotype interpretation might occur due to phenoconversion, which especially complicates the medication of polypharmacy patients. (Westergaard et al., 2020)

1.4. Genes and alleles in the focus of this study

1.4.1 CYP-genes

Pharmacogenetics is highly defined by the genes encoding cytochrome P450 (CYP) drug metabolizing enzymes. Altogether 57 functional CYP-genes has been described in humans, and they have been categorized into 18 families and 44 subfamilies by their sequence similarity. Genes belonging to families 1-3 are responsible of coding enzymes, which metabolize majority (70-80%) of the hepatically cleared drugs, as the rest of the CYP-genes have a role in synthesis or metabolism of several endogenic compounds such as bile acids, eicosanoids and steroids. (Raunio and Huupponen, 2018; Tornio and Backman, 2018)

CYP-enzymes catalyse oxidative biotransformation of the drugs converting them to either active substances or inactive metabolites. CYP-enzymes are unspecific and several structurally different compounds can act as a substrate, although a single CYP-enzyme is usually the predominant metabolizing pathway for many drugs. (Raunio and Huupponen, 2018; Tornio and Backman, 2018) Of the *CYP*-genes, *CYP2C9, CYP2C19, CYP2D6* and *CYP3A5* shown polymorphism of major clinical significance. (Tornio and Backman, 2018)

1.4.2. Other pharmacokinetic genes

Clinically relevant genetic variation occurs in pharmacokinetic genes *DPYD, SLCO1B1, TPMT,* and *NUDT15.* Dihydropyrimidine dehydrogenase (DPD) protein encoded by gene *DPYD* is a phase I drug metabolizing enzyme and a rate-limiting factor in uracil and thymidine catabolism pathway. Cytostatic fluorouracil, capecitabine and tegafur belonging in the fluoropyrimide-group transform into inactive metabolites mainly via DPD-enzyme. Patients suffering from a rare genetic DPD-deficiency might experience severe, even life-threatening adverse effects when using the

associated drugs in chemotherapy. (Niemi, 2016; https://www.ncbi.nlm.nih.gov/gene/1806#gene-expression; Wei et al., 1998) On April 2020 the European Medicines Agency (EMA) recommended (EMA/367286/2020) that all patients initiating cancer treatment with fluorouracil, capecitabine or tegafur should be pre-emptively tested for the lack of DPD-enzyme to ensure safety of the pharmacotherapy. (https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal)

Organic anion transporting polypeptide 1B1 (OATP1B1), encoded by the gene *SLCO1B1* is a liver-specific transmembrane receptor protein, which mediates the Na-independent uptake of several different endogenous compounds, such as bilirubin (Niemi et al., 2011; Pasanen et al., 2006; The Search Collaborative Group, 2008). It also transports cholesterol-lowering statins and a number of other drugs from blood to liver hepatocytes. A common single nucleotide variant (c.521T>C, rs4149056) impairs the ability of OATP1B1 to transport statins into the liver, which causes especially high simvastatin concentrations in plasma and an increased risk for muscle-related symptoms, ranging from mild muscle pain to severe rhabdomyolysis. Due to marked increase of systemic simvastatin levels and a higher risk of muscle toxicity, these patients require either a lower simvastatin dose or another statin alternative. (Niemi, 2016; https://www.ncbi.nlm.nih.gov/gene/10599; https://www.ncbi.nlm.nih.gov/gtr/conditions/CN128903/; Pasanen et al., 2006; The Search Collaborative Group, 2008)

Gene *TPMT* encodes thiopurine S-methyltransferase (TPMT) enzyme, which metabolizes chemotherapeutic thiopurine drugs, such as azathioprine, 6-mercaptopurine and thioguanine. Genetic variation affects the enzyme activity, which correlates interpatient differences in thiopurine drug sensitivity and toxicity. Patients heritably lacking the TPMT enzyme suffer from thiopurine S-methyltransferase deficiency and are especially prone to develop bone marrow suppression when using thiopurine drugs in normal therapeutic doses. (Niemi, 2016; https://www.ncbi.nlm.nih.gov/gene/7172)

Another factor regulating the thiopurine metabolism is nudix hydrolase 15 (NUDT15) enzyme encoded by gene *NUDT15*. The enzyme belongs to a superfamily of Nudix hydrolases, which catalyse the hydrolysis reactions of nucleoside diphosphates. Patients suffering from NUDT15 deficiency due to having loss-of function variants of *NUDT15* are prone to excessive DNA damage, bone marrow suppression and thiopurine-induced early leukopenia. (https://www.ncbi.nlm.nih.gov/gene/55270; Schaeffeler et al., 2019)

1.4.3. Vitamin K epoxide reductase complex subunit 1

The vitamin K epoxide reductase complex subunit 1 (VKORC-1) encodes the pharmacological drug target of anticoagulant warfarin. It participates to the vitamin K activation in the endoplasmic reticulum membrane, which is a crucial co-factor in blood-clotting enzyme formation. Generally, the significance of this type of genes affecting the drug response via drug targets is less known than the impact of pharmacokinetic genes. Genetic differences of the warfarin drug target VKORC-1 have a considerable impact on the warfarin dose needed. A common single nucleotide variant with an allele frequency approximately 40% in patients with a European ancestry increases the anticoagulation effect of warfarin. Together with patient-specific factors such as age and weight, and *CYP2C9*, the other warfarin metabolism associated gene, the allelic variation of VKORC-1 explains over 50% of the interpatient variation in warfarin dose. (Niemi, 2016; https://www.ncbi.nlm.nih.gov/gene/79001; Wadelius et al., 2009)

1.4.4. HLA-alleles

Variability in genes encoding the human leukocyte antigens type class I A or B (HLA-A and HLA-B) of the major histocompatibility complex alter the patient to a risk for developing drug hypersensitivity syndromes with an immunological mechanism. Generally, these types of adverse effects are difficult to predict and rare but when occurring, even fatal. They are not dependent on pharmacologic response to the drug or the dose. The type of the drug-induced reaction depends on the associated drug and patient's allele-carrying status. (Niemi, 2016; Pavlos et al., 2012; Yip et al., 2015) For example, if a patient carrying an HLA-allele *HLA-B*58:01* initiates allopurinol, a risk for experiencing severe skin reactions Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is high. Allele carriers of *HLA-B*15:02* are susceptible for developing SJS or TEN in case they are prescribed with carbamazepine, oxcarbazepine or phenytoin. However, carbamazepine is also associated with carrying an allele HLA-A*31:01 and a high risk for developing drug-induced hypersensitivity syndrome in addition to SJS and TEN. In addition to anticonvulsants and allopurinol, particular drugs of antiretrovirals, NSAIDs, sulpha antimicrobials and β-lactam antimicrobials can predispose the patient to drug-induced reactions along with HLA-allele carrying status. (Pavlos et al., 2012) A common feature of the drug hypersensitivity syndromes is that they develop within 3 months of drug initiation and the recovery phase is long. Often the HLA-allele frequency is strongly dependent on the patient's ethnical ancestry, which

supports targeted genetic testing. (Niemi, 2016; https://www.ncbi.nlm.nih.gov/gene/3105; https://www.ncbi.nlm.nih.gov/gene/3106; Pavlos et al., 2012; Yip et al., 2015)

1.5. Pharmacogenetics-based guidelines

To facilitate the implementation of PGx into daily clinical routines and to provide up-to-date information for clinicians, several evidence-based pharmacogenetic guidelines have been published. This study mainly utilizes the guidelines of Clinical Pharmacogenetics Implementation Consortium (CPIC) as a reference for the drugs in interest as for the prescribing recommendations. CPIC guidelines are peer-reviewed, evidence-based, updatable, detailed and freely available in the internet (https://cpicpgx.org/). A prescribing action proposed in the CPIC prescribing recommendations refers to a recommendation to choose alternative therapies or to adjust dose which highly likely results in more effective and safe treatment to the patient. CPIC lists drug-gene interaction pairs with respective guidelines and gives prescribing recommendations for clinicians to help drug selection and dose adjustment. Guidelines are categorized by the levels of evidence linking genotype to phenotype. Grading is based on literature evidence and consists of three categories; high, moderate and weak. Guidelines with the highest level of evidence are compiled based on consistent results from well-designed and well-conducted studies. Respectively, a guideline with weak level of evidence lacks adequate information due to small number of studies conducted or studies with inadequate design and evidence is insufficient when assessing the effects on health outcomes. To date, the CPIC has published 25 guidelines associated with wide range of drugs such as common analgesics, cardiovascular drugs and immunosuppressants, and the number of guidelines is constantly increasing and the existing guidelines are frequently updated. One guideline might refer to several drugs belonging into a same therapeutic group (e.g., *CYP2D6, CYP2C19* and selective serotonin reuptake inhibitors), while one gene encoding for a particular CYP-enzyme might be associated to several drugs from different therapeutic group (e.g. *CYP2C19* affecting both clopidogrel and voriconazole). (https://cpicpgx.org/; Lunenburg et al., 2020)

In addition to international and national expert consortia published PGx prescribing guidelines, the drug regulatory authorities in the United States and in Europe have regulatory guidelines concerning the conduction of genomic studies and use of genomic biomarkers in drug development. Genomic data is evaluated in the drug regulatory approval process if it is expected to affect the efficacy and/or safety of the drug.

(https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacogenomic-practice-first-version_en.pdf; https://www.fda.gov/drugs/science-and-research-drugs/other-fda-resources-related-pharmacogenomics#FDAGuidances)

Abdullah-Koolmees et al., 2020, made a comparison of the guidelines published in English by the Dutch Pharmacogenetics Working Group (DPWG), the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network (Réseau) of Pharmacogenetics (RNPGx). (Abdullah-Koolmees et al., 2020)

In their comparison Abdullah-Koolmees et al., found differences in e.g., methodologies to grade the scientific evidence, the amount of drug-gene interaction pairs evaluated, and differing recommendations for the drug dosing and patients to be genotyped. The guidelines are compiled similarly by multidisciplinary boards or committees, and all aim for compiling recommendations with high evidence-base and they constantly develop new recommendations and evaluate new data. The four committees have conducted harmonization projects and aim to use standardized terms as described in Caudle et al. (2017). Lately, one harmonization project resulted a consensus to downgrade the *CYP2D6*10* allele activity score value. (Abdullah-Koolmees et al., 2020)

In general, it has been recognised that the guidelines are of benefit for both clinicians and for patients as well as other stakeholders. Each PGx guideline project was based on different objectives, which have resulted unique guideline profiles and differing approaches but considering all guidelines simultaneously brings the most value. (Abdullah-Koolmees et al., 2020; Bank, PCD et al., 2017)

1.6 Clinical implementation of pharmacogenetics

Clinical implementation of pharmacogenetics into daily practise requires integration of genetic test results into electronic health records, and clinical decision support tools to provide patient-specific recommendations for clinicians. (Mukerjee et al., 2018) Various articles highlights the fact that the prescribing professionals are unfamiliar with PGx data and they are not educated to interpret the PGx test results. (Mukerjee et al., 2018; Bank, P. C. D. et al., 2019; Westergaard et al., 2020) Education is recognized to bridge the gap between the clinical reality and PGx prescribing guidelines, and which aspects should be considered regarding the gene test interpretation, genotype-to-phenotype translation, drug-drug interactions and comorbidities. (Just et al., 2019) In addition, engagement of patients is seen as an important factor in clinical implementation as

pharmacogenetics aims to personalised pharmacotherapy, improved adherence to drug therapy and increasing the patient's quality of life. (Mukerjee et al., 2018; Westergaard et al., 2020; Lunenburg et al., 2020)

Of the European countries, the Netherlands has implemented pharmacogenetics as a part of their drug database in electronical health care systems as a result an initiative by the Dutch Pharmacogenetics Working Group (DPWG). (Abdullah-Koolmees et al., 2020) The system gives an alert if it notices an interaction between the patient's genotype and a drug prescribed or dispensed, and informs the clinician for the actions as well as the mechanisms behind the interaction. (Abdullah-Koolmees et al., 2020)

Multiple prospective and large-scale PGx studies are ongoing, of which one of the most relevant is conducted by the Ubiquitous Pharmacogenomics consortium (U-PGx). Funded by the European Commission's Horizon2020 program, they investigate in a controlled clinical trial (PREPARE-study) how pre-emptive gene testing with a panel of clinically relevant PGx-markers would prevent adverse drug reactions. Furthermore, the impact on patient outcomes and cost-effectiveness will be discussed. The U-PGx study is conducted in seven European countries, and they aim to "make effective treatment optimization accessible to every European citizen", according to the study web site. (van der Wouden, C. H. et al., 2017; http://upgx.eu/)

In Finland, pharmacogenetics has been recognised as valuable tool in health care, although a wide implementation is still lacking. (Heliste et al., 2016) Costs related to increased number of pharmacogenetic tests, investments related to providing electronic decision support tools to clinicians and educating health care professionals to become familiar with pharmacogenetics were already 2016 seen as problems to slow the wide-scale clinical implementation. (Heliste et al., 2016) As a solution, Heliste et al., would include pharmacogenetics into national Current Care Guidelines (Käypä Hoito), including pharmacogenetics as a part of education programs for doctors and other health care professionals and that regulatory authorities would require pharmacogenetic data in summaries of product characteristics. They also proposed an interesting idea that reimbursements for medicine expenses would be approved after gene testing.

Currently, the drug database by Duodecim includes a section GeneRx, to which all relevant information concerning pharmacogenetics has been included. The database provides basic information about the phenotypes associated with the drug, how they affect the drug dosing and metabolism, and which tests are recommended. The recommendations are primarily based on the CPIC prescribing guidelines. (https://www.terveysportti.fi/apps/generx/) The main problem is that this information is not included in the electronic decision support systems for doctors to utilize in

prescribing situations. Practise for conducting pharmacogenetic tests is variable and is mainly based on single recommendations. The Current Care Guidelines on treatments related to psychiatric disorders recognises pharmacogenetic aspects important in successful pharmacotherapy (https://www.kaypahoito.fi/en) but the general common practise to utilize pharmacogenetics in prescribing is lacking, although significant attempts for genomic data utilization exists such as the National Genome Strategy (http://julkaisut.valtioneuvosto.fi/handle/10024/74514).

A comprehensive analysis on the current implementation of PGx in the population level and its potential impact on improving health care and its economic consequences is still lacking. This might be the main reason for PGx not being routinely utilized in health care (Bank, P. C. D. et al., 2019; Lunenburg et al., 2020; Westergaard et al., 2020). Also, lack of widely adapted electronic decision support in clinics to utilize PGx information in daily prescribing and dispensing routines slows the clinical implementation (Bank, P. C. D. et al., 2019; Westergaard et al., 2020)

1.7 Unique Finnish genetic heritage

High variation occurs in worldwide distribution of genetic variation in drug metabolizing genes. Polymorphisms especially in genes coding for CYP-enzymes are common and extensively studied (Zhou et al., 2017). Low genetic drift between different ethnic groups and drift occurring mainly between individuals of the same population is the main factor of high interethnic genetic variation in worldwide scale. Demographic history and the germline variations present in individuals being settled in a specific area of the world create a genetic foundation for a population, which still has an impact. (Zhou et al., 2017; Sistonen et al., 2009)

Finnish population represents a well-known genetic isolate, which express a unique genetic makeup due to several population bottlenecks and founder effects. (Jakkula et al., 2008; Sistonen et al., 2009; Varilo, 2016) First colonials arrived from south and south-east soon after the deglaciation of Fennoscandian Peninsula approximately 10,000 years ago. Later came settles from the Baltic region and west-Scandinavia, and the population was concentrated in the south-western and southern coastal parts of the country. The norther, eastern and middle parts of Finland were permanently inhabited relatively lately during the 16th and 17th centuries mainly by internal colonials. As a small number of settlers founded and inhabited each village, genetically and geographically distinct subpopulations were generated. (Jakkula et al., 2008; Sistonen et al., 2009)

Gene mutations occurred in the founder population also generated rare Finnish genetic diseases, which are more prevalent here than in any other parts of the world. Altogether 36 mainly recessively heritable diseases caused by mutations in a single gene have been identified. (Varilo, 2016) Studies conducted with the late generations have revealed the geographic origin of the founder mutations. Moreover, genetic studies have revealed a difference in coronary heart disease mortality between the patients from eastern Finland and western Finland in addition to Y-chromosomal variation. (Jakkula et al., 2008; Sistonen et al., 2009) However, genetics linked to the Finnish heritable diseases are beyond the interest of this study.

Due to the unique genetics, the distribution of particular variants of pharmacogenetically relevant genes differs from other European countries, and differences can be found even when comparing Finnish population with a population of East-Asian or African origin. (Tarkiainen et al., 2021) Due to genetic characteristics, results of the studies conducted with population other than Finnish origin are not entirely applicable with Finnish population.

1.8 Summary

Current knowledge on the topic pharmacogenetics is constantly increasing as the area is widely studied. Significant improvements in pharmacotherapy are recognized to be able to achieve by utilizing pharmacogenetic knowledge and patient-specific pharmacogenetic test results. Educating professionals to interpret the PGx test results and implement them into daily prescribing habits has been seen crucial. Up-to-date electronical health records and clinical decision support tools are recognised important factors as well as the patient engagement to obtain safe, effective, and personalized pharmacotherapy. Cost-effectiveness of pharmacogenetic testing requires additional studies to which this study or similar studies provide basic information to be further utilized.

1.9 Aims of the study

The purpose of this retrospective, register-based pharmacoepidemiologic study was to analyse the post-discharge purchases of drugs with an actionable pharmacogenetics-based prescribing guideline compiled and made available by the Clinical Pharmacogenetics Implementation Consortium (CPIC) in a patient cohort consisting of Finnish hospital patients. The aim was to produce data to evaluate the potential impact of introduction of wide-scale (pre-emptive) pharmacogenetic testing in Finnish health care.

The main hypothesis was that the drugs included into this study would be frequently used, which should have been seen in number of post-discharge drug purchases. Drug purchase frequency might be explained by patient group-specific factors and national treatment recommendations. Differences in post-discharge drug purchases between the patient groups included were studied.

Additionally, the hypothesis was that generally the most relevant pharmacogenes, such as CYP-genes equals with the most relevant pharmacogenes in this patient cohort. It was studied, which genes the drug purchases were associated to and which are pharmacogenetically the most relevant phenotypes in Finnish population by combining the Finnish phenotype frequencies with the drug incidence data and actionable prescribing recommendations.

Based on these results, it was discussed whether it is possible to define a group of patients clearly benefiting from (pre-emptive) pharmacogenetic testing. Generally, it might be difficult to define exact criteria for the patient population and the current practise on pharmacogenetic testing is rather complex as there is need for reactive testing but clear benefits for both the patient and the society have been found with pre-emptive testing in intervention trials and attempts to implement PGx testing into clinics.

2. Results

2.1 Patient cohort

Total number of hospitalised patients meeting eligibility criteria was 1.42 million, half of them being men and 70% of them being discharged from surgical units. The median age of the patients was 59 years. Demographic details of the patient cohort can be found in the Table 2.

Table 2. Demographic details of the patient cohort

	Number of patients	**Proportion of total n (%)**
Total	1 425 263	100
- **men**	715 934	50.23
- **women**	709 329	49.77
Age – 18 – 24 yrs.	77 337	5.43
- **25 – 44 yrs.**	265 197	18.61
- **45 – 64 yrs.**	530 660	37.23
- **65 – 80 yrs.**	391 916	27.50
- **80 – yrs.**	160 153	11.24
Patient distribution between units*		
- **internal medicine**	431 092	30.25
- **surgical**	994 171	69.75

*) This was the first qualifying hospital admission, which initiated the following as described in the Methods.

2.2 Study drugs

Altogether 33 unique drugs meeting eligibility criteria were identified from the CPIC prescribing recommendations. The drugs were related to five different drug-metabolizing CYP-genes, four other pharmacokinetic genes, one gene encoding a pharmacological drug target and three HLA-alleles associated with adverse drug reactions. Drugs with their respective genes or gene alleles are listed in the Figure 3. Note that a particular drug can appear in multiple boxes when associated with several genes.

Figure 3. Drugs of interest in this study with each of their associated genes and HLA-alleles. Warfarin-associated CYP4F2 marked in parenthesis is not included in actual analyses but the CPIC recommendation for the gene is to be found in the table in the Appendix part of the thesis.

2.3 Prevalence, incidence, CPIC recommendations and Finnish phenotype frequencies

Drug purchases 180 days before the initiative hospital admission were noted in prevalence rate calculations to describe the active drug use at the moment of hospital admission. The prevalence rates varied from <0.1% to 14.6% proportionated in the total population. Drugs such as atomoxetine, fluvoxamine, mercaptopurine and trimipramine had the lowest prevalence rates (<0.1%). Drugs such as codeine, ibuprofen, pantoprazole, simvastatin and warfarin had the highest prevalence rates, varying from 6.6% for both codeine and warfarin to 14.6% for simvastatin. No drug purchases before the initiative hospital admission were detected for thioguanine, and prevalence rate for tamoxifen was not available.

Drug purchases during 2-year follow-up were noted in incidence rate calculations. The incidence rate varied from <0.1% to 25.0%, being lowest for drugs such as atomoxetine, fluvoxamine, mercaptopurine and tacrolimus (<0.1%) and highest for codeine (19.4%), ibuprofen (25.0%), pantoprazole (12.5%), simvastatin (5.9%) and warfarin (5.4%). No new drug initiations were detected for piroxicam.

Finnish phenotype frequencies retrieved from literature references or from the SISU-database varied for each gene or HLA-allele. Regarding the phenotypes categorized as actionable, the frequencies of actionable phenotypes in Finnish population varied from 0.27% for *HLA-B*58:01* associated with allopurinol to 63% for *VKORC1* associated with warfarin. Phenotype frequency of *HLA-B*15:02* was not found for Finnish population as the allele is extremely rare in Finland. Drug purchases over 1% of the total study population, which were estimated to be associated with an actionable phenotype were of clopidogrel, codeine, ibuprofen, meloxicam, simvastatin and warfarin in 2-year follow-up.

Prevalence and incidence rates of drug purchases, a symbol indicating the content of CPIC recommendation, actionability of the recommendations, the Finnish phenotype frequencies reported in the literature and a calculated prediction of new drug initiations for each phenotype were assembled into Table 3 below. The full CPIC recommendations were truncated in the table but the main details of the recommendations can be found in the Appendices of this thesis and the full recommendations in the original CPIC publications (https://cpicpgx.org/).

It is to be noted that a single drug can appear more than one time in the table if it is associated with multiple genes or alleles. Both the prevalence and the incidence rates, as well as the predicted number of new drug initiations for each phenotype were proportionated to the total number of study participants to allow comparison of impact on population level.

Table 3. Prevalence and incidence of the drug purchases for each gene or allele and the predicted number of new drug initiations for each phenotype in 2-year follow up

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Allopurinol	HLA-B*58:01	31415 (2,2 %)	23563 (1,7 %)	HLA-B*58:01 positive/ allele carrier	●	0,27 %	64 (<0,1%)
(Ref. 5)				HLA-B*58:01 negative/ non-carrier	□	99,73 %	23499 (1,6 %)
Amitriptyline	CYP2D6	22529 (1,6 %)	16054 (1,1 %)	UM (AS >2.25)	● (or ▲)	7,00 %	1124 (<0,1 %)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	9953 (0,7 %)
				IM (AS >0 - <1.25)	▼	29,00 %	4656 (0,3 %)
				PM (AS 0)	● (or ▼)	3,00 %	482 (<0,1 %)
Amitriptyline	CYP2C19	22529 (1,6 %)	16054 (1,1 %)	UM and RM	● (or ▲)	26,00 %	4174 (0,3 %)
(Ref. 3)				NM	□	33,00 %	5298 (0,4 %)
				IM	□	36,00 %	5779 (0,4 %)
				PM	● (or ▼)	5,00 %	803 (<0,1%)
Atomoxetine	CYP2D6	17 (<0,1%)	28 (<0,1%)	UM (AS >2.25)	□	7,00 %	2 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	17 (<0,1%)
				IM (AS 1)	□	29,00 %	8 (<0,1%)
				IM (AS 0.25-0.75)	»		
				PM (AS 0)	»	3,00 %	1 (<0,1%)
Azathioprine	NUDT15	5790 (0,4 %)	5501 (0,4 %)	NM	□	96,30 %	5297 (0.4%)
(Ref. 2)				IM or possible IM	▼	3,60 %	198 (<0,1%)
				PM	▼	0,10 %	6 (<0,1%)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Azathioprine	TPMT	5790 (0,4 %)	5501 (0,4 %)	NM	□	93,10 %	5121 (0,4 %)
(Ref. 1)				IM or possible IM	▼	6,80 %	374 (<0,1%)
				PM	▼	0,10 %	6 (<0,1%)
Capecitabine	DPYD	1843 (0,1 %)	9267 (0,7 %	NM (AS 2)	□	92,20 %	8544 (0,6 %)
(Ref. 1)				IM (AS 1.5)	▼	7,70 %	714 (<0,1%)
				IM (AS 1)	▼		
				PM (AS 0.5)	● or ▼	0,14 %	13 (<0,1%)
				PM (AS 0)	●		
Carbamazepine	HLA-B*15:02	10316 (0,7 %)	4206 (0,3 %	HLA-B*15:02 positive/ allele carrier	●	N/A	
(Ref. 3)				HLA-B*15:02 negative/ non-carrier	□	N/A	
Carbamazepine	HLA-A*31:01	10316 (0,7 %)	4206 (0,3 %)	HLA-A*31:01 positive/ allele carrier	●	3,50 %	147 (<0,1%)
(Ref. 5)				HLA-A*31:01 negative/ non-carrier	□	96,50 %	4059 (0,30 %)
Celecoxib	CYP2C9	9299 (0,7 %)	13109 (0,9 %)	NM (AS 2)	□	67,00 %	8783 (0,6 %)
(Ref. 3)				IM (AS 1.5)	□	30,00 %	3933 (0,3 %)
				IM (AS 1.0)	▼		
				PM (AS 0 - 0.5)	▼ or ●	3,00 %	393 (<0,1%)
Citalopram	CYP2C19	42005 (2,9 %)	26786 (1,9 %)	UM	●	26,00 %	6964 (0,5 %)
(Ref. 3)				EM	□	33,00 %	8839 (0,6 %)
				IM	□	36,00 %	9643 (0,7 %)
				PM	▼ or ●	5,00 %	1339 (<0,1%)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Clomipramine	CYP2D6	833 (<0,1%)	340 (<0,1%)	UM (AS >2.25)	● (or ▲)	7,00 %	24 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	211 (<0,1%)
				IM (AS >0 - <1.25)	▼	29,00 %	99 (<0,1%)
				PM (AS 0)	● (or ▼)	3,00 %	10 (<0,1%)
Clomipramine	CYP2C19	833 (<0,1%)	340 (<0,1%)	UM and RM	● (or ▲)	26,00 %	88 (<0,1%)
(Ref. 3)				NM	□	33,00 %	112 (<0,1%)
				IM	□	36,00 %	122 (<0,1%)
				PM	● (or ▼)	5,00 %	17 (<0,1%)
Clopidogrel	CYP2C19	12403 (0,9 %)	58690 (4,1 %)	UM	□	26,00 %	15259 (1,1 %)
(Ref. 3)				EM	□	33,00 %	19368 (1,4 %)
				IM	●	36,00 %	21128 (1,5 %)
				PM	●	5,00 %	2935 (0,2 %)
Codeine	CYP2D6	94609 (6,6 %)	275979 (19,4 %)	UM (AS > 2.25)	●	7,00 %	19319 (1,4 %)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	171107 (12,0 %)
				IM (AS >0 - <1.25)	□	29,00 %	80034 (5,6 %)
				PM (AS 0)	●	3,00 %	8279 (0,6 %)
Doxepine	CYP2D6	4453 (0,3 %)	2470 (0,2 %)	UM (AS >2.25)	● (or ▲)	7,00 %	173 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	1531 (0,1 %)
				IM (AS >0 - <1.25)	▼	29,00 %	716 (<0,1%)
				PM (AS 0)	● (or ▼)	3,00 %	74 (<0,1%)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Doxepine	CYP2C19	4453 (0,3 %)	2470 (0,2 %)	UM and RM	● (or ▲)	26,00 %	642 (<0,1%)
(Ref. 3)				NM	□	33,00 %	815 (<0,1%)
				IM	□	36,00 %	889 (<0,1%)
				PM	● (or ▼)	5,00 %	124 (<0,1%)
Escitalopram	CYP2C19	28680 (2,0 %)	31095 (2,2 %)	UM	●	26,00 %	8085 (0,6 %)
(Ref. 3)				EM	□	33,00 %	10261 (0,7 %)
				IM	□	36,00 %	11194 (0,8 %)
				PM	▼ or ●	5,00 %	1555 (0,1 %)
Fluvoxamine	CYP2D6	887 (<0,1%)	286 (<0,1%)	UM (AS >2.25)	—	7,00 %	20 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	177 (<0,1%)
				IM (AS >0 - <1.25)	□	29,00 %	83 (<0,1%)
				PM (AS 0)	▼ or ●	3,00 %	9 (<0,1%)
Ibuprofen	CYP2C9	201320 (14,1 %)	356925 (25,0 %)	NM (AS 2)	□	67,00 %	239140 (16,8 %)
(Ref. 3)				IM (AS 1.5)	□	30,00 %	107078 (7,5 %)
				IM (AS 1.0)	▼		
				PM (AS 0 - 0.5)	▼ or ●	3,00 %	10708 (0,8 %)
Lansoprazole	CYP2C19	55121 (3,9 %)	58922 (4,1 %)	UM	▲	4,00 %	2357 (0,2 %)
(Ref. 3)				RM	□	22,00 %	12963 (0,9 %)
				NM	□	33,00 %	19444 (1,4 %)
				IM and likely IM	□	36,00 %	21212 (1,5 %)
				PM and likely poor	□	5,00 %	2946 (0,2 %)
Meloxicam	CYP2C9	28260 (2,0%)	43680 (3,0%)	NM (AS 2)	□	67,00 %	29266 (2,1 %)
(Ref. 3)				IM (AS 1.5)	□	30,00 %	13104 (0,9 %)
				IM (AS 1.0)	▼ or ●		
				PM (AS 0 - 0.5)	●	3,00 %	1310 (0,1 %)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Mercaptopurine	NUDT15	259 (<0,1%)	907 (<0,1%)	NM	□	96,30 %	873 (<0,1%)
(Ref. 2)				IM or possible IM	▼	3,60 %	33 (<0,1%)
				PM	▼	0,10 %	1 (<0,1%)
Mercaptopurine	TPMT	259 (<0,1%)	907 (<0,1%)	NM	□	93,10 %	844 (<0,1 %)
(Ref. 1)				IM or possible IM	▼	6,80 %	62 (<0,1 %)
				PM	▼	0,10 %	1 (<0,1 %)
Nortriptyline	CYP2D6	1046 (<0,1%)	1545 (0,1%)	UM (AS >2.25)	● (or ▲)	7,00 %	108 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	958 (<0,1%)
				IM (AS >0 - <1.25)	▼	29,00 %	448 (<0,1%)
				PM (AS 0)	● (or ▼)	3,00 %	46 (<0,1%)
Omeprazole	CYP2C19	32745 (2,3 %)	59117 (4,1 %)	UM	▲	4,00 %	2365 (0,2 %)
(Ref. 3)				RM	□	22,00 %	13006 (0,9 %)
				NM	□	33,00 %	19509 (1,4 %)
				IM and likely IM	□	36,00 %	21282 (1,5 %)
				PM and likely poor	□	5,00 %	2956 (0,2 %)
Oxcarbazepine	HLA-B*15:02	5688 (0,4 %)	3475 (0,2 %)	HLA-B*15:02 positive/ allele carrier	●	N/A	
(Ref. 3)				HLA-B*15:02 negative/ non-carrier	□	N/A	
Pantoprazole	CYP2C19	100569 (7,1 %)	178195 (12,5 %)	UM	▲	4,00 %	7128 (0,5 %)
(Ref. 3)				RM	□	22,00 %	39203 (2,8 %)
				NM	□	33,00 %	58804 (4,1 %)
				IM and likely IM	□	36,00 %	64150 (4,5 %)
				PM and likely poor	□	5,00 %	8910 (0,6 %)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Paroxetine	CYP2D6	5193 (0,4 %)	2316 (0,2 %)	UM (AS >2.25)	●	7,00 %	162 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	1436 (0,1%)
				IM (AS >0 - <1.25)	□	29,00 %	672 (<0,1%)
				PM (AS 0)	● (or ▼)	3,00 %	69 (<0,1%)
Phenytoin	HLA-B*15:02	1939 (0,1 %)	1323 (0,1 %)	HLA-B*15:02 positive/ allele carrier	●	N/A	
(Ref. 3)				HLA-B*15:02 negative/ non-carrier	□	N/A	
Phenytoin	CYP2C9	1939 (0,1 %)	1323 (0,1 %)	NM, AS 2	□	67,00 %	886 (<0,1%)
(Ref. 3)				IM, AS 1.5	□	30,00 %	397 (<0,1%)
				IM, AS 1.0	▼		
				PM, AS 0.5	▼		
				PM, AS 0	▼	3,00 %	40 (<0,1%)
Piroxicam	CYP2C9	100 (<0,1%)	not any new drug initiations detected	NM	□	67,00%	N/A
(Ref. 3)				IM, AS 1.5	□	30,00%	N/A
				IM, AS 1.0	●		
				PM	●	3,00%	N/A
Sertraline	CYP2C19	9558 (0,7 %)	7944 (0,6 %)	UM	□	26,00 %	2065 (0,1 %)
(Ref. 3)				EM	□	33,00 %	2622 (0,2 %)
				IM	□	36,00 %	2860 (0,2 %)
				PM	▼ or ●	5,00 %	397 (<0,1%)
Simvastatin	SLCO1B1	208416 (14,6 %)	83632 (5,9 %)	normal function	□	60,00 %	50179 (3,5 %)
(Ref. 3)				intermediate function	▼ or ●	35,00 %	29271 (2,1 %)
				low function	▼ or ●	5,00 %	4182 (0,3 %)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Tacrolimus	CYP3A5	485 (<0,1%)	590 (<0,1%)	EM (CYP3A5 expresser)	▲	0,50 %	3 (<0,1%)
(Ref. 3)				IM (CYP3A5 expresser)	▲	13,00 %	77 (<0,1%)
				PM (CYP3A5 nonexpresser)	□	86,00 %	507 (<0,1%)
Tamoxifen	CYP2D6	Not available	8180 (0,6 %)	UM (AS > 2.25)	□	7,00 %	573 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	5072 (0,4 %)
				IM (AS >0,25-<1.25)	● (or ▲)	29,00 %	2372 (0,2 %)
				PM (AS 0)	● (or ▲)	3,00 %	245 (<0,1%)
Thioguanine	NUDT15	0 (0 %)	2 (<0,1%)	NM	□	96,30 %	2 (<0,1%)
(Ref. 2)				IM or possible IM	▼	3,60 %	0 (<0,1%)
				PM	▼	0,10 %	0 (<0,1%)
Thioguanine	TPMT	0 (0 %)	2 (<0,1%)	NM	□	93,10 %	2 (<0,1%)
(Ref. 1)				IM or possible IM	▼	6,80 %	0 (<0,1%)
				PM	▼	0,10 %	0 (<0,1%)
Trimipramine	CYP2D6	1198 (<0,1%)	864 (<0,1%)	UM (AS >2.25)	● (or ▲)	7,00 %	60 (<0,1%)
(Ref. 3)				NM (AS >1.25 - <2.25)	□	62,00 %	536 (<0,1%)
				IM (AS >0 - <1.25)	▼	29,00 %	251 (<0,1%)
				PM (AS 0)	● (or ▼)	3,00 %	26 (<0,1%)
Trimipramine	CYP2C19	1198 (<0,1%)	864 (<0,1%)	UM and RM	● (or ▲)	26,00 %	225 (<0,1%)
(Ref. 3)				NM	□	33,00 %	285 (<0,1%)
				IM	□	36,00 %	311 (<0,1%)
				PM	● (or ▼)	5,00 %	43 (<0,1%)

Drug	Gene	Prevalence (% of total n)	Incidence in 2-year follow-up (% of total n)	Phenotype (+ AS if relevant)	CPIC recommendation + actionable/non-actionable	Phenotype frequency in Finnish population	Predicted number of drug users (% of total n)
Voriconazole	CYP2C19	25 (<0,1%)	283 (<0,1%)	UM	●	4,00 %	11 (<0,1%)
(Ref. 3)				RM	●	22,00 %	62 (<0,1%)
				NM	□	33,00 %	93 (<0,1%)
				IM	□	36,00 %	102 (<0,1%)
				PM	● or ▼	5,00 %	14 (<0,1%)
Warfarin	CYP2C9	94151 (6,6 %)	77234 (5,4 %)	NM (AS 2) Non-African *1	□	67,00 %	51747 (3,6 %)
(Ref. 3)				IM (AS 1 - 1.5) Non-African *2	▼	30,00 %	23170 (1,6 %)
				PM (AS 0 - 0.5) Non-African *3	▼	3,00 %	2317 (0,2 %)
Warfarin	VKORC1	94151 (6,6 %)	772347 (5,4 %)	NM, Non-African 1639G/G	□	37,00 %	28577 (2,0 %)
(Ref. 3)				IM, Non-African 1639G/A	▼	48,00 %	37072 (2,6 %)
				PM, Non-African 1639A/A	▼	15,00 %	11585 (0,8 %)

AS = activity score, N/A = not applicable, symbols: dose increase ▲ , dose decrease ▼ compared to normal dosing strategy, alternative drug recommended/drug contraindicated ●, normal starting dose/no specific actions needed □, no recommendation due to lack of evidence ▬, slower dose increase/titration to therapeutic level », recommendation in parenthesis as a secondary option and requiring specific monitoring. Red indicates actionable and green non-actionable recommendations. Phenotype frequency references: 1) Zhou et al, 2020; 2) Häkkinen et al., preprint 2020; 3) Tarkiainen et al., 2021; 4) SISU-database http://www.sisuproject.fi/; 5) Haimila et al., 2013

2.4 New drug initiations for associated genes and HLA-alleles of interest

Following graphical visualization (Figure 4) shows the post-discharge drug purchases associated to genes and HLA-alleles of interest. The whole study period of 2008-2016 was considered. When associated with several genes, the drug purchase was considered in analyses of every associated gene. Note, that *CYP4F2* associated with warfarin is not included here but its proportion is the same as another warfarin-associated gene, *VKORC1*.

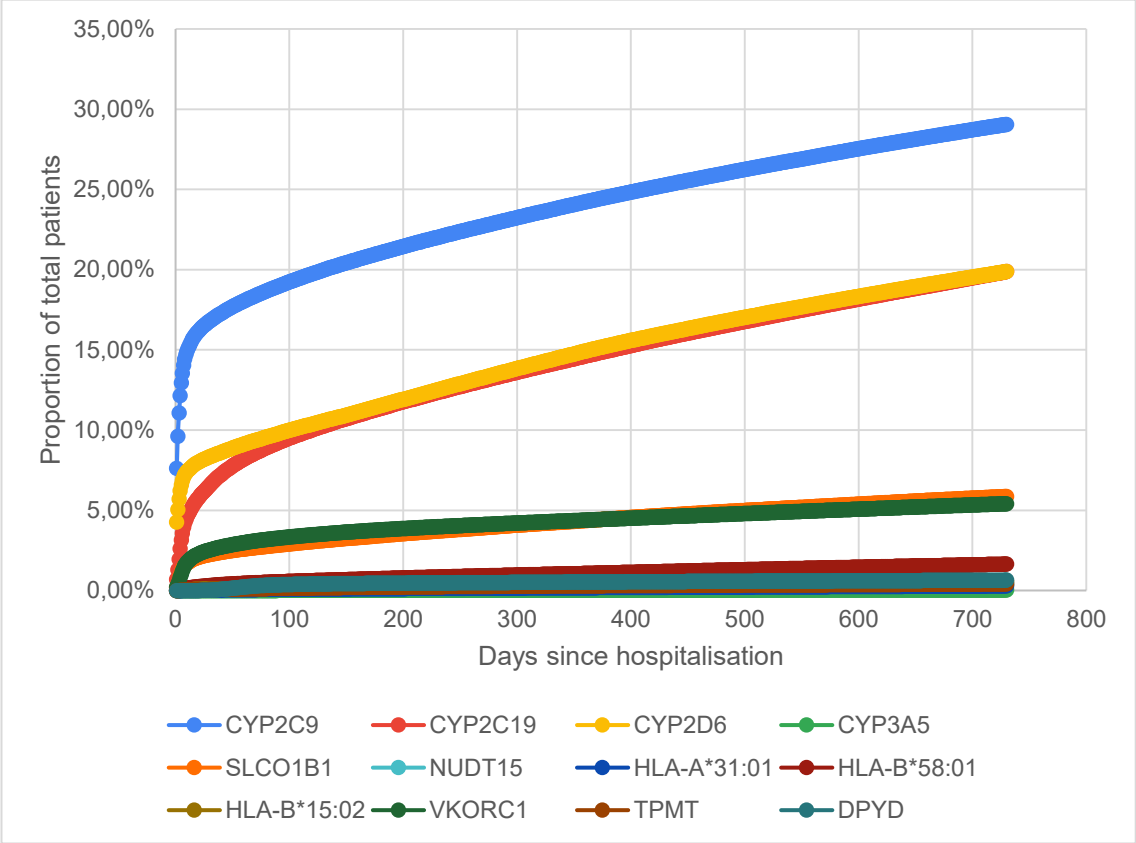

Figure 4. Post-discharge drug purchases associated to genes and HLA-alleles of interest during the whole study period 2008-2016 (730 days). X-axis shows the days since hospitalisation and y-axis the proportion of patients of total number of patients, whose drug purchase were associated to the gene or HLA-allele of interest.

2.5 Drugs purchased in 2-year follow-up

Of the drugs included into this study, ten of the most frequently purchased drugs in 2-year follow-up included common analgesics, proton pump inhibitors, a cholesterol-lowering drug, an anticoagulant drug, an antiplatelet drug and a selective serotonin reuptake inhibitor. (Figure 5).

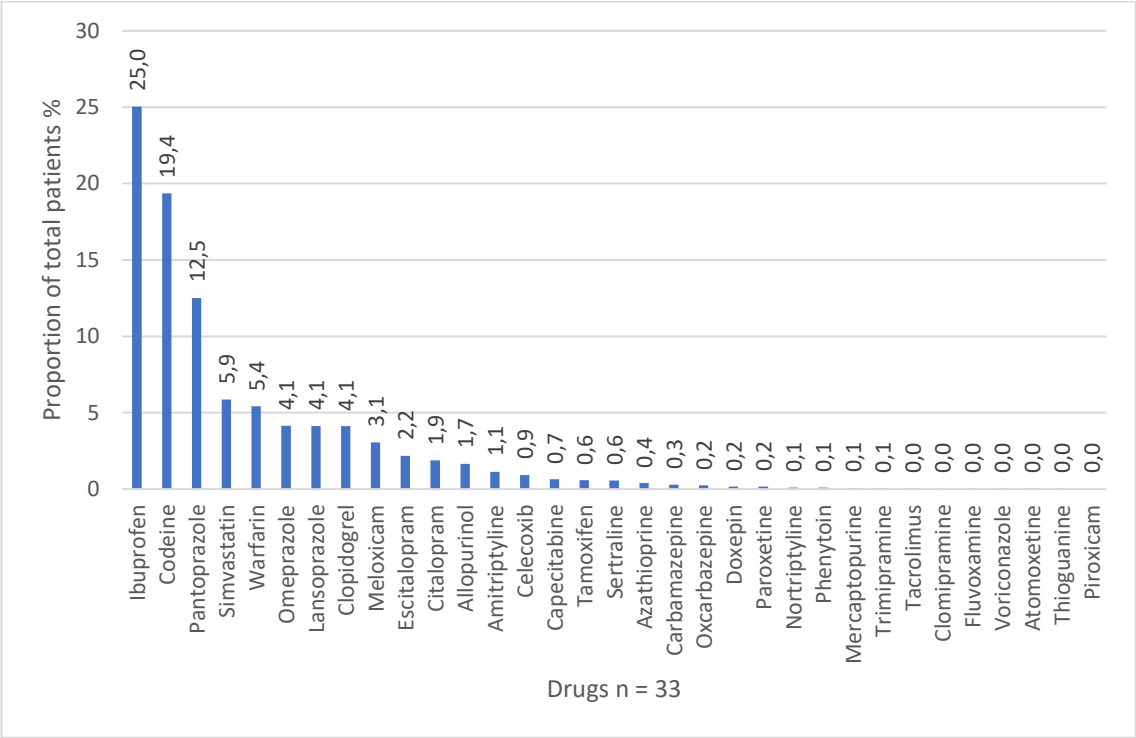

Figure 5. New drug initiations in 2-year follow-up from most used to less used (x-axis) proportionated in total patients (y-axis). A digit above each of the bars represents the proportion of patients in % initiated the drug.

2.6 Cumulative account of post-discharge drug purchases

Results showed that in 1-year follow up, 51% of patients (n=722194 patients) purchased at least one of the drugs of the interest (Figure 6). The amount of patients increased in 2-year follow-up, when 60% of patients (n=860449 patients) initiated at least one of the drugs of interest. Patients buying ≥ 5 drugs was relatively rare but occurred even up to 9 single drugs for a few patients (n=4).

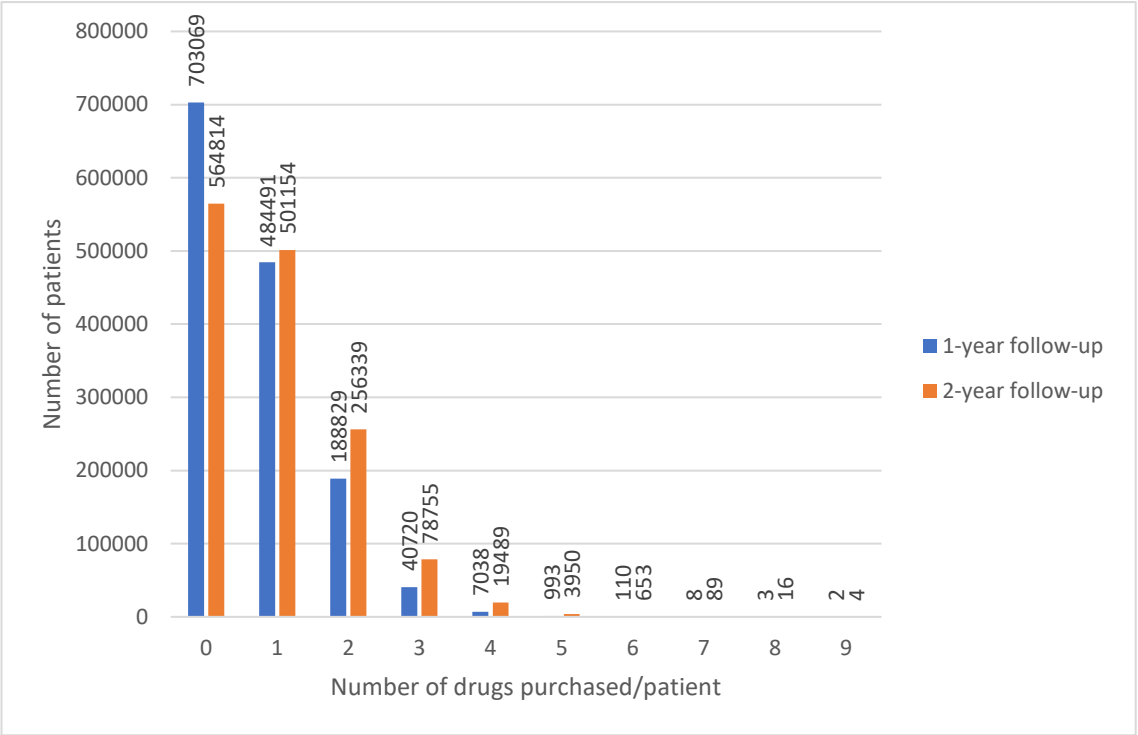

Figure 6. Number of drugs purchased per patient in 1-year (blue bars) and 2-year follow up (orange bars). Number of drugs in x-axis (n=0-9) and number of patients in y-axis.

In this study, the number of different genes associated to overall number of post-discharge drug purchases for a patient were calculated. Results showed that 22% of the study population (311318 patients) purchased drugs associated with ≥ 2 different genes (Figure 7). Drug purchases associated with ≥4 genes were rare but occurred even up to 7 associated genes for a patient.

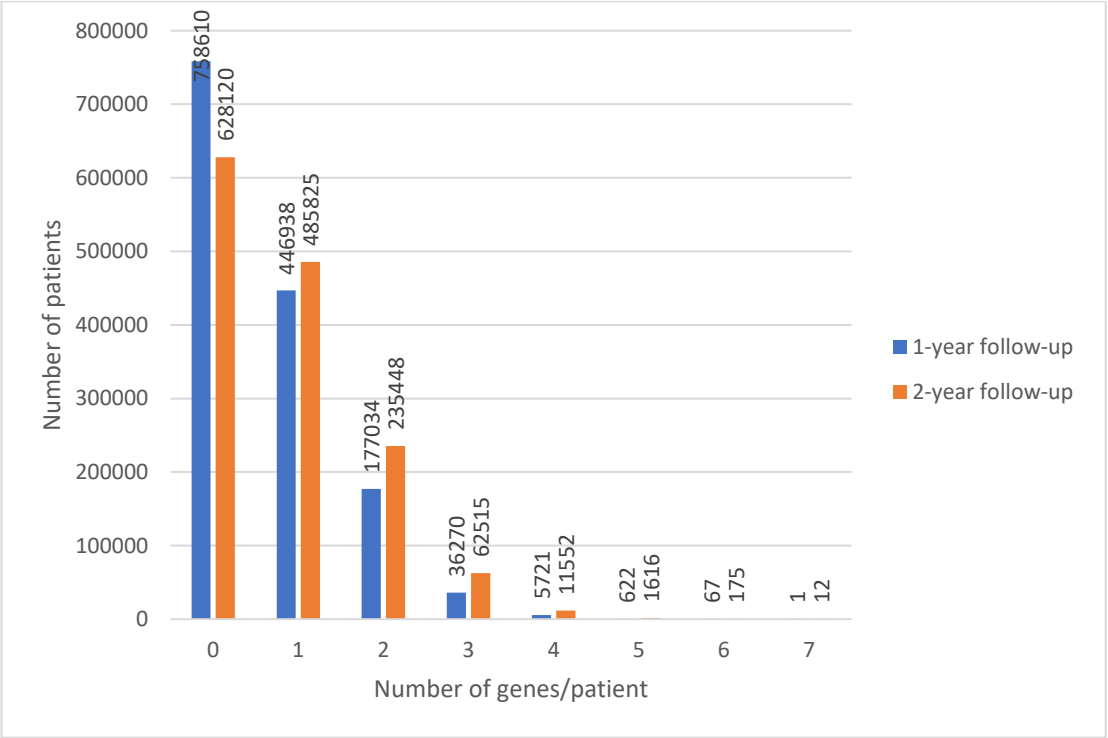

Figure 7. Drug purchases associated to the number of genes in 1-year and 2-year follow-up

2.7 Cox regression analysis

Table 4 shows the Cox regression analysis model results with p-values, hazard ratios and confidence interval with 95% range. In case the hazard ratio (HR) is above 1, the surgical unit patients have a higher risk for drug purchase, while HR being under 1, the risk for a drug purchase is higher in patients discharged from the internal medicine unit. The Cox regression model showed that patients being discharged from the surgical unit had an overall greater probability to purchase any of the study drugs compared to patients discharged from the internal medicine unit (hazard

ratio 1.23, 95% confidence interval 1.22-1.23). Analysing single genes separately, the results indicate that surgical unit patients had a greater probability to purchase a drug metabolized by *CYP2C9* (HR 1.66, 95% CI 1.65-1.67), *CYP2D6* (HR 1.54, 95% CI 1.53-1.55) and *DPYD* (HR 2.32, 95% CI 2.21-2.43).

Table 4. Cox regression univariate analysis on proportional risk for drug purchase, patients discharged from the internal medicine unit vs. patients discharged from the surgical unit

Gene	HR*	95% CI** low	95% CI high	P-value
any/all combined	1.23	1.22	1.23	<.0001
CYP2C19	0.64	0.63	0.64	<.0001
CYP2C9	1.66	1.65	1.67	<.0001
CYP2D6	1.54	1.53	1.55	<.0001
CYP3A5	0.25	0.22	0.28	<.0001
DPYD	2.32	2.21	2.43	<.0001
NUDT15	0.32	0.31	0.34	<.0001
TPMT	0.32	0.31	0.34	<.0001
SLCO1B1	0.41	0.41	0.42	<.0001
VKORC1	0.28	0.28	0.28	<.0001
HLA-A*31:01	0.88	0.84	0.92	<.0001
HLA-B*15:02	0.83	0.80	0.86	<.0001
HLA-B*58:01	0.46	0.45	0.46	<.0001

*HR = hazard ratio, **CI = confidence interval

3. Discussion

The primary aim of this study was to produce data to evaluate the potential impact of introduction of wide-scale (pre-emptive) pharmacogenetic testing in Finnish health care. The main hypothesis was that the drugs included into this study would be frequently used, which should have been seen in number of post-discharge drug purchases. It was studied to which genes the drug purchases of this study cohort were associated with and the results were compared to the most relevant pharmacogenes in general. Possible differences in post-discharge drug purchases between the patient groups included were shortly studied.

3.1 Drug use of the patient cohort

The drugs of interest were identified from the CPIC recommendations represents commonly used drugs from several pharmacological groups; analgesics, anticonvulsants, antidepressants, immunosuppressants, antineoplastics and drugs for cardiovascular and gastrointestinal diseases in addition to singular drugs from selective norepinephrine reuptake inhibitors, antigout and antimycotic drug groups (Figure 3). Of these ten of the most frequently initiated drugs were ibuprofen, codeine, pantoprazole, simvastatin, warfarin, omeprazole, lansoprazole, clopidogrel, meloxicam and escitalopram (Figure 5). Drugs with a lower incidence rate represent drugs, which were expected to be less used, such as tricyclic antidepressants (e.g., trimipramine and clomipramine), immunosuppressants (e.g., mercaptopurine and thioguanine) and a selective norepinephrine reuptake inhibitor atomoxetine. Marketing authorisation of oral piroxicam was terminated during the study years, and no new drug initiations of piroxicam was seen. This verifies our hypothesis that the drugs of interest are widely used and represent various drug categories. The results were expected and any surprisingly high or low incidence rates of the drugs were not seen.

Most of the drugs (25 out of 33) are related to the CYP450-system and therefore genetic polymorphism of genes coding CYP-enzymes affects their dosing (Figure 3). In addition to CYP-genes, four other pharmacokinetic genes, one gene encoding a pharmacological drug target and three HLA-alleles altering to susceptibility to adverse effects were included.

Most frequently the drug purchases were associated with genes CYP2C9, CYP2D6 and CYP2C19 (Figure 4). Low number of drug initiations were associated with genes *CYP3A5, NUDT15, TPMT, DPYD* and HLA-alleles *HLA-A*31:01, HLA-B*15:02* and *HLA-B*58:01*. Differences in incidence

rates related to the genes can be explained by the number of drugs associated to each of the genes and differences in incidence rates of these drugs.

Of the most used drugs a clear need for post-operative pain management explains the high incidence rate of ibuprofen, codeine, meloxicam and celecoxib. High incidence rate of simvastatin, clopidogrel and warfarin might be explained by the diagnoses of the patients discharged from the internal medicine unit. Both are indicated to treat conditions related to cardiovascular diseases, which are typical diagnoses of the patients in the internal medicine unit. If more recent drug purchase data would have been available, the incidence rates for clopidogrel and warfarin would highly like have been lower as the current common practise recommends prescribing of novel drugs such as apixaban or dabigatran instead of clopidogrel or warfarin.

High incidence rates for each of the proton pump inhibitors involved (pantoprazole, lansoprazole and omeprazole) might be explained by the indications strongly linked to the conditions treated in internal medicine unit. On the other hand, a proton pump inhibitor can be used in a combination with a NSAID-drug to prevent NSAID-induced ulcers. NSAID-drugs being frequently used in this population might lead to higher incidence rates for proton pump inhibitors used for this indication.

Factors explaining low incidence rates for drugs such as tricyclic antidepressants, immunosuppressants, voriconazole and anticonvulsants might be the patients-specific factors such as the diagnoses of the patients and common practises to prescribe drugs. For example, the use of tricyclic antidepressants is relatively low as novel antidepressants have accessed the markets. Low number of drug purchases of atomoxetine might be explained by the fact that the drug is not the primary alternative in the treatment of adulthood ADHD and the number of patients having an adulthood ADHD is relatively low. Patient cohort of this study consists only adult patients, which highly likely explains the low rate of new drug initiations.

Prevalence was calculated for each of the study drugs to describe the active drug use at the moment of hospital admission in 180 days before the initiative hospital admission (Table 3). Typically, the prevalence rate correlates with the incidence rate. If the prevalence of a drug was low, the incidence was low as well, although in general, the incidence rate was slightly higher than the prevalence rate for a drug. The most significant differences between the prevalence and incidence rates are in codeine (prevalence 6.6%, incidence 19.4%) and ibuprofen (prevalence 14.1%, incidence 25.0%) which clearly indicates the need of post-operative pain management after discharge from surgical units. Moreover, prevalence and incidence differ from each other also in pantoprazole and clopidogrel (pantoprazole prevalence 7.1%, incidence 12.5%, clopidogrel 0.9% and 4.1%, respectively), which are generally common drugs to initiate during inpatient care. For

simvastatin and warfarin, the incidence rate was lower than prevalence rate (simvastatin prevalence 14.6%, incidence 5.9%, warfarin 6.6.% and 5.4%, respectively), which are commonly initiated drugs in both inpatient care and outpatient care.

Drugs identified for this study were similar with other pharmacoepidemiologic register studies with rather similar or otherwise comparable study setting (Lunenburg et al., 2020; Alshabeeb et al., 2019; McInnes et al., 2020; Westergaard et al., 2020) Differences are explained by the reference prescribing guidelines used, availability of the drugs, and which drugs the researches have seen relevant to include in their study. In addition, McInnes et al., were able to utilize biobank data in their study. In these studies, it was estimated that approximately 23-25% of the study population had an actionable phenotype. This was not possible to simply calculate in this study as we did not have the individual level drug purchases available and drug purchases were registered in each of their associated genes or alleles leading to purchase duplications.

A cumulative account of the post-discharge drug purchases showed that in 2-year follow up 60% of the total population initiated at least one of the study drugs (Figure 6). Should the patient have an actionable phenotype associated to the drug purchase, the drug initiation would have been pharmacogenetically actionable. It would have been interesting to know how many of these patients had an actionable phenotype requiring either dose increase or decrease or an alternative drug but unfortunately such data was not available.

The post-discharge drug purchases associated with the number of different genes for a patient showed that purchases of 56% of the population was associated with at least one of the genes of interest (Figure 7). In this analysis, each drug purchase was registered in each of its associated genes.

Both cumulative analyses show that the drugs were frequently used by the majority of the patients. A great number of patients purchased several drugs of interest during the follow-up and the drug purchases were associated in multiple different genes in significant number of the patients. This indicates that majority of the patients were polypharmacy patients. In addition, it is to be noted that this does not represent all the drugs in use for a patient and the number of drugs in use is higher in reality. This leads to more complicated situation as there is a high likelihood to drug-gene interactions, drug-drug interactions and even phenoconversion.

3.2 Cox regression analysis results

One of the aims of this study was to examine the differences in post-discharge drug purchases between patients discharged from surgical unit with patients discharged from internal medicine unit in Cox proportional-hazards model adjusted for type of the hospital unit (Table 4). Based on the results, patients being discharged from the surgical unit had a greater probability to initiate new drug therapy associated with genes *CYP2C9, CYP2D6* and *DPYD*, which might lead to the overall greater probability to drug purchases than patients discharged from the internal medicine unit. Frequently purchased analgesics ibuprofen and codeine associated with genes *CYP2C9* and *CYP2D6* definitely explain the majority of the results. Also, warfarin and meloxicam, both in ten most frequently purchased drugs, associated with *CYP2C9* have an impact on the probability. The use of analgesics is highlighted in this study population, which can be thought to give a reason for pre-emptive PGx testing to achieve sufficient post-surgery pain management. For warfarin, specific dosing algorithms are already in use, which include both clinical and genetic factors to determine individual drug dose.

Antineoplastic capecitabine is the only drug associated with the gene *DPYD* in this study. A factor explaining the greater probability to initiate capecitabine after discharge from surgical unit might be that it is used for the adjuvant treatment of patients following surgery of stage III colon cancer according to the summary of product characteristics of Xeloda (one of the brand names of capecitabine) (https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf). In April 2020 the European Medicines Agency (EMA) published a recommendation to test patients for the lack of enzyme dihydropyrimidine dehydrogenase (DPD) encoded by gene *DPYD* before initiating fluorouracil or fluorouracil-related drug treatment. Patients suffering from complete lack of DPD cannot utilize pharmacotherapy such as capecitabine, which is an orally administered precursor of 5-fluorouracil. In partial DPD deficiency, diminished capecitabine doses should be used. Patients having a complete or partial DPD deficiency are at increased risk for fatal or life-threatening fluoropyrimidine-related toxicity, such as stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity (https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf) Phenotype frequency for partial DPD deficiency in Finnish population is 7.7% and 0.14% for complete lack of the DPD enzyme. Conclusively, pre-emptive testing of DPYD variants is highly recommended but as a basis of general recommendation, not specifically based on the results of this Cox regression analysis.

Internal medicine unit patients had a higher probability to a drug purchase associated with *CYP2C19, CYP3A5, NUDT15, TPMT, SLCO1B1, VKORC1* and each of the HLA-alleles. Patient-specific factors such as the diagnoses might have an impact on the drug purchase. For example, a higher probability to drug purchase associated with *SLCO1B1* could be explained by its associated drug simvastatin, which is more linked to the diagnoses of the internal medicine unit patients than with the surgery unit patients.

However, based on these results, it is challenging to recommend any specific PGx tests to a certain patient group. This would have required more elaborate analysis focusing specifically on the background factors and comorbidities, which falls beyond the scope and time resources of this study. Generally, it has been discussed whether it is possible to define any clear and simple criteria for a patient group clearly benefiting from pre-emptive pharmacogenetic testing. Most of all, it should be considered that the type of gene assay chosen is sensitive enough to detect all relevant alleles in the population to be genotyped, validated laboratory technology is used to provide reliable results, the test results should be stored to a database from which they are easily available and that the results are interpreted by a professional with adequate knowledge on pharmacogenetics, which requires education of health care professionals most preferably already in their degree programmes. As direct costs of the testing might not be the main problem as the price for the testing has decreased due to modern sequencing technology, it should be concentrated that the testing is cost-effective. This study and similar studies are needed to provide valuable information of the drug initiations and to which genes they are associated with to be further utilized in cost-effectiveness studies.

3.3 Finnish phenotype frequencies

Phenotype frequencies of each metabolizing phenotypes were estimated using previously published studies and the SISu-database for single nucleotide variants (Table 3). Article references approved should have been relatively lately published to ensure up-to-date interpretation of allele functions as the area is constantly updating and developing. Furthermore, it was preferred that the study population for genotyping should not have been skewed in any way, for example represent a specific patient group in which some alleles might be linked to the disease to ensure that no specific allele is unusually frequent. If possible, studies conducted with a great number of participants for genotyping were preferred to provide statistical power. In general, adequate phenotype frequency references were possible to find. For the gene *NUDT15*, an article reference by Häkkinen et al. (preprint 2020) was used as any other relevant source was not found. They had

studied individuals with psychotic disorders, which refers to a skewed study population and leads to an assumption that results cannot be applied to whole population level. However, NUDT15 variants are usually interpreted together with TPMT variants for the associated drugs azathioprine, mercaptopurine and thioguanine, which decreases the impact of either of the genes alone. A general problem in finding relevant previously published studies of phenotype frequencies was that in multi-ethnic studies persons of Finnish origin had been excluded due to unique genetic heritage. Any phenotype frequency for HLA-B*15:02 was not found as it is considered very rare in Finland but the allele is common in East-Asian and African populations.

3.4 Pharmacogenetic prescribing recommendations

Due to limited time resources of this thesis project, the prescribing recommendations of only the CPIC were possible to include. CPIC recommendations were chosen due to easy-access via internet, up-to-date information, comprehensively evaluated drug-gene pairs and easy application with the drugs marketed in Finland. All relevant updates were aimed to include, although it is to be noticed that the area is constantly updating and developing. By choosing different guidelines or conducting this study earlier without newest guidelines on proton pump inhibitors or non-steroidal anti-inflammatory drugs or the update to the guideline on opioids, the results would have been totally different.

As mentioned earlier, interpretation of the results should be made by a health care professional with knowledge on pharmacogenetics. Although the testing results remain unchangeable, the interpretation might change due to novel information about the allele functions. The most relevant update in recent years have occurred with allele *CYP2D6*10* function status. Recently, CPIC and DPWG reached a consensus to downgrade the allele activity score from 0.5 to 0.25. In addition, normal metabolizer phenotype with an activity score 1 is currently translated as intermediate metabolizer in consistency with the novel information of the allele function. (Caudle et al., 2020) The allele activity score downgrading was observed in the latest update to the CPIC guideline on opioids. In this study, this update was noticed also in the context of other phenotypes associated with *CYP2D6*.

3.5 Pharmacogenetic testing

Currently, the pharmacogenetic testing is based on either reactive ("as needed") or pre-emptive testing. Specific, well-known single nucleotide variants are tried to detect in gene assays. In choosing a suitable assay depends on the target population to be tested. The assay chosen should be specific and sensitive enough to detect the variants frequent in the target population. Tests to detect variants of a specific gene or a panel consisting of multiple genes are used. As mentioned, the interpretation of pharmacogenetic testing is rather complex and should be conducted with relevant knowledge on pharmacogenetics. Although testing results has been widely underlined as "life-long" and permanent, the possible changes in the interpretation should be noticed. The test results obtained in a specific time point might need to be re-evaluated after discovery of novel alleles or novel information on allele functions of the earlier identified alleles. The area of pharmacogenetics is constantly changing and evolving, which has been seen as well during this study.

3.6 Drug use in Finland

In Finland, patients can utilize world-wide rather exceptional reimbursements for medical expenses provided by the Social Insurance Institution of Finland (KELA). This leads to the situation that health care costs for drug purchases are reasonable and the drug is not selected by the patients' ability to pay. The reimbursements are categorised in three categories based on the indication and how critical the drug is for the patient. In the USA for example, the situation is different and inequal for the patients. Medical expenses are frequently covered by insurances, which are not similar for the citizens. This can have an effect in both which drugs doctor selects for the patients and which drugs are dispensed from the pharmacies.

The most frequently initiated drug in this study was ibuprofen. This might be explained by the current national practise to initiate ibuprofen after an operation, which might be seen in patients discharged from the surgical unit. Another reason might be the exceptional status of ibuprofen in Finland due to strong national brand Burana from the pharmaceutical company Orion.

Moreover, national Current Care Guidelines (Käypä Hoito suositukset) guide doctors in prescribing, which have a strong impact in drug initiations. The Current Care Guidelines might differ from recommendations in other countries, although they are compiled based on national guidelines with strong scientific evidences.

3.7 Patients other than Finnish origin

This study was conducted with a patient cohort consisting of Finnish patients. It was assumed that the majority of patients represent people of Finnish origin, and Finnish citizens other ethnic origin represent a minority. As the exact ethnical origin of the patients was not known, nor the genotype data was available, phenotype frequencies reported in previous studies for individuals of Finnish origin were utilized in assessing the impact of the results in Finland.

As mentioned earlier, the unique Finnish gene heritage compared to other north European countries was a strong argument for the study execution, as a clear need is recognized for national pharmacogenetic studies, which consider various ethnical aspects of the study population. However, multiethnicity is common in daily patient care situations. Clinicians should be aware of the aspects in different ethnical groups, which are relevant to consider in pharmacotherapy planning and execution and in patient care in general. Mandated in law, all people without regarding their ethnical background have an equal right to health care.

In pharmacogenetics, differences in phenotype frequency distribution between different ethnical groups but also among them are significant. The aim should be to identify the ethnical groups having a high possibility to carry a pharmacogenetically relevant actionable phenotype or alleles linked to that. For example, carrying an HLA-allele *HLA-B*15:02* is rare among individuals of Finnish origin but the allele is common in East-Asian and African populations. In case a patient of East-Asian origin needs a drug associated with *HLA-B*15:02*, a pre-emptive pharmacogenetic testing is highly recommended in order to avoid possible severe adverse drug reactions. Initiation of HLA-B*15:02 associated drugs can lead to drug hypersensitivity reactions such as Steven's Johnson syndrome.

3.8 Study strengths

The most significant strength of this study is the high number of patients involved in the patient cohort (n=1.42 million), which represents about 26% of the whole Finnish population (5.54 million). Most of the patients belong to a group of 45-64-year-old patients (37%), followed by 65-80-year-old patients (28%). Young adults in 18-24 years of age represent the smallest age group (5%), although the uneven sizes of the age groups are to be noticed. The median age of the patients was

59 years, and the patient cohort was a comprehensive sample of adult population in Finland (Table 2).

In this study the register data was based on three registers of hospital admissions, drug purchases and mortality data. Different Finnish population registers provide with an exceptionally wide and detailed information platform to be utilized in register-based studies. Additionally, utilizing Finnish registers leads to the conclusion that the results of this study are directly applicable to Finnish population as such. Moreover, it is utmost important to utilize Finnish phenotype frequencies because significant differences have been found in phenotype frequencies of other ethnicities, which would have led to different results.

This study utilized prescribing recommendations compiled by CPIC, which were carefully reviewed manually to identify eligible drugs for the study. All eligibility criteria for both the drugs and for the patient cohort were detailed carefully to meet high level standards for pharmacoepidemiologic study. In prescribing recommendation actionability determination, thoughts were put on reasonable and practical criteria, which defined the recommendation either as actionable or non-actionable.

In conclusion, this study provides strong and reliable pharmacoepidemiologic research results to be utilized in further studies and attempts to implement wide-scale pharmacogenetic testing in Finland.

3.9 Study limitations

This study also had some limitations. To be able to obtain data on the exact number of patients requiring dose adjustment or a change into an alternative drug, individual level genotype data would have been needed. This study utilized the population level phenotype frequency data previously published studies, which was utilized in calculating the estimated number of new drug users for each phenotype. In the future, individual level genotype data in biobanks might be utilized in pharmacoepidemiologic studies similar to this.

Register data utilized did not reach up to the most recent years possible but only to 2014 for hospital admissions and to 2016 for drug purchases and mortality data. This might result in that the most recent treatment recommendations and common practises of prescribing were not able to be seen in the analyses. For example, prescribing of warfarin has decreased during the recent years according to the drug purchase database administered by KELA as the new oral anticoagulants with lesser adverse effects and a wider therapeutic range have accessed the markets. However,

according to results of this study warfarin was the fifth most frequently initiated drug. If the latest drug purchase data would have been available, lesser warfarin initiations might have been seen.

Regarding the drugs included into this study, antiemetic ondansetron and opioid-analgesic tramadol were not included. The ATC-code of ondansetron was not available in the existing drug purchase data. An update to the guideline on opioids and CYP2D6, OPRM1, and COMT was published at a time the drug identification was already conducted and addition of tramadol was not possible. It might have seen relatively low incidence rate for ondansetron in this patient cohort but the incidence rate for tramadol might have been significant based on relatively high DDD-number compared to other drugs of interest.

It would have been interesting to see the total medication actively in use more individually. It was not possible to obtain individual medication list due to program coding technical reasons. However, in cumulative account of drug purchases it was seen that even 9 different drugs associated with 7 different genes were purchased by a few patients during a 2-year follow-up. This indicates that patient cohort included polypharmacy patients, which have an overall greater risk for drug-drug interactions as well drug-gene interactions and a greater risk for adverse drug effects.

This study was conducted by utilizing the selection of drugs marketed in Finland and the phenotype frequencies reported in the literature for the population of Finnish origin. This leads to a conclusion that the results are not applicable in other ethnicities or in other countries as such.

The patients of this study cohort were discharged from either surgical or internal medicine unit, which caused a skewed study population in two ways. First, the sample consists of patients being hospitalized of various reasons, which might increase the average probability to initiate new drugs. Secondly, the data was originally collected for other study purposes and the hospital units in focus were determined to answer on other study hypotheses. Therefore, the results can neither be applied in the whole population level nor to represent all hospital-discharged patients. However, studying new drug initiations with this patient cohort can be expected to answer well in our study hypothesis and aim to discuss the relevance of pre-emptive pharmacogenetic testing for hospital patients in particular. Several new per oral drugs associated with relevant pharmacogenes are typically initiated after admission to either surgical or internal medicine unit.

3.10 Future prospects

There are several international projects aiming to implement pharmacogenetics into clinical practise, of which the EU-funded Ubiquitous Pharmacogenomics (U-PGx) project might be the most important. U-PGx focuses on bringing PGx based treatment optimization accessible for every European citizen in the near future (http://upgx.eu/). Moreover, the genomic data gained in Finnish FinnGen research project might be a valuable data source in biobank-based pharmacogenetic, pharmacoepidemiologic studies in Finland.

To implement pre-emptive pharmacogenetic testing into clinical practise, clinicians are required to have better knowledge on how to interpret the PGx testing results. Educating health care professionals to utilize PGx information is crucial. Furthermore, precise and up-to-date electronic decision support tools are essential in implementing PGx data into clinical practise. An ideal would be that when prescribing, the system provides the doctor patient's genotype data and a suggestion of suitable drug with a likely suitable dose. The system would propose the suitable drug not only based on genotype but also considering possible drug-drug interactions of other concomitant medication, as described by Liu et al. (2021) in their tutorial. In addition, van der Wouden et al. (2019) suggest, that the genotype data could also be accessible in electronic medical records in pharmacies, where the drug compatibilities and interactions are checked at dispensing. This leads to double-verification of the medication by several health care professionals and minimizing the risk of missing a drug-gene interaction. (Van der Wouden, C H et al., 2019)

Currently, both the modern sequencing and information technology provide fast and reliable genetic testing results to be widely implemented. Costs related to the testing itself might not be the greatest barrier but the cost-effectiveness of the testing. It should be demonstrated in cost-effectivity studies that wide-scale implementation of pharmacogenetics in daily clinical practise would generate savings rather than costs for the society. In Finland, public resources are usually utilized in health care, although the trend is towards patients being interested in their genetic makeup themselves. Private companies providing easy homemade genetic tests have become popular and they should be seen as complimentary as long as they are validated and reliable.

It should be concentrated to develop safe and easy-accessible data storage platform for pharmacogenetic testing results, which would facilitate the information to be utilized both in all health care providing units, including hospitals, health care centers and pharmacies both in public and private sectors. Pharmacogenetic aspects should be evaluated similarly as the other patient-specific factors such as other concomitant medication, concomitant illnesses, age, other laboratory results or blood pressure. Instead of constantly developing novel drugs for indications already met

their unmedical need, it would be wise to most optimal way utilize the drugs already in the markets by carefully choosing the target patients. This was seen in a study of genotype-guided oral $P2Y_{12}$ drug selection for patients undergoing primary percutaneous coronary intervention. By genotyping and identifying patients at risk for bleeding, pharmacotherapy was successfully conducted. (Claassens et al., 2019)

Attempts has been made to implement genome data and pharmacogenetics in Finnish health care in government strategies, such as in the National Genome Strategy and Report on medicinal data repository (http://julkaisut.valtioneuvosto.fi/handle/10024/74514; https://julkaisut.valtioneuvosto.fi/handle/10024/162655). The final decision for implementation is still lacking but hypothesis in favour of implementation has been widely proposed.

3.11 The impact of these results in drug development

It has been recognised that implementing pharmacogenetics into daily clinical practise requires multidisciplinary team work. (Just et al., 2019) One of the aspects this requires, is the involvement of pharmacogenetic studies already in the drug developmental phase. In the review by Liou et al., it is suggested that pharmacogenetic aspects would be included in both the target and dose selection, efficacy determination and in reviewing safety. (Liou et al., 2012) In Europe, the EMA has published guideline on Good Pharmacogenomic Practise for evaluating pharmacogenetic aspects in marketing authorisation applications of novel drugs (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacogenomic-practice-first-version_en.pdf). However, in an analysis by Maliepaard et al., it is stated that the drug developers and regulatory authorities should work together to be able to provide safe and effective pharmaceutical products for the patients, and that there is a need for harmonising the evaluation of the pharmacogenetic and pharmacokinetic interactions in marketing authorisation applications. (Maliepaard et al., 2020) An interesting perspective is utilizing pharmacogenetics in studies to find out whether drugs withdrawn from the markets due to major safety concerns might have a possibility to re-accessing the markets. (Zhang et al., 2012)

Results of this study might not be directly applicable in the drug discovery and development phases. However, it is reasonable to consider pharmacogenetic aspects already from the beginning of drug discovery and development process as it is seen in this study that the pharmacogenetically relevant drugs are widely and commonly used and high variation occurs in phenotype frequencies leading to adverse drug reactions, rehospitalisation and impacting the patient's quality of life.

3.12 Summary and conclusions

Drugs having an actionable pharmacogenetic prescribing guideline are worldwide frequently used and clinically relevant. Genes affecting their metabolism and risk for adverse drug effects are highly polymorphic. Significant interethnic variation occurs in allele frequencies, which emphasizes the need for national studies concentrating locally relevant drugs and to which genes they are associated with. Currently, utilizing pharmacogenetic testing in prescribing is still limited mainly because of difficulties to interpret the testing results and apply them in common practise despite of major advances in PGx and several PGx testing panels becoming commercially available. However, it is known that risk for adverse drug effects and rehospitalization can be decreased by including patient's genotype data into electronic decision support systems. Identification of patients clearly benefiting from pre-emptive pharmacogenetic testing to optimize personalized drug therapy will facilitate the implementation of PGx testing into common clinical practise in hospitals.

Conclusively, this study alleviates the significance of pharmacogenetics in daily prescribing. Pharmacogenetically relevant drugs are common and frequently used, and majority of the patients have at least one pharmacogenetically relevant genetic variant present in their genome. As the general aim is to provide more personalized pharmacotherapy to the patients, pharmacogenetics should be considered as the normal practise in prescribing process. It is expected that in case cost-effectiveness studies would turn out in favour of wide-scale (pre-emptive) pharmacogenetic testing, implementing pharmacogenetics into health care would begin.

4. Materials and methods

4.1 Reviewing the CPIC guidelines and determining the actionable study drugs and recommendation actionability

A systematic and deep review of the drug prescribing guidelines compiled by the Clinical Pharmacogenetics Implementation Consortium (CPIC) was conducted and actionable drugs meeting eligibility criteria were identified. A drug was considered eligible when all following criteria were fulfilled; at least one actionable genotype was mentioned in the CPIC guidelines, a drug was marketed in Finland for a minimum time of 2 years during years 2008-2016, a drug was sold in community pharmacies by prescription, and its Anatomical Therapeutic Chemical (ATC) code was to be found in the pre-collected drug purchase data. All three CPIC levels of classification of

prescribing recommendations were considered; strong, moderate and optional. FimeaWeb -search tool provided by the Finnish Medicines Agency (FIMEA) and the drug database compiled by the Finnish Medical Society Duodecim were utilized to determine the ATC-codes for the drugs and their marketing status in Finland during the study years. (https://www.fimea.fi/web/en/databases_and_registeries/fimeaweb; https://www.duodecim.fi/tuotteet-ja-palvelut/terveysportti/laaketieto/) Identification was conducted by including all guidelines and their relevant updates to the known gene-drug interaction pairs published by October 2020. Figure 8. describes the process of identifying actionable drugs for the study.

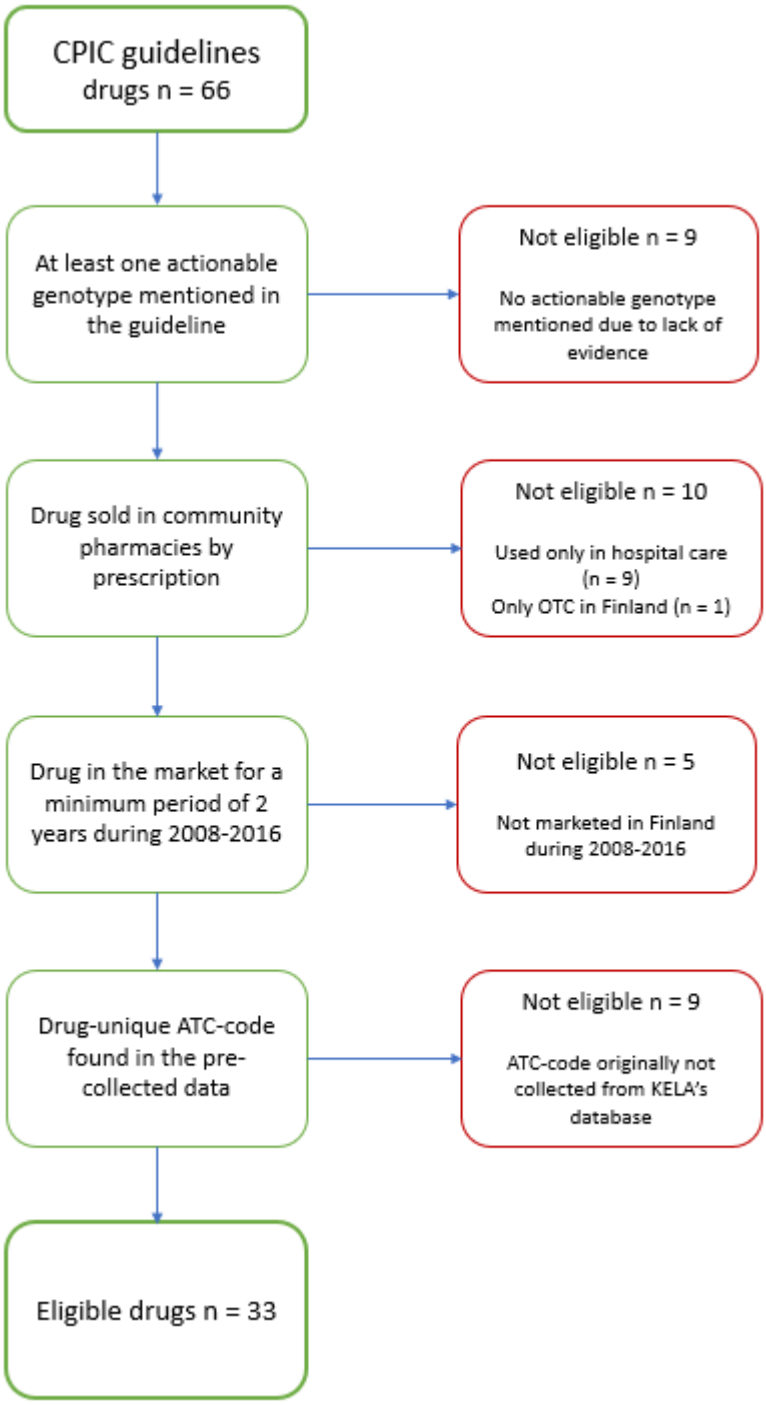

Figure 8. Process of identifying actionable drugs. (CPIC = Clinical Pharmacogenetics Implementation Consortium, OTC = over the counter, ATC-code = The Anatomical Therapeutic Chemical code, KELA = the Social Insurance Institution of Finland)

The CPIC prescribing recommendations were categorized as actionable or non-actionable regarding each metabolizing phenotype or allele carrying status. All relevant updates on recommendations, activity score calculations or interpreting the allele functions published by the end of January 2021 were noticed for the eligible drugs, although any additions to drugs of interests

were not possible at this point. However, the December 2020 update to the Guideline for Opioids and CYP2D6, OPRM1, and COMT was left unnoticed regarding opioids other than codeine because the drug identification and data analyses were already conducted earlier in October 2020, although the latest update to the *CYP2D6* decreased function allele *10 activity score was adapted from the December 2020 update to the guideline for opioids. In determining the actionability, the FDA drug labels, PharmGKB-database for clinical annotations and general summaries for product characteristics were used as supplementary references in comparing the CPIC prescribing recommendations to the normal dosing strategy.

In case the following criteria were fulfilled, the recommendation was classified as actionable; a clear recommendation to either increase or decrease the drug dose, a clear recommendation to choose another drug substance either with an entirely different metabolism route or with the same metabolism route but which has a smaller impact on the drug's metabolism rate or a recommendation to a deviating dose titration scheme to achieve a therapeutic drug level. Recommendations concerning HLA-alleles *HLA-A*31:01, HLA-B*15:02* and *HLA-B*58:01* were considered as actionable for both homo- and heterozygous allele carries.

All recommendations to prescribe a normal dose or a standard starting dose or recommendations to follow a normal dose titration scheme were considered as non-actionable even if the genotype was linked to abnormal metabolism but any adjustments from typical dosing strategy was not recommended. All recommendations for HLA-allele non-carriers were considered as non-actionable.

Only the main indication for each drug was considered when the recommendation actionability was determined leaving the possible additional indications unobserved, such as treatment of *Helicobacter pylori* infection or erosive esophagitis with proton pump inhibitors and neuropathic pain treatment with tricyclic antidepressants. In case the recommendation varied between different ethnic populations, recommendations for Europeans or other white ethnicities most close to Finnish population were included into the study.

4.2. Defining the eligibility criteria for the patient cohort and data collection

The main eligibility criterion was a hospital admission to either surgical, neurosurgical or internal medicine unit between 2008 and 2014, and the first hospital admission to either of the units of interest initiated the following time. Subsequent hospitalisations during the follow-up were not

considered. Hospital stays in public hospitals providing specialist care in mainland Finland were observed. Only patients with an individual Finnish personal identity code were accepted. Patients treated in neurosurgical unit were combined with the group of patients treated in surgical unit. Surgical unit as a term will be used hereafter to refer the both units together. The study inclusion and exclusion criteria are listed in Table 5 below.

Table 5. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Inpatient period during the years 2008-2014 in either internal medicine or surgical (incl. neurosurgical unit) in specialized care in public hospitals in mainland Finland	Patients with a generated personal identity code
Patients in both genders	Death occurring during the initiative hospital admission
Age ≥ 18 years	Age under 18 years

4.3 Data collection from the individual level register data

The register data utilized in this study was collected for an epidemiological research purposes and was already available during the time of initiation of the thesis project. Pseudonymised, individual level data from three different national registers were used in the current study. The register data consisted of data from the Care Register for Health Care in Finland (CRHF, fin. HILMO, Hoitoilmoitusjärjestelmä). The CRHF is administered by the Finnish Institute for Health and Welfare (THL), and collects information of all hospital admissions in Finland, including patient specific details, diagnoses, procedures and interventions during inpatient period, dates for admission and discharging and a reason for seeking care. (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care) Moreover, data from the nationwide prescription register administered by the Social Insurance Institution on Finland (KELA) was utilized, which includes drug purchase data and purchase dates with drug-specific Anatomical Therapeutic Chemical codes (ATC codes). Additionally, mortality data provided by the Statistics Finland was utilized. Based on the inclusion criteria, hospital admission data between 2008 and 2014, drug purchase data between 2008 and 2016 and mortality data between 2008 and 2016 was utilized in the current study.

Data manipulation and individual level analyses were conducted with the SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA) by the study statistician who had been granted permissions to handle the pseudonymized individual level data. The study statistician performed the data manipulation and individual level analyses based on the criteria defined by the other research group members. According to the permissions, other research group members were only allowed to receive aggregate level anonymous data for the data analyses.

The hospital admission date was considered as the index date to begin the follow-up time as defined above in section 4.2. In the individual level analyses, each patient was followed until the end of year 2016 or until death, whichever came first. However, death occurring already during the hospital stay was an exclusion criterion.

Active drug use of the study drugs was determined for each patient 180 days before entering the study to describe the prevalence of the drug use at the moment of hospital admission. Prevalence rates were calculated for each drug and for each gene separately. New post-discharge drug initiations of the study drugs were recorded to describe the incidence of drug purchases. Incidence rates were calculated for each drug and associated genes. A drug was considered new if the patient had not been using it 365 days before entering the study. The primary outcome was the first post-discharge drug purchase of any of the study drugs. Additionally, the cumulative account of different post-discharge drug purchases of the drugs of interest was determined for each patient at 1 and 2 years after the hospital discharge. Both the patient specific number of different post-discharge-initiated study drugs and a number of genes associated to the drug purchases were calculated. Long-term post-discharge drug purchases were analysed with and visualised in the Microsoft Excel (version 2102).

4.4. Combining Finnish phenotype frequencies with the drug incidence data

Finnish phenotype frequencies for each different drug metabolizing phenotypes associated with the genes of interest were determined by utilizing previously published studies and the SISU-database, which is a search engine on sequence variants in Finns (http://www.sisuproject.fi/). The phenotype frequencies were combined with the drug incidence rates to predict the phenotype-specific number of new drug users in 2-year follow-up. Only frequencies of people with Finnish heritage were accepted due to unique Finnish gene heritage, excluding phenotype frequencies of other ethnical origins.

Both the prevalence and the incidence rates, as well as the predicted number of new drug initiations for each phenotype were proportionated to the total number of study participants to reason the significance in the total cohort level.

4.5. Analysing the explanatory factors behind drug initiations with Cox proportional-hazards model

Long-term drug purchase data was analysed with the Cox proportional-hazards model adjusted for type of the hospital unit using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA) by the study statistician. The purpose was to examine the differences in post-discharge drug purchases between patients discharged from surgical unit with patients discharged from internal medicine unit. The Cox analysis was conducted with patients without previous drug purchases of the drugs of interest associated with the genes. Death occurring during the follow-up time led to censoring of the patient.

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Ethical standards

Official permissions to handle the pseudonymized individual level data has been granted to the statistician (Ville Kytö, Turku University Hospital) and this study was conducted within approvals by the National Institute for Health and Welfare of Finland (permission no: THL/2245/5.05.00/2019), the Social Insurance Institution of Finland (91/522/2015), and the Statistics Finland (TK-53-484-20). Only aggregate level anonymous data and no individual level data was shared to other research group members. Ethics committee approval was not needed because the study was purely epidemiological and did not require any actual contact with patients.

Abbreviations List

ADR	adverse drug reaction
AS	Activity Score
ATC	Anatomical Therapeutic Chemical
CPIC	the Clinical Pharmacogenetics Implementation Consortium
CRHF	Care Register for Health Care
CYP	cytochrome P450
DPD	dihydropyrimidine dehydrogenase (enzyme)
DPWG	The Dutch Pharmacogenetics Working Group
DPYD	dihydropyrimidine dehydrogenase (gene)
EM	extensive metabolizer
EMA	the European Medicines Agency
FDA	the United States Food and Drug Administration
FIMEA	the Finnish Medicines Agency Fimea
HLA	human leukocyte antigen
IM	intermediate metabolizer
KELA	the Social Insurance Institution of Finland
NM	normal metabolizer
NUDT15	Nudix Hydrolase 15 gene or enzyme
OATP1B1	Organic anion transporting polypeptide 1B1 protein
PGx	interchangeably used for pharmacogenetics (PGt) and pharmacogenomics
PM	poor metabolizer
RM	rapid metabolizer
SJS	Stevens-Johnsons Syndrome
SLCO1B1	Solute Carrier Organic Anion Transporter Family Member 1B1 gene
TEN	toxic epidermal necrolysis
THL	the Finnish Institute for Health and Welfare
TPMT	thiopurine S-methyltransferase gene or enzyme
UM	ultrarapid metabolizer
U-PGx	Ubiquitous Pharmacogenomics consortium
VKORC1	Vitamin K Epoxide Reductase Complex Subunit 1 gene, vitamin K epoxide reductase protein

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Appendices

Drug	Gene	Phenotype	CPIC recommendation
Mercaptopurine	TPMT	NM	Lower concentrations of TGN metabolites Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Normal starting dose.
		IM or possible IM	Moderate to high concentrations of TGN metabolites. Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease. Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses or alternative drug.
Azathioprine	TPMT	NM	Lower concentrations of TGN metabolites. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Normal starting dose.
		IM or possible IM	Moderate to high concentrations of TGN metabolites. Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease. Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced doses or alternative drug.
Thioguanine	TPMT	NM	Lower concentrations of TGN metabolites. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Normal starting dose.
		IM or possible IM	Moderate to high concentrations of TGN metabolites. Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease. Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced doses or alternative drug.

Drug	Gene	Phenotype	CPIC recommendation
Mercaptopurine	NUDT 15	NM	Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression, normal starting dose, dose adjustments in at least 2 weeks intervals (variation by race/ethnicity and treatment regimens)
		IM or possible IM	Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses or alternative drug.
Azathioprine	NUDT 15	NM	Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Normal starting dose.
		IM or possible IM	Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses or alternative drug.
Thioguanine	NUDT 15	NM	Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Normal starting dose.
		IM or possible IM	Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses.
		PM	Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression. Reduced starting doses or alternative drug.
Simvastatin	SLCO 1B1	normal function	normal myopathy risk, normal starting dose
		intermediate function	intermediate myopathy risk, lower starting dose or alternative statin, routine monitoring of CK levels
		low function	high myopathy risk, lower starting dose or alternative statin, routine monitoring of CK levels
Capecitabine	DPYD	NM (AS 2)	Two copies of normal function DPYD alleles. Normal DPD activity and “normal” risk for fluoropyrimidine toxicity, normal dosage
		IM (AS 1.5)	One normal function and one decreased function allele. 30-70% decreased DPD activity and increased risk for severe or even fatal drug toxicity, 50% dose reduction from standard starting dose.

		IM (AS 1)	Either one normal and one no function allele OR two decreased function alleles. 30-70% decreased DPD activity and increased risk for severe or even fatal drug toxicity. 50% dose reduction from the standard starting dose.
		PM (AS 0.5)	One copy of a decreased function allele and one copy of a no function allele. DPD deficiency and increased risk for severe or even fatal drug toxicity, avoid use of capecitabine, strongly reduced starting doses (<25% of the normal dose) if alternative therapies are not suitable
Drug	**Gene**	**Phenotype**	**CPIC recommendation**
		PM (AS 0)	Two copies of no function alleles of the DPYD gene. Complete DPD deficiency and increased risk for severe or even fatal drug toxicity, avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens (capecitabine)
Warfarin	VKORC1	NM, Non-African VKORC1-1639G/G	"normal", non-mutant carrier, dose according to validated pharmacogenetic algorithms
		IM, Non-African: VKORC1-1639G/A	Dose according to validated pharmacogenetic algorithms, decreased warfarin dose
		PM, Non-African: VKORC1-1639A/A	Dose according to validated pharmacogenetic algorithms, decreased warfarin dose
	VKORC1	African ancestry: VKORC1-1639G>A	Dose according to validated pharmacogenetic algorithms
		African ancestry: VKORC1 A/G or A/A	Dose according to validated pharmacogenetic algorithms, decrease dose by 10-25%
Warfarin	CYP4F2	NM, CYP4F2*1	Normal metabolism, dose according to validated pharmacogenetic algorithms
		Non-African: CYP4F2*3	Calculate dose with a validated pharmacogenetic algorithm and increase calculated dose by 5-10%

Drug	Gene	Phenotype	CPIC recommendation
Warfarin	CYP2C9	NM (AS 2), *1/*1 heterozygous Non-African	normal metabolism, dose according to validated pharmacogenetic algorithms
		IM (AS 1 - 1.5) Non-African *2 either homo- or heterozygous	decreased metabolism leading to dose decrease, dose according to validated pharmacogenetic algorithms
		PM (AS 0 - 0.5) Non-African: CYP2C9*2/*3 or *3/*3	decreased metabolism leading to dose decrease, dose according to validated pharmacogenetic algorithms
		Non-African *5, *6, *8 or *11	Decrease calculated dose by 15-30% per variant allele or consider an alternative drug
		African ancestry: CYP2C9*2	Dose according to validated pharmacogenetic algorithms
		African ancestry: CYP2C9*3	Dose according to validated pharmacogenetic algorithms
		African ancestry: CYP2C9*5, *6, *8 or *11	Decrease calculated dose by 15-30% per variant allele or consider an alternative agent
Phenytoin	HLA-B*15:02	HLA-B*15:02 positive allele carrier	Increased risk of phenytoin-induced SJS/TEN, phenytoin contraindicated, avoid use of carbamazepine and oxcarbazepine
		HLA-B*15:02 negative allele non-carrier	normal dosing strategy depending on CYP2C9 phenotype
Phenytoin	CYP2C9	CYP2C9 NM	No adjustments needed from typical dosing strategies.
		CYP2C9 IM, AS 1.5	Patient has one normal function allele plus one decreased function allele. Slightly reduced phenytoin metabolism. No adjustments needed from typical dosing strategies.

		CYP2C9 IM, AS 1.0	Patient has one normal function allele plus one no function allele OR two decreased function alleles. Reduced phenytoin metabolism, higher plasma concentrations increasing the probability to toxicities. Use approximately 25% less than typical maintenance dose.
		CYP2C9 PM, AS 0.5	Patient has one no function allele and one decreased function allele, reduced phenytoin metabolism, higher plasma concentrations increasing the probability to toxicities. Use approximately 50% less than typical maintenance dose.
		CYP2C9 PM, AS 0	Patient has two no function alleles, reduced phenytoin metabolism, higher plasma concentrations increasing the probability to toxicities. Use approximately 50% less than typical maintenance dose.
Drug	**Gene**	**Phenotype**	**CPIC recommendation**
Allopurinol	HLA-B*58:01	HLA-B*58:01 positive allele carrier	Allopurinol contraindicated due to significantly increased risk of SCAR
		HLA-B*58:01 negative allele non-carrier	Standard dosing, low or reduced risk of allopurinol-induced SCAR
Carbamazepine	HLA-B*15:02	HLA-B*15:02 positive allele carrier	Greater risk for carbamazepine-induced reactions (SJS/TEN), carbamazepine contraindicated, use alternative anticonvulsants.
		HLA-B*15:02 negative non-carrier	Normal risk of carbamazepine-induced reactions (SJS/TEN, DRESS and MPE), standard dosing
Carbamazepine	HLA-A*31:01	HLA-A*31:01 positive allele carrier	Greater risk of carbamazepine-induced reactions (SJS/TEN, DRESS and MPE), carbamazepine contraindicated, use alternative anticonvulsants.
		HLA-A*31:01 negative allele non-carrier	Normal risk of carbamazepine-induced reactions (SJS/TEN, DRESS and MPE), standard dosing

Drug	Gene	Phenotype	CPIC recommendation
Oxcarbazepine	HLA-B*15:02	HLA-B*15:02 positive allele carrier	Greater risk of oxcarbazepine-induced reactions (SJS/TEN), oxcarbazepine contraindicated, use other anticonvulsants.
		HLA-B*15:02 negative allele non-carrier	Normal risk of oxcarbazepine-induced reactions (SJS/TEN), standard dosing
Tacrolimus	CYP3A5	EM (CYP3A5 expresser)	Extensive metabolizer, lower drug concentration, increase starting dose 1.5–2 times recommended starting dose
		IM (CYP3A5 expresser)	Intermediate metabolizer, lower drug concentration, increase starting dose 1.5–2 times recommended starting dose
		PM (CYP3A5 nonexpresser)	Poor metabolizer = normal metabolism, drug initiation with standard recommended dose
Codeine	CYP2D6	UM (AS > 2.25)	Increased formation of morphine leading to higher risk of toxicity. Avoid codeine use because of potential for serious toxicity. If opioid use is warranted, consider a non-tramadol opioid.
		NM (AS >1.25 - <2.25)	Expected morphine formation. Use codeine label recommended age- or weight-specific dosing.
		IM (AS >0 - <1.25)	Reduced morphine formation. Use codeine label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.
		PM (AS 0)	Greatly reduced morphine formation leading to diminished analgesia. Avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid.
Atomoxetine	CYP2D6	UM (AS >2.25)	Likely inadequate serum concentrations for intended effect in standard dosing, normal dose titration to therapeutic level
		NM (AS >1.25 - <2.25)	normal metabolism, normal dose titration to therapeutic level
		IM (AS 1)	patient may not achieve adequate serum concentrations for the intended effect at standard dosing, normal dose titration to therapeutic level.
		IM (AS 0.25-0.75)	increased risk of a atomoxetine-related adverse events. Slower dose titration to therapeutic level.
		PM (AS 0)	significantly decreased atomoxetine metabolism leading to higher concentrations. Slower dose titration to therapeutic level.

Drug	Gene	Phenotype	CPIC recommendation
Fluvoxamine	CYP2D6	UM (AS >2.25)	no data available, no recommendation due to lack of evidence
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may increase the probability of side effects, normal starting doses
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may increase the probability of side effects, consider a 25-50% reduction of recommended starting dose or an alternative drug
Paroxetine	CYP2D6	UM (AS >2.25)	increased metabolism, low plasma concentration may lead to treatment failure, alternative drug recommended
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting dose
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentration may lead to side effects, normal starting dose
		PM (AS 0)	greatly reduced metabolism, higher plasma concentration may lead to side effects, alternative drug recommended or consider a 50% reduction in starting dose
Amitriptyline	CYP2D6	UM (AS >2.25)	Increased metabolism, lower plasma concentrations may lead to therapy failure, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider only with dose titrations and drug monitoring
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may lead to side effects, consider a 25% reduction in starting dose
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may lead to side effects, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider with 50% reduction in starting doses

Drug	Gene	Phenotype	CPIC recommendation
Amitriptyline	CYP2C19	UM and RM	Increased metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with drug monitoring
		NM	normal metabolism, normal starting doses
		IM	reduced metabolism, drug initiation with normal starting doses
		PM	greatly reduced metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with 50% reduction of recommended starting doses and therapeutic drug monitoring
Clomipramine	CYP2D6	UM (AS >2.25)	Increased metabolism, lower plasma concentrations may lead to therapy failure, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider only with dose titrations and drug monitoring
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may lead to side effects, consider a 25% reduction in starting dose, drug monitoring to guide dose adjustments
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may lead to side effects, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider with 50% reduction in starting doses, drug monitoring
Clomipramine	CYP2C19	UM and RM	Increased metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with drug monitoring to guide dose adjustments
		NM	normal metabolism, normal starting doses
		IM	reduced metabolism, drug initiation with normal starting doses
		PM	greatly reduced metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with 50% reduction of recommended starting doses and therapeutic drug monitoring to guide dose adjustments

Drug	Gene	Phenotype	CPIC recommendation
Doxepine	CYP2D6	UM (AS >2.25)	Increased metabolism, lower plasma concentrations may lead to therapy failure, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider only with dose titrations and drug monitoring
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may lead to side effects, consider a 25% reduction in starting dose, drug monitoring to guide dose adjustments
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may lead to side effects, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider with 50% reduction in starting doses, drug monitoring
Doxepine	CYP2C19	UM and RM	Increased metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with drug monitoring to guide dose adjustments
		NM	normal metabolism, normal starting doses
		IM	reduced metabolism, drug initiation with normal starting doses
		PM	greatly reduced metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with 50% reduction of recommended starting doses and therapeutic drug monitoring to guide dose adjustments
Nortriptyline	CYP2D6	UM (AS >2.25)	Increased metabolism, lower plasma concentrations may lead to therapy failure, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider only with dose titrations and drug monitoring
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may lead to side effects, consider a 25% reduction in starting dose, drug monitoring to guide dose adjustments
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may lead to side effects, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider with 50% reduction in starting doses, drug monitoring

Drug	Gene	Phenotype	CPIC recommendation
Trimipramine	CYP2 D6	UM (AS >2.25)	Increased metabolism, lower plasma concentrations may lead to therapy failure, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider only with dose titrations and drug monitoring
		NM (AS >1.25 - <2.25)	normal metabolism, normal starting doses
		IM (AS >0 - <1.25)	reduced metabolism, higher plasma concentrations may lead to side effects, consider a 25% reduction in starting dose, drug monitoring to guide dose adjustments
		PM (AS 0)	greatly reduced metabolism, higher plasma concentrations may lead to side effects, avoid TCA use due to potential lack of efficacy, consider an alternative drug, TCAs to consider with 50% reduction in starting doses, drug monitoring
Trimipramine	CYP2 C19	UM and RM	Increased metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with drug monitoring to guide dose adjustments
		NM	normal metabolism, normal starting doses
		IM	reduced metabolism, drug initiation with normal starting doses
		PM	greatly reduced metabolism of TCAs leading to sub-optimal drug response and side effects, avoid TCAs, consider an alternative drug, TCAs to be considered only with 50% reduction of recommended starting doses and therapeutic drug monitoring to guide dose adjustments
Citalopram	CYP2 C19	UM	increased metabolism, lower plasma concentrations may lead to therapy failure, consider an alternative drug
		EM	normal metabolism, normal starting doses
		IM	reduced metabolism, normal starting doses
		PM	greatly reduced metabolism, higher plasma concentrations may lead to side effects, consider a 50% reduced starting dose, titrate to response or choose an alternative drug

Drug	Gene	Phenotype	CPIC recommendation
Escitalopram	CYP2C19	UM	increased metabolism, lower plasma concentrations may lead to therapy failure, consider an alternative drug
		EM	normal metabolism, normal starting doses
		IM	reduced metabolism, normal starting doses
		PM	greatly reduced metabolism, higher plasma concentrations may lead to side effects, consider a 50% reduced starting dose, titrate to response or choose an alternative drug
Sertraline	CYP2C19	UM	increased metabolism, drug initiation with a recommended starting dose
		EM	normal metabolism, normal starting doses
		IM	reduced metabolism, normal starting doses
		PM	greatly reduced metabolism, higher plasma concentrations may lead to side effects, consider a 50% reduced starting dose, titrate to response or choose an alternative drug
Tamoxifen	CYP2D6	UM (AS > 2.25)	therapy initiation with recommended standard dosing
		NM (AS >1.25 - <2.25)	therapy initiation with recommended standard dosing
		IM (AS >0,25- <1.25)	Lower than normal CYP2D6 activity and increased risk of a poor tamoxifen response. Consider an alternative drug or use a higher tamoxifen dose.
		PM (AS 0)	Decreased tamoxifen metabolism, an alternative drug recommended or in special cases higher tamoxifen dose
Celecoxib	CYP2C9	NM (AS 2)	normal metabolism, normal starting doses
		IM (AS 1.5)	mildly reduced metabolism, slightly higher risk for adverse events, normal starting doses
		IM (AS 1.0)	moderately reduced metabolism, higher plasma concentrations leading to increased risk for toxicities, therapy initiation with lowest possible dose
		PM (AS 0 - 0.5)	significantly reduced metabolism and prolonged half-life, higher plasma concentrations leading to increased risk for toxicities, therapy initiation with lower dose or an alternative drug

Drug	Gene	Phenotype	CPIC recommendation
Ibuprofen	CYP2C9	NM (AS 2)	normal metabolism, normal starting doses
		IM (AS 1.5)	mildly reduced metabolism, slightly higher risk for adverse events, normal starting doses
		IM (AS 1.0)	moderately reduced metabolism, higher plasma concentrations leading to increased risk for toxicities, therapy initiation with lowest possible dose
		PM (AS 0 - 0.5)	significantly reduced metabolism and prolonged half-life, higher plasma concentrations leading to increased risk for toxicities, therapy initiation with lower dose or an alternative drug
Meloxicam	CYP2C9	NM (AS 2)	normal metabolism, normal starting doses
		IM (AS 1.5)	mildly reduced metabolism, normal starting doses
		IM (AS 1.0)	moderately reduced metabolism, higher plasma concentrations leading to increased risk for toxicities, therapy initiation with lower dose or an alternative drug
		PM (AS 0 - 0.5)	significantly reduced metabolism and prolonged half-life, higher plasma concentrations leading to increased risk for toxicities, choose alternative drug
Piroxicam	CYP2C9	NM	Normal metabolism, normal starting doses
		IM (AS 1.5)	Mildly reduced metabolism, normal starting doses
		IM (AS 1.0)	Moderately reduced metabolism, higher plasma concentrations leading to increased risk for toxicities, choose alternative drug
		PM (AS 0 - 0.5)	Significantly reduced metabolism and prolonged half-life, higher plasma concentrations leading to increased risk for toxicities, choose alternative drug
Omeprazole	CYP2C19	UM	decreased plasma concentrations, risk for therapeutic failure, increase starting daily dose by 100%
		RM	decreased plasma concentrations, risk for therapeutic failure, therapy initiation with normal dose but consider increasing dose by 50-100% in treatment of H. pylori and erosive esophagitis
		NM	normal metabolism, normal starting doses, but consider increasing starting dose by 50-100% in treatment of H. pylori and erosive esophagitis
		IM and likely IM	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered

		PM and likely poor	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered
Drug	**Gene**	**Phenotype**	**CPIC recommendation**
Lansoprazole	CYP2C19	UM	decreased plasma concentrations, risk for therapeutic failure, increase starting daily dose by 100%
		RM	decreased plasma concentrations, risk for therapeutic failure, therapy initiation with normal dose but consider increasing starting dose by 50-100% in treatment of H. pylori and erosive esophagitis
		NM	normal metabolism, normal starting doses, but consider increasing starting dose by 50-100% in treatment of H. pylori and erosive esophagitis
		IM and likely IM	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered
		PM and likely poor	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered
Pantoprazole	CYP2C19	UM	decreased plasma concentrations, risk for therapeutic failure, increase starting daily dose by 100%
		RM	decreased plasma concentrations, risk for therapeutic failure, therapy initiation with normal dose but consider increasing starting dose by 50-100% in treatment of H. pylori and erosive esophagitis
		NM	normal metabolism, normal starting doses, but consider increasing starting dose by 50-100% in treatment of H. pylori and erosive esophagitis
		IM and likely IM	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered
		PM and likely poor	increased plasma concentration, likely increased efficacy and potentially toxicity, initiation with normal doses, in chronic treatment (>12 weeks) 50% reduction in daily dose to be considered

Drug	Gene	Phenotype	CPIC recommendation
Voriconazole	CYP2C19	UM	subtherapeutic concentrations, risk for treatment failure, alternative antifungal treatment recommended
		RM	subtherapeutic concentrations, risk for treatment failure, alternative antifungal treatment recommended
		NM	normal metabolism, normal drug concentration, initiate therapy with recommended standard dosing
		IM	higher drug concentration, initiate therapy with recommended standard dosing
		PM	higher concentration, risk for adverse events, alternative antifungal treatment recommended, voriconazole to be considered only with lower dosing and careful monitoring
Clopidogrel	CYP2C19	UM	increased platelet inhibition, decreased residual platelet aggregation, normal doses
		EM	normal platelet inhibition, normal residual platelet aggregation, normal doses
		IM	reduced platelet inhibition, increased residual platelet aggregation, increased risk for adverse cardiovascular events, alternative antiplatelet therapy recommended
		PM	significantly reduced platelet inhibition, increased residual platelet aggregation, increased risk for adverse cardiovascular events, alternative antiplatelet therapy recommended