Evaluating the current knowledge and perceptions among Finnish physicians and pharmacists of pharmacogenetics

Master's thesis by

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Abstract

Over 90 percent of the population has a genetic variation in any of the significant genes that metabolize drugs in the body (David, et al., 2021). These variants can be detected with a pharmacogenetic (PGx) test and, hence, avoid any adverse drug reactions or side effects that may occur due to abnormal drug metabolism. A PGx test alone is not enough for improved drug treatment. The physician needs to understand the results and know what changes need to be implemented based on the results, either by discontinuing the treatment, dose adjustment or choosing another drug.

PGx testing has previously been perceived as something that is relevant only in the future. The fact is that PGx testing has lately received much more attention and it has become an important tool for personalized medicine (Edris, et al., 2021). However, its clinical implementation still remains limited.

In this study, a 28-question survey was distributed online to Finnish physicians and pharmacists, including students in respective professions, working in either/both the municipal and/or private sector in Finland. The survey aimed to evaluate the current knowledge and perceptions among Finnish physicians and pharmacists of pharmacogenetics. The first eighteen questions and/or statements examine participants´ characteristics and general knowledge about pharmacogenetics. The following ten questions and/or statements examine participants´ deeper knowledge about pharmacogenetics.

Altogether, 151 answers were submitted, of which 88 by pharmacists, 46 by physicians, and 17 by students. Forty-six percent strongly agreed, and forty-two percent agreed to the statement: "*I believe that pharmacogenetic testing is helpful for predicting the risk of side effects for the patient*". However, only 6.5% (n=3) of all physicians stated that they have used PGx testing in their clinical practice more frequently.

Even though twenty-six percent either strongly disagreed or disagreed with the statement: "*I have basic knowledge of pharmacogenetics",* the results showed that the majority were nevertheless interested in receiving PGx education.

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List of abbreviations

AUC= Area under curve

CYP= Cytochrome P450

EMA= European Medicines Agency

FIMEA= Finnish Medicines Agency

IM= Intermediate metabolizer

NM= Normal metabolizer

PGx= Pharmacogenetics

PM= Poor metabolizer

RM= Rapid metabolizers

SNPs= Single nucleotide polymorphisms

UM= Ultrarapid metabolizer

1. Introduction

All substances, except endogenous substances, are considered foreign to the human body. Drugs are no exception, even though they can contain endogenous substances, for example, testosterone or estradiol. However, regarding drugs, the risk-benefit ratio must be evaluated (Srivastava, 2018). Can the disease cause more harm to the body than the drug treating it?

Progression in the healthcare system results in impressive improvement in disease management. The development of more target-specific and potent drugs that are more effective with less unwanted side effects has significantly improved the quality of life. In order to receive the optimal benefit of the drug, physicians' decisions about dose regimen are entirely based on the results of clinical studies. The parameters of clinical studies, such as patients' age, gender, weight, and disease severity, are essential for the physician to obtain an idea about the population average dose. This dose recommendation is for the most part enough for treating a disease or reducing symptoms for the majority of the population, but unfortunately not for all. There are variations in drug treatment among the population: from no response to good response. A minority of the population does not tolerate the drug and serious adverse drug reactions can occur. For example, the antimicrobial drug flucloxacillin can have the desired effect for some individuals and cause drug-induced liver injury (DILI) for others. What could be the explanation for these differences? Genetics can provide an answer to this (Srivastava, 2018).

Pharmacogenetics is how our genes affect the drug treatment (Bousman, et al., 2019). Friedrich Vogel brought into existence the term pharmacogenetics in 1959. Since then, the science of pharmacogenetics has increasingly grown (Srivastava, 2018). Pharmacogenetics has been shown to improve the efficacy and safety of drug therapy, particularly in psychiatry, polypharmacy, and cardiology (Bousman, et al., 2019; Brixner, et al., 2016; Magavern, et al., 2021). Today, physicians are starting to recommend PGx testing before prescribing drugs (Srivastava, 2018). However, it seems that the dissemination of knowledge about pharmacogenetics is deficient (Edris, et al., 2021).

1.1. Research problem

Before the discovery of PGx tests, the patient could visit the physician several times to receive the right medication for his/her medical condition. Each new visit becomes more and more difficult, and the thread between life and death becomes thinner and thinner. In fact, this is not too far from the truth for many patients. Now imagine a world where the patient only needs to go to the physician once for a certain disease. The patient receives both the right medicine and the right dose immediately. This, and much more, are the benefits of PGx testing.

The return visit to the physician not only uses up resources of the health care system, but also takes away the opportunity for others to start their treatment process (Brixner, et al., 2016). In addition, return visits make it more difficult to treat acute cases. These visits increase prices for customers, making the poorer ones suffer more and more (KELA, 2022). Since PGx testing reduces the hospitalization rate, resulting in cost savings both for the community and the patient (Brixner, et al., 2016).

A study conducted in Spain was able to show that between 2013 and 2016, when no PGx test for the participants had been performed, the cost of medicines averaged 10,102.93€ per patient (Carrascal-Laso, et al., 2021). In 2016–2019, a PGx test was performed on the same group of patients, which showed that the cost of medicines decreased to 9096.44€ per patient. This represents a 9.96% decrease in drug costs. Regarding hospital days, the study showed that before the PGx test, the cost was about 2269€ per patient, and after that about 868.37€. This represents a 61.7% decrease in hospital costs.

Taking a PGx test can reduce the risk of iatrogenic drug misuse, adverse drug reactions, and medication errors (Michaud, et al., 2022). The trust for healthcare systems increases, hence making patients more likely to follow medicinal recommendations that are based on a PGx test (Brixner, et al., 2016). Patients are more satisfied with their treatment and the threshold for seeking help will be lower, since they receive the right medicine without delay.

The general research problem of this thesis is:

- How knowledgeable are Finnish physicians and pharmacists, including students in respective professions, of pharmacogenetics?

1.2. Focus and objectives

The objective of this thesis is twofold. The first focus is to superficially study Finnish physicians', pharmacists', and students' knowledge of pharmacogenetics. The focus objective is to be able to compare Finnish results with other countries that have conducted similar studies.

By participating in the research, physicians, pharmacists, and students in respective professions will be able to examine their current knowledge of pharmacogenetics. They will obtain a slightly more comprehensive general understanding of pharmacogenetics.

1.3. Thesis outline

This thesis is divided into two parts. The first part will present the current knowledge of pharmacogenetics among Finnish physicians and pharmacists. The second part will compare the Finnish results with results from other countries.

This will involve the use of PGx tests in the practice and both physicians' and pharmacists' identification of suitable drugs that are indications for performing a PGx test. Not only will physicians' and pharmacists' individual knowledge be measured, but also the interaction between them and the patient. For example, how physicians and pharmacists present the results of a PGx test to the patient and if any guidance has been given to the patient. Moreover, factors that affect the dissemination of knowledge will also be studied, as well as their interest in future training of pharmacogenetics.

Chapter 2 discusses terms and general facts about the topic, which can be advantageous to know before reading the study. This chapter explains the background to the study.

Chapter 3 describes the aims of this study. The first two clarify the current knowledge and future aspects. The third presents the comparisons between countries. The main goal is listed at the end.

Chapter 4 of this thesis presents materials and methods utilized in the study.

In Chapter 5, the results of the study are presented. Participants' characteristics are firstly discussed, followed by the geographical distribution of participants and, lastly, the proportion of participants with prior education in PGx and their interest in applying PGx test in clinical practice.

Chapter 6 continues discussing the results regarding participants' perceptions and knowledge about PGx testing.

Chapter 7 and *8* review participants' general knowledge and deeper knowledge of PGx.

In Chapter 9, further education, and preferred learning methods about PGx are presented.

Chapter 10 gives a comparison of the Finnish results with the Dutch and American results.

Chapter 11 discusses the results of participants' general knowledge regarding PGx testing in a more summarized way.

Finally, chapter 12 concludes this study. The results of the study are presented in a simpler and compact way.

2. Literature review

Human genome sequencing was completed in 2003 (Wheeler & Wang, 2013). The information obtained has since been used as a tool to understand the link between diseases and genetic variation. Everyone has a unique genome, based on differences in base pair sequencing (Makalowski, 2001). Since 2003, many important genes have been

identified, especially genes that are a part of the P450 superfamily (Owen, et al., 2009). These genes encode the membrane-bound proteins, cytochrome P450 enzymes, that are mostly located on the endoplasmic reticulum of the liver (Saha, 2018). CYP enzymes have their function through monooxygenation and are crucial for the production of e.g. prostacyclins, steroids, cholesterol, and thromboxane A2 (Saha, 2018; Lynch & Price, 2007). Moreover, these enzymes are essential for metabolizing drugs and other unnatural substances in the human body (Lynch & Price, 2007). CYP enzymes can be classified into different families, described as a number after the CYP, followed by a letter describing the sub-family, and lastly a number, which represents the sequence of discovery (Saha, 2018). For example, CYP2C19, belongs to the family 2 and sub-family C, whilst being the 19th sequence found. Over 50 enzymes have been classified to belong to the cytochrome P450 class (Lynch & Price, 2007). Six of these 30 enzymes all together metabolize 90% of drugs. Some common substrate drugs and their metabolizing CYP enzymes are listed in Table 1.

Table 1. Common substrate drugs and their metabolizing CYP enzyme (adapted from Saha, 2018)

Enzyme	**Substrate drugs**
CYP1A2	Amitriptyline, caffeine, clozapine, haloperidol, olanzapine, ondansetron, theophylline
CYP2C9	Amitriptyline, diclofenac, fluoxetine, ibuprofen, losartan, phenytoin
CYP2C19	Amitriptyline, citalopram, diazepam, omeprazole, clopidogrel, voriconazole
CYP2D6	Amitriptyline, codeine, clozapine, fluoxetine, haloperidol, metoclopramide, metoprolol, olanzapine, ondansetron, risperidone, sertraline
CYP2E1	Paracetamol, caffeine, chlorzoxazone, dextromethorphan, ethanol, theophylline

CYP3A4	Alprazolam, amitriptyline, bupropion, caffeine, carbamazepine, diazepam, donepezil, estradiol, fluoxetine, lansoprazole, loratadine, nifedipine, omeprazole, progesterone, sertralin, sildenafil, tacrolimus, testosterone

Each individual inherits one allele from the mother and the other from the father (Lynch & Price, 2007). A genetic variant is often caused by DNA errors, and usually decreases the function of the CYP enzyme (Friend, 2020; Lynch & Price, 2007). The most common genetic variant is single nucleotide polymorphism (SNPs) (Meng, et al., 2021). These types of variants change the structure and function of the protein by exchanging amino acids in the protein (Gu, et al., 2015). Wild types alleles are also referred to as normal alleles, in other words, alleles that function normally (NIH, 2022). An individual with normal metabolic rate has two copies of wild type alleles, which is commonly occurring (Srivastava, 2018). These individuals will receive the standard dose that has a positive effect on the average population. The drug concentration is within the therapeutic window, meaning enough effect for a fixed time with few unwanted side effects (see Figure 1) (Kathuria, 2021). However, there is a variety of P450-metabolizing enzymes that are regulated by one or more variants of genes (Owen, et al., 2009). When a variant allele replaces at least one or more wild type alleles, polymorphism is the term used (Lynch & Price, 2007). Individuals with two inherited copies of a variant allele, are classified as 'poor metabolizers' (PMs), meaning that their enzymatic function is decreased. Individuals that inherit one wild type allele and one variant allele are called intermediate metabolizers (IMs). Their enzymatic function is slightly decreased but not to the same extent as PMs. In contrast, individuals that inherit two copies of wild type alleles, have a slightly increased enzymatic function. These individuals are called rapid metabolizers (RMs). Individuals that are ultrarapid metabolizers have inherited more than two wild type copies. To give an example, citalopram is a drug that is metabolized by the CYP2C19 enzyme (Abomics, 2022). Poor metabolizers should consider a 50% dose reduction to avoid unwanted side effects that may come from excessive drug concentrations (see Figure 1). Intermediate metabolizers

have a higher risk of QT prolongation; therefore, a dose reduction should be required. Ultrarapid metabolizers will have insufficient efficacy of citalopram and should require a higher dose or switch to an alternative drug that is not metabolized by CYP2C19.

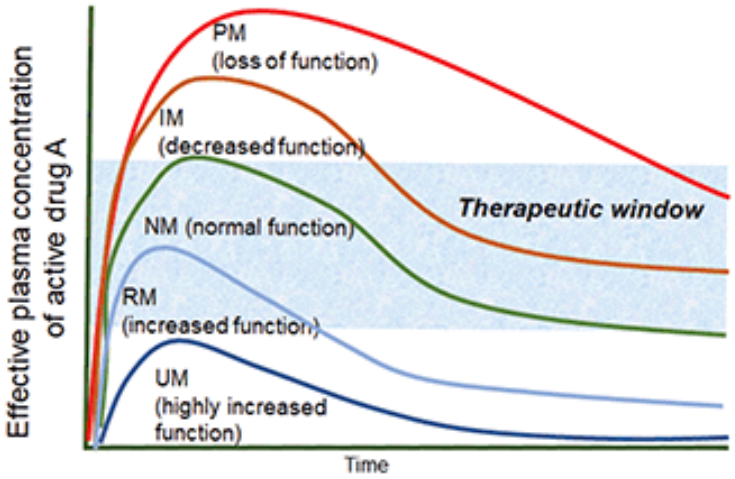

Figure 1. Cytochrome P450-enzymes' effect on drug metabolism (Kathuria, 2021). PM: poor metabolizer; IM: intermediate metabolizer; NM: normal metabolizer; RM: rapid metabolizer; UM: ultra-rapid metabolizer.

Polymorphism can be the explanation for differences in drug therapy between individuals, as it affects the metabolism, efficacy, and toxicity of the drug (Lynch & Price, 2007). A study conducted in UK in 2020 showed that more than 90 % of the population could have an atypical response to at least one prescribed drug by carrying at least one variant of the 14 pharmacogenes that affect the human drug response. Of 487,409 participants that participated in the study, approximately 24% was predicted to have an atypical reaction to one or more of their prescribed drugs (McInnes, et al., 2021). A clinical example could be obtained from reports from Finnish Statistical Database – Kelasto (Kelasto, 2022). In 2020, the proportion of prescriptions for clopidogrel in Finland was 77,389, distributed among 20,095 patients. Approximately 30% of the Finnish population are either a PM (3.1%) or IM (27.54%) (Häkkinen, et al., 2022). In other words, of 20,095 patients, 623 patients had a poor metabolic rate, and 5534 patients had a partially poor metabolic rate, both resulting in impaired drug treatment.

Differences in drug therapy does not only apply within a country but also between countries (see Chaper 10). Fifteen percent of the East Asian population are PMs, whereas only 2.5 percent of the Caucasian population are PMs. The term ''Caucasian population"

refers to individuals from North America and Europe. On the contrary, 2.0% of the East Asian population are RMs, compared to 26.9% of the Caucasian population (Caudle, et al., 2017). These differences between ethnic populations can be related to environmental factors that affect the expression of cytochrome P450-enzymes (Zhoua, et al., 2019).

Enzymes such as CYP2C19 and CYP2D6 have a clinical significance that is unavoidable (Owen, et al., 2009; Lee, 2012). To give a few clinical examples, PMs of CYP2C19 will only need 10mg of escitalopram per day to attain the same pharmacological response as NMs would attain from 20mg per day (see Figure 2) (Strawn, 2019). However, UMs would require 30mg of escitalopram per day. In a similar way, PMs require 100 mg of sertraline per day to attain the same pharmacological response as NMs would attain from 150mg per day. Again, UMs require higher doses, up to 200mg per day. On the subject of the CYP2D6 enzyme, the recommended dose of eliglustat is 84mg twice daily for IMs and 84mg once daily for PM in order to receive an optimum treatment (Balwania, et al., 2016) (Lääketietokanta, 2022).

It is important to emphasize that when it comes to the active metabolite of the substance, the outcome of the treatment is the opposite of the previously mentioned in figure 1. For example, individuals that have partially decreased metabolic rate (IM) or decreased metabolic rate (PM) of CYP2C19 receive a lower proportion of the active metabolite of clopidogrel, resulting in a lower antithrombotic effect (Feske, 2021). In contrast, an ultrarapid metabolizer (UM) of CYP2D6 enzyme receives a higher proportion of the active metabolic of codeine compared to a normal metabolic rate (Kirchheiner, et al., 2007).

Even drugs have an impact on the enzymatic function, either through inducing or reducing their capability to function, leading to an undesired therapeutic response (Lynch & Price, 2007). This is also called drug interactions. To reduce the risk of unsuccessful treatment, a grouping of all drugs has been done. They are placed into groups depending on their risk ratio (either A, B, C, or D), where ‘A’ stands for lowest risk of interaction and ‘D’ for highest risk of interaction (Shetty, 2018). A number after the letter stands for how well studied the risk is: 0= no evidence identified; 1= evidence based on incomplete case reports; 2= evidence based on well documented case reports; 3= evidence based on controlled studies; 4= evidence based on controlled studies of good quality (GeneRx, 2022). For

example, the interaction between amitriptyline and St. John's wort (a plant) are classified as D3 (InxBase, 2022). Studies showed that the AUC of the active metabolite, nortriptyline, decreased by 41% and the AUC of amitriptyline decreased by 21%. The risk of anticholinergic effects, e.g. dry mouth, when using amitriptyline is significantly increased (D-group) (InxBase, 2022). The risk ratio applies on the following conditions:

- Anticholinergic effects
- Serotonergic effects
- Potassium and sodium balance
- Risk of seizures
- Renal toxicity
- Orthostatism
- QT-time prolongation
- Sedation
- Constipation
- Risk of bleeding

The Abomics GeneRx database has a similar ABCD categorization as InxBase. Drugs that are not affected by pharmacogenetic variation belong to the first group, A (Abomics, 2022). No changes in the treatment need to be made, as the treatment is considered to be safe. Drugs that may be affected by genetic variation are classified in the following group, B. The risk of side effects is greater while the effect of the drug may be lower. Switching to an alternative drug or adjusting the dosing should be considered. The following two groups, C and D, consist of drugs that will be affected by pharmacogenetic variation, thus, have a clinical significance to varying degrees. Changes in the medication should be made depending on the results of a PGx test. In group D, a PGx test is strongly recommended before prescribing the drug.

Pharmacogenetic databases, e.g. Duodecim Drug Database for Pharmacogenetics – GeneRx (https://www.terveysportti.fi/apps/generx/), U.S Food and Drug Administration (https://www.fda.gov), and European Medicinal Agency (https://www.ema.europa.eu/), examine these pharmacogenetic interactions between drugs mentioned above. GeneRx's website contains data on 240 drugs, the effect of which is due to pharmacogenetic

variations and thus affects the individual metabolism or response of the patient (GeneRx, 2022). FDA suggest subgroups of patients with specific genetic variants and evaluates the risk of adverse side effects of a certain drug of these subgroups (FDA, 2021). EMA gives recommendations, either directly or indirectly, related to pharmacogenomics (EMA, 2019). Tietoevry Lifecare collects information about patient visits, exams, screenings, medication, and communications on a single platform and includes a module that provides the Abomics GeneRx-database to the user (https://www.tietoevry.com/) (Vähäkainu, 2022). The Clinical Pharmacogenetics Implementation Consortium (CPIC) have guidelines for physicians on how to interpret PGx test results and thus adjust the drug therapy (https://cpicpgx.org/) (CPIC, 2021). PharmGKB is a website with pharmacogenetic knowledge, including clinical guidelines and pharmacogenomic genes (https://www.pharmgkb.org/) (PharmGKB, 2021).

As previously presented, PGx testing makes a significant difference in drug treatment. Figure 2 illustrates the differences in the concentration of escitalopram in the blood between different metabolic rates (see Figure 2). Right from the beginning of the treatment, PMs have a higher drug concentration of escitalopram, whereas UMs have a lower drug concentration (see figure to left). However, when the dose has been adjusted based on the results from a PGx test, both PMs and UMs have similar treatment outcomes as NMs (see figure to right).

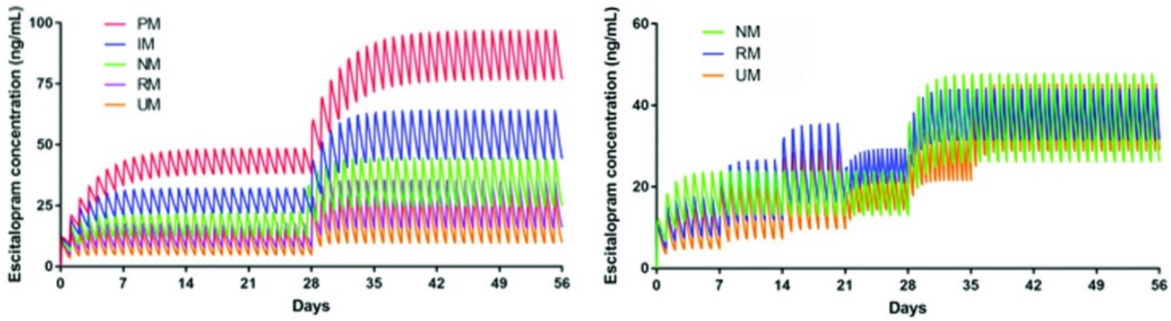

Figure 2. Differences in the treatment outcome of escitalopram when not implemented a PGx test (to left) versus when adjusting the dose based on the results from a PGx test (to right) (Strawn, 2019). The treatment initiated with 10mg of escitalopram daily and was increased to 20mg daily after 28 days. PM: poor metabolizer; IM: intermediate metabolizer; NM: normal metabolizer; RM: rapid metabolizer; UM: ultra-rapid metabolizer.

Pharmacogenetic tests are conducted on individuals to evaluate the potential drug response and, therefore, determine the right dose of the right drug (Malsagova, et al., 2020). The results show the metabolic rate of drugs metabolized by P450 enzymes, in other words, how quickly the body can eliminate a certain drug (see Figure 1) (Kathuria, 2021). In addition, a PGx test can evaluate the risk of myopathy and assess the risk of venous thrombosis, for example, with regard to the use of contraceptive pills. Genetic information remains the same throughout life, meaning that the pharmacogenetics of the same genes never need to be re-examined.

Pharmacogenetics tests are available and used all around Finland (Forsström & Rönnholm, 2021). Figure 3 illustrates to what extent the PGx tests are used in Finland. The green areas demonstrate areas in which they are used extensively, while red and orange areas represent the opposite. Pharmacogenetic testing is implemented to a large extent in western Finland and to a lesser extent in eastern Finland.

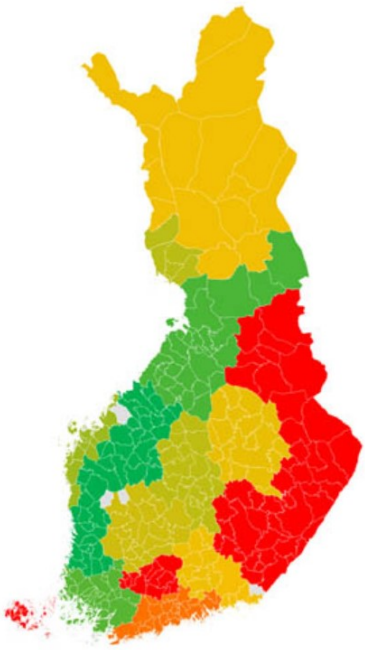

Figure 3. Use of pharmacogenetics per capita in Finland. Use of PGx tests is widely implemented in the green areas, and to a lesser extent in the yellow areas, and barely in the red areas (Forsström & Rönnholm, 2021).

Most large laboratories in Finland have already implemented PGx testing (Forsström & Rönnholm, 2021). A variety of different types of PGx tests are available in Finland, B-FarmL-D, B-Farma-D, and B-PGX-D. The broader test type of B-FarmL-D analyze 24 genes while

the broader test type of B-Farma-D tests analyze 20 genes (see Table 2) (Synlab, 2022; Fimlab, 2022). For the most part, they are similar regarding which CYP enzymes they analyze. B-PGX-D tests have only recently been introduced in Finland (01/2022) and analyzes 12 genes (Tarkiainen, et al., 2021). The PGx tests can be taken orally as a buccal swab or by a blood sample at a healthcare center (Synlab, 2022; Fimlab, 2022; GeneAccount, 2022). The laboratory analyses the samples, and within 30 days, the results are presented as an online report.

The hospital district of South Ostrobothnia has implemented B-FarmL-D tests, while the private sector (e.g. Mehiläinen, Terveystalo) has implemented B-Farma-D tests (Mehiläinen, 2022; Terveystalo, 2022). B-PGX-D tests are only used in the hospital district of Helsinki and Uusimaa (Tarkiainen, et al., 2021). Pharmacogenetic tests can be bought at the pharmacy without a prescription. However, with a doctor's referral, the Social Insurance Institution of Finland (KELA) will reimburse the PGx test with approximately 40-60€ (Mehiläinen, 2022; Terveystalo, 2022).

Table 2. The difference between B-FarmL-D, B-Farma-D, and B-PGX-D tests regarding which CYP enzymes they analyze (Mehiläinen, 2022; Terveystalo, 2022; Tarkiainen, et al., 2021)

B-FarmL-D	**B-Farma-D**	**B-PGX-D**	**B-FarmL-D**	**B-Farma-D**	**B-PGX-D**
-	-	ABCG2	CYP2B6	CYP2B6	CYP2B6
ABCB1	-	-	DPYD	DPYD	DPYD
CYP2D6	CYP2D6	CYP2D6	SLCO1B1	SLCO1B1	SLCO1B1
GRIK4	-	-	CYP2C19	CYP2C19	CYP2C19
ALDH2	ALDH2	-	F2	F2	-
CYP4A4	-	-	TPMT	TPMT	TPMT
IFNL3	IFNL3	-	CYP2C8	-	-
BCHE	BCHE	-	F5	F5	-
CYP3A5	CYP3A5	CYP3A5	UGT1A1	UGT1A1	-
MTHFR	-	-	CYP2C9	CYP2C9	CYP2C9
CYP1A2	CYP1A2	-	G6PD	G6PD	-
CYP4F2	-	CYP4F2	VKORC1	VKORC1	VKORC1
NUDT15	-	NUDT15			

In 2015, an article was published at the Ministry of Social Affairs and Health in which a future strategy for the use of genetic information was prominently featured. The vision of the strategy was that Finland will effectively utilize genomic information for improving human health. In addition, by the year of 2020, Finland will have widely used genomic information in health care both at the individual level and in a population (STM, 2015). The survey can also be considered to have provided an indicative idea of how this strategy has succeeded.

3. Aims

Aims of this study is to:

- Clarify the current knowledge and perceptions among Finnish physicians and pharmacists, including students in each field. This would involve the use of PGx tests in practice, how healthcare professionals proceed with the presentation of the results and which factors affect the dissemination of knowledge.
- Clarify the future interest of education in PGx testing, and most popular learning methods.
- To compare Finnish results with the results from the Dutch and American study, to get an overview of countries' differences in knowledge among countries.
- The overall goal is to bring more awareness to Finnish physicians and pharmacists and in that way arise more interest in pharmacogenetics. This would mean, among other things, more discussion with colleagues and/or patients about PGx and PGx testing.

4. Material and methods

A two-part web-based survey with 28 questions and/or statements altogether was conducted from 27 January 2022 to 8 March 2022 (see Appendix 15.1. and 15.2.). The questions and/or statements are strongly inspired by the questions used in similar studies conducted by Edris et al. and Johengen et al. in order to make it possible to compare the results with each other. The survey was addressed to either Finnish physicians or pharmacists, including students in the respective field. The survey was freely translated into three languages: Finnish, Swedish and English, to receive more reliable answers. The survey was distributed online to healthcare professionals and disseminated through contacts, such as colleagues. An article about PGx testing was also published to Finnish Medical Association – Duodecim to reach a wider range of Finnish physicians and pharmacists (see Appendix 15.3.). An online link was sent to Åbo Akademi University to reach Finnish pharmacy students (www.abo.fi). In addition, Tietoevry Lifecare distributed the survey online to their customers. The participants responded to the questions and/or statements online. The answers were then saved and evaluated online.

The participants had 41 days to respond, and they had access to all material related to the topic. All parts of the survey were voluntary. All answers were anonymous and only used for research purposes. The participants did not receive any compensation for participating.

Part 1 of the survey included 18 questions and/or statements that examined participants' characteristics, e.g. sex, years of experience, and education, and their knowledge about the basics in pharmacogenetics. Most of the questions were multiple-choice questions. Some questions had the 'I do not know' option, and the 'Select all that apply' option (for example choosing job description and prior education). However, a few questions were mandatory (e.g. sex, education, years of experience). The question regarding the participants' specialty was mainly addressed to physicians; if pharmacists answered the question, they had to write in the textbox on their own initiative.

Part 2 of the survey included 10 questions and/or statements that examined deeper knowledge about pharmacogenetics. All questions were multiple-choice questions, including the 'I do not know' option. In part 2, the respondent received 1 point for the correct answer, 10 points being the maximum. The final correct number was given as a

percentage. The statements were as follows, with the correct answers in parenthesis:

1. Single nucleotide polymorphisms (SNPs) are variations of (a single nucleotide).
2. In pharmacogenetics, allelic variations are generally referred to as star alleles. Mostly *1 refers to one specific allele that is (wild-type).
3. Genetic variation can also occur in drug targets, leading to an impact on the (therapeutic response).
4. With a poor metabolizer due to a genetic polymorphism, a prodrug always has (a limited therapeutic effect).
5. According to your knowledge, which of the following drugs require pharmacogenetic testing according to the European Medicines Agency, EMA (abacavir)?
6. A pharmacogenetic test for clopidogrel was conducted and the results showed that the patient has a CYP2C19*2/*2 genotype. According to this, we can estimate that the patient has a metabolic pattern that is (poor).
7. According to the guidelines of Clinical Pharmacogenetics Implementation Consortium (CPIC), it is recommended that slow metabolizers avoid the use of voriconazole due to genetic variation in gene encoding (CYP2C19).
8. Dihydropyrimidine dehydrogenase (DPD) is an enzyme that metabolizes pyrimidines in the human body. DPD deficiency can cause serious side effects when using drugs such as (fluorouracil, and the prodrugs tegafur and capecitabine).
9. Codeine is metabolized by CYP2D6 to morphine. Side effects such as drowsiness, superficial breathing and nausea can occur, even with a standard dose of codeine, if the patient is CYP2D6 (ultrarapid metabolizer).
10. According to the most recent studies, only 40% of the Finnish population have normal CYP2C19 metabolism (Häkkinen, et al., 2022). As for CYP2D6, about 63% of the Finnish population have normal metabolism. Do you know what proportion of the drugs used in Finland are metabolized by CYP2C19 and/or CYP2D6? (5%)

5. Results

Of all participants (n=103), 68.2% chose to answer in Finnish, 30.5% (n=46) of all participants chose Swedish, and 1.3% (n=2) chose English.

5.1. Participants' characteristics

There were 151 answers, 76.8% (n=116) were women, 22.5% (n=34) were men, and 0.7% (n=1) preferred not to say the sex. The largest group of participants were pharmacists (n=88), the second largest were physicians (n=46) and the smallest group were students (n=17) (see Table 3). Of the 116 participants who were women, 75 were pharmacists, 29 physicians, and 12 students. Of the 34 participants who were men, 12 were pharmacists, 17 physicians, and 5 students. The one participant whose sex was not revealed, was a pharmacist.

Most participants had 21-30 years of experience, which included 23 pharmacists and 14 physicians. The second largest group, 0-3 years of experience, included 18 pharmacists, 8 physicians, and 5 students. The smallest group, 7–10 years of experience, included 7 pharmacists and 4 physicians. The remaining groups were as follows: 11–20 years (n=24), 4–6 years (n=18), 30+ years (n=16) and students (n=14). In the case of students, 3 participants chose 0-3 years of experience instead of the 'Student' option. Thirty-six percent had a higher degree education, while 53% had a lower degree education. Eleven percent of all participants were students.

Pharmacists worked mainly at a pharmacy, but also with administrative tasks. A rather small number of pharmacists worked with research, teaching, and with clinical tasks. The option 'Other' included marketing authorization for medicinal products, responsibility for a specific unit at a hospital, subject matter expert, and/or registration of medicinal products. Physicians worked mainly with clinical tasks, while some also had tasks in the administrative field. A meager number of physicians worked with research. Most of the students were still studying, while a small number were part-time workers with clinical tasks, research, teaching, and/or at a pharmacy.

Table 3. Participants' characteristics: sex, years of experience, degree level, and job description

Characteristic	**Total (100%)**	**Pharmacists**	**Physicians**	**Students**
	n=151	n=88	n=46	n=17
Sex				
Female	116 (76.8)	75	29	12
Male	34 (22.5)	12	17	5
Other	1 (0.7)	1	-	-
Years of experience				
0–3	31 (20.5)	18	8	5
4–6	18 (11.9)	13	5	-
7–10	11 (7.3)	7	4	-
11–20	24 (15.9)	18	6	-
21–30	37 (24.5)	23	14	-
30+	16 (10.6)	7	9	-
Student	14 (9.3)	2	-	12
Degree education				
Higher	54 (36)	22	32	-
Lower	80 (53)	66	14	-
Student	17 (11)	-	-	17
Job description				
Clinical	61	9	43	9
Administrative	27	13	14	-
Research	15	6	4	5
Pharmacy	64	60	-	4
Teaching	9	8	-	1
Student	24	8	-	16
Other	9	8	1	-

Not all participants chose to answer the question regarding which healthcare district they work in. Ninety-one percent (n=138) chose to answer the question, of which 43 participants worked for the hospital district of Helsinki and Uusimaa (see Figure 4). The

second largest group of participants worked for the hospital district of Southwest Finland (n=32). Following up by Northern Ostrobothnia hospital district (n=10), Päijät-Häme hospital district (n=9), Vaasa hospital district (n=8), South Karelia Social and Health Care district (Eksote) (n=7), North Savo hospital district (n=6), Satakunta hospital district (n=5), Pirkanmaa hospital district (n=5), Social and Health services in Kymenlaakso (Kymsote) (n=3), Central Finland hospital district (n=3), East Savo hospital district Joint Municipal Authority (Sosteri) (n=2), Siun Sote – Joint Municipal Authority for North Karelia Social and Health services (n=2), South Ostrobothnia hospital district (n=1), Lapland hospital district (n=1), and Kanta-Häme hospital district (n=1). Six participants chose the 'none of the above' option. The remaining 7 participants did not answer the question.

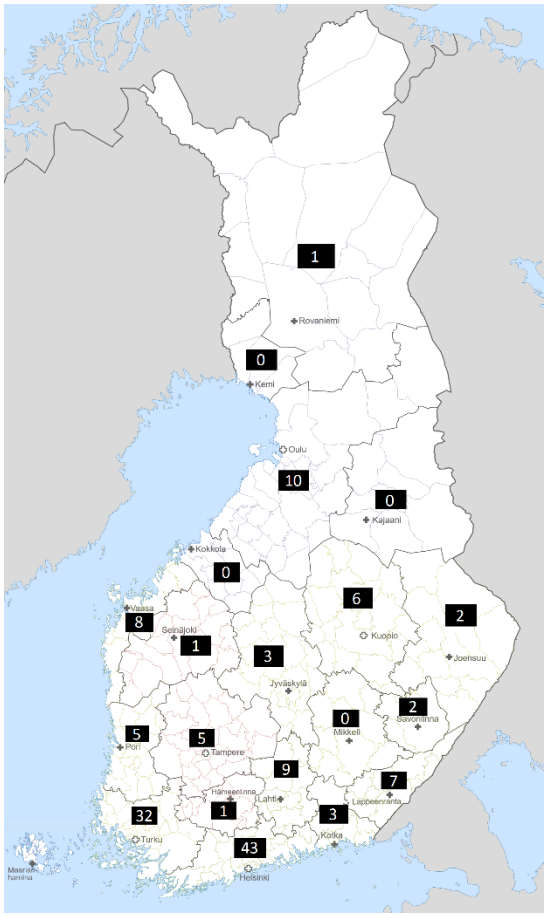

Figure 4. The geographical distribution of the participants (adapted from Wikipedia, 2021).

More than half of all physicians (n=41) chose to mention their specialty, of whom 19 physicians chose 'Other specialties' option. In this category, specialties such as

occupational health care, and general practice, could be included. Internal medicinal specialties (e.g. endocrinology, infectious diseases, cardiology) and other conservative specialties (e.g. dermatology, lung diseases, child neurology, oncology) had an almost equal share of physicians (n=7; n=6). Only 1 physician had other operational specialties (e.g. anesthesiology, ear-, nose-, and throat diseases, gynecology, obstetrics), another physician had specialty in diagnostics (e.g. clinical pharmacology and pharmacotherapy, pathology, radiology), and another had a specialty in drug treatment for children and off-label treatment. Others were dentists (n=3), geriatrics (n=2) and some had specialties in acute medicine (n=1). When it comes to pharmacists, 3 participants had a specialty in the evaluation of pharmacotherapy, 3 participants had a specialty in the pharmaceutical industry, and 1 participant had a specialty regarding a specific unit at a hospital. The remaining participants chose to not answer the question (n=14) or the 'I do not have a specialty' option (n=89).

5.2. Prior training or education

More than half of the participants did have a prior training or education in PGx: 56% of all pharmacists, 83% of all physicians, and 88% of all students (see Table 4). Only 32% (n=49) did not have a prior training or education in pharmacogenetics.

Table 4. The proportion of participants with prior training or education in pharmacogenetics

Prior PGx education	**Physicians (%)**	**Pharmacists (%)**	**Students (%)**
Yes	38 (83)	49 (56)	15 (88)
No	8 (17)	39 (44)	2 (12)

It is noteworthy that though, that participants could select multiple choices, which made the number of responses greater than the total number of participants (see Table 5). Almost all of whom answering multiple choices, had received PGx education during basic education and during postgraduate education. A few participants (n=3) had received

pharmacogenetic education during basic education and wanted to receive further education. Eighty-eight percent of all students were knowledgeable about PGx. The remaining participants, who had not received any PGx education, were nearly all interested in learning more. Moreover, a very small proportion of participants (n=5), noticeable only pharmacists, were not interested in receiving additional education in pharmacogenetics.

Table 5. The proportion of responses from each profession

Statement	**Physicians**	**Pharmacists**	**Students**
Yes, during my basic education	32	33	14
Yes, during postgraduate education	5	6	1
Yes, as a trainee/intern	5	-	-
Yes, as continuing education or courses arranged by employers	7	12	-
No, but interested in receiving any education	10	35	2
No, not interested in receiving any education	-	5	-

5.3. Participants' interest in applying pharmacogenetic tests in practice

Only 2 participants were very uninterested in applying PGx tests to patient care, whereas a slightly larger group of participants (n=6) were uninterested. The largest group (n=51) were interested, while a quite similar number of participants (n=50) were neutral. Twenty-eight percent of all participants (n=42) were very interested in applying PGx testing to patient care.

6. Perception and knowledge of PGx testing

When asking if the participants had any possibility to get a referral for a PGx test at their workplace (e.g. B-Farma-D, B-FarmL-D), the answers were clear. Quite near all participants

(96%) chose to answer the question. Forty-seven percent of the responders had no idea if this possibility were offered at their workplace. Forty-three percent had no possibility for a referral at their workplace, whilst only 10 percent had. Of these were 12 physicians and 2 pharmacists. The responses of physicians showed the 22% had no possibility for a referral at their workplace, whilst 26% had. Fifty-two percent of physicians had no idea if this possibility were offered at their workplace.

When asking if the participant ever prescribed/ordered a PGx test for a patient (e.g. B-FarmL-D, B-Farma-D), the answers were quite like the ones above. Ninety-five percent of all participants chose to answer the question, with only 3 participants answering 'Yes'. Of those 3 participants, 1 physician prescribed/ordered a PGx test 1-5 times, and both remaining physicians had prescribed/ordered a PGx test 6-15 times. Both physicians that had prescribed a PGx test 6-15 times, were from the hospital district of Southwest Finland. The physician that only had prescribed a PGx test 1-5 times, was from the Lapland hospital district. No one from the remaining hospital districts in Finland had prescribed/ordered a PGx test for the patient. The reason why a PGx test was performed was primarily to check suitable antidepressants, and pain medications for the patient, but also to evaluate the risk of polypharmacy. Cardiovascular medications, anticoagulants, and cancer medications were also checked up, but not to the same extent.

When asking if a patient ever visited them in their clinic with the results of a PGx test, the results were well reflected from previous results. Ninety-four percent of all participants chose to answer the question, with the majority of all, 95 percent (n=135), answering 'No'. A small proportion, 5%, has been involved in a situation mentioned above, where 3 participants had been involved only once, 2 participants 2-3 times and 2 participants 5+ times.

The participants had to state their opinion regarding the cost of PGx test (approximately 300€). The majority of all (n=92) thought it was either very expensive (n=12) or expensive (n=80). About one third of all participants thought it was a reasonable price. A clear minority (n=6) thought it was an inexpensive price.

The final question was a multiple-choice question regarding the usage of pharmacogenetic databases. Ninety-nine participants had not used any PGx databases. For those ones that

had, the Duodecim Drug Database for Pharmacogenetics, and more specifically the Abomics GeneRx database, was the most popular database (see Figure 5). Only an insignificant number of participants, 1-2 participants, had used FDA's website, EMA's website, the pharmacogenetic module in Tietoevry's Lifecare, CPIC's website and/or PharmGKB's website.

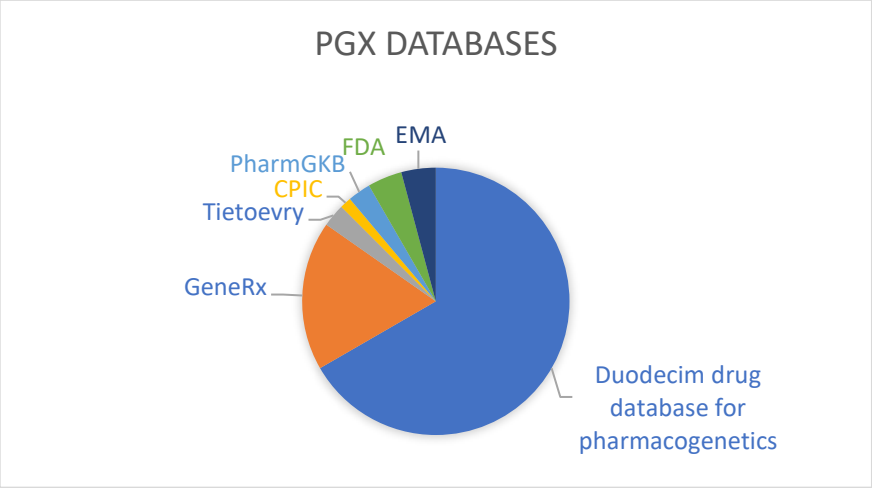

Figure 5. The proportion of participants who have used the Duodecim drug database for pharmacogenetics, the Abomics GeneRx database, FDA's website, EMA's website, the pharmacogenetic module in Tietoevry's Lifecare, CPIC's website and/or PharmGKB's website.

7. Assessment of the participants' general knowledge

Three participants chose not to answer any of the statements that measured their general knowledge of pharmacogenetics. In their case, the results were reported as "Neutral". All statements are listed below in table 6 (see Table 6).

Regarding the first statement, '*I have general knowledge with the basics of genetics*', of the participants with over 10 years of experience, 8 participants (5.3%) strongly agreed, 22 participants (14.6%) agreed, 24 participants (15.9%) were neutral, 12 participants (7.9%) disagreed, and 11 participants (7.3%) strongly disagreed. On the other hand, 19 participants (12.6%), under 10 years of experience, strongly agreed, 21 participants (13.9%) agreed, 11 participants (7.3%) were neutral, 4 participants (2.6%) disagreed, and

2 participants (1.3%) strongly disagreed. Results from the smallest group, students, showed that 7 students (4.6%) strongly agreed, 9 students (6.0%) agreed, and 1 student (0.7%) disagreed.

Regarding the second statement, '*I have knowledge with the basics of pharmacogenetics*', of the participants with over 10 years of experience, 5 participants (3.3%) strongly agreed, 17 participants (11.3%) agreed, 26 participants (17.2%) were neutral, 16 participants (10.6%) disagreed, and 13 participants (8.6%) strongly disagreed. Eleven participants (7.3%), under 10 years of experience, strongly agreed, 25 participants (16.3%) agreed, 11 participants (7.3%) were neutral, 6 participants (4.0%) disagreed, and 4 participants (2.6%) strongly disagreed. Four students (2.6%) strongly agreed, 10 students (6.6%) agreed, 1 student (0.7%) were neutral, and 2 students (1.3%) disagreed.

Regarding the third statement, '*I consider myself able to interpret the results of a pharmacogenetic test*', of the participants with over 10 years of experience, 1 participant (0.7%) strongly agreed, 6 participants (4.0%) agreed, 17 participants (11.3%) were neutral, 20 participants (13.2%) disagreed, and 33 participants (21.9%) strongly disagreed. Correspondingly, of the participants with under 10 years of experience, 2 participants (1.3%) strongly agreed, 10 participants (6.6%) agreed, 2 participants (1.3%) were neutral, 25 participants (16.6%) disagreed, and 18 participants (11.9%) strongly disagreed. Two students (1.3%) strongly agreed, 1 student (0.7%) agreed, 4 students (2.6%) were neutral, 6 students (4.0%) disagreed, and 4 students (2.6%) strongly disagreed.

Regarding the fourth statement, '*I can identify which drugs may require a pharmacogenetic test*', of the participants with over 10 years of experience, 3 participants (2,0%) strongly agreed, 11 participants (7.3%) agreed, 17 participants (11.3%) were neutral, 21 participants (13.9%) disagreed, and 25 participants (16.6%) strongly disagreed. Whilst, 4 participants (2.6%), under 10 years of experience, strongly agreed, 10 participants (6.6%) agreed, 13 participants (8.6%) were neutral, 24 participants (15.9%) disagreed, and 6 participants (4.0%) strongly disagreed. Seven students (4.6%) agreed, 2 students (1.3%) were neutral, 6 students (4.0%) disagreed, and 2 students (1.3%) strongly disagreed.

Regarding the fifth statement, '*I feel it is my responsibility to inform patients about the availability of pharmacogenetic tests'*, of the participants with over 10 years of experience, 5 participants (3.3%) strongly agreed, 8 participants (5.3%) agreed, 27 participants (17.9%) were neutral, 16 participants (10.6%) disagreed, and 21 participants (14.0%) strongly disagreed. Whereas, 2 participants (1.3%), under 10 years of experience, strongly agreed, 12 participants (7.9%) agreed, 21 participants (13.9%) were neutral, 15 participants (9.9%) disagreed, and 7 participants (4.6%) strongly disagreed. One student (0.7%) strongly agreed, 1 student (0.7%) agreed, 6 students (4.0%) were neutral, 7 students (4.6%) disagreed, and 2 students (1.3%) strongly disagreed.

Regarding the sixth statement, *'I believe that pharmacogenetic testing can both increase safety and efficacy of drugs'*, of the participants with over 10 years of experience, 24 participants (15.9%) strongly agreed, 37 participants (24.5%) agreed, 13 participants (8.6%) were neutral, 2 participants (1.3%) disagreed, and 1 participant (0.7%) strongly disagreed. When 31 participants (20.5%), under 10 years of experience, strongly agreed, 22 participants (14.6%) agreed, 2 participants (1.3%) were neutral, and 1 participant (0.7%) disagreed. Eight students (5.3%) strongly agreed, and 9 students (6.0%) agreed.

Regarding the seventh statement, '*I believe that pharmacogenetic testing is helpful for predicting the risk of side effects for the patient'* (see Figure 6), of the participants with over 10 years of experience, 27 participants (17.9%) strongly agreed, 36 participants (23.8%) agreed, 11 participants (7.3%) were neutral, 2 participants (1.3%) disagreed, and 1 participant (0.7%) strongly disagreed. Whilst, 32 participants (21.2%), under 10 years of experience, strongly agreed, 22 participants (14.6%) agreed, and 2 participants (1.3%) disagreed. Ten students (6.6%) strongly agreed, 5 participants (3.3%) agreed, and 2 participant (1.3%) were neutral.

Table 6. Statements that measure participants' general knowledge regarding pharmacogenetics

	Statement
1.	I have general knowledge with the basics of genetics.
2.	I have knowledge with the basics of pharmacogenetics.
3.	I consider myself able to interpret the results of a pharmacogenetic test.
4.	I can identify which drugs may require a pharmacogenetic test.
5.	I feel it is my responsibility to inform patients about the availability of pharmacogenetic tests.
6.	I believe that pharmacogenetic testing can both increase safety and efficacy of drugs.
7.	I believe that pharmacogenetic testing is helpful for predicting the risk of side effects for the patient.

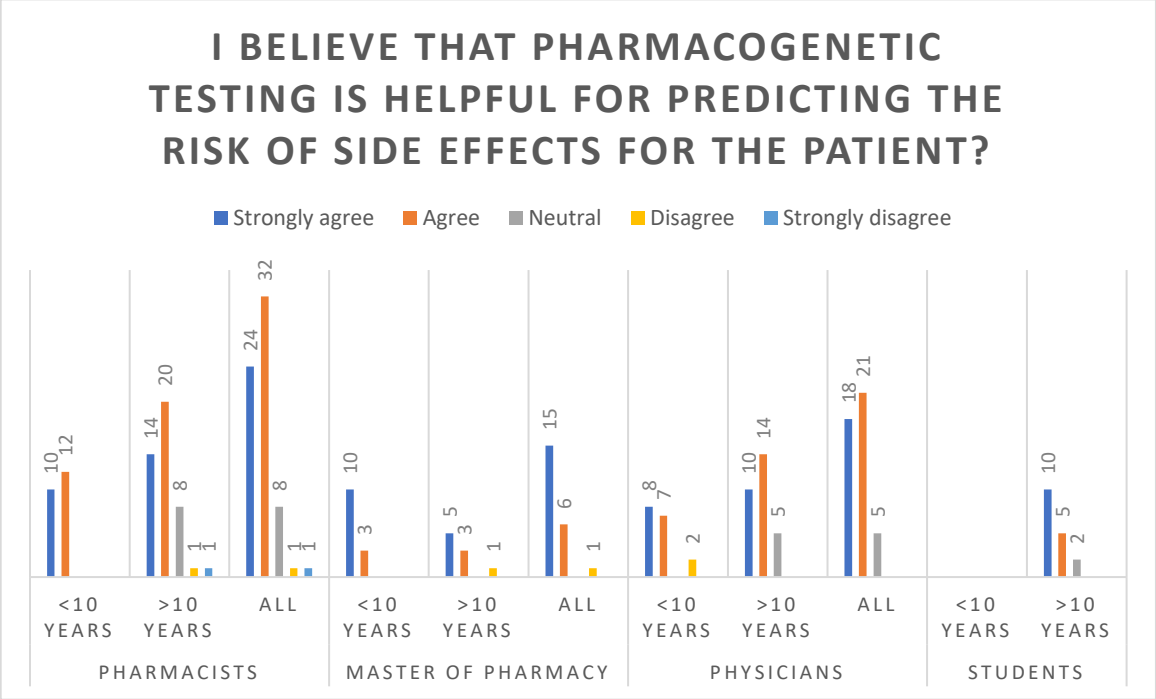

Figure 6. Proportion of answers to the statement 'I believe that pharmacogenetic testing is helpful for predicting the risk of side effects for the patient' categorized by profession and years of experience.

8. Assessment of the participants' deeper knowledge

Another aim of the thesis was to examine the participants' deeper knowledge regarding pharmacogenetics. Almost half of all participants (n=68) chose to continue to this part (see Figure 7). The third statement, which concerned the effects of genetic variation on drug treatment, got the greatest number of correct answers. It was followed by the first statement, which concerns correct terminology. The fourth and ninth statement, both regarding how genetic polymorphism affects drug treatment, had about the same proportion of correct, incorrect and 'I do not know' answers, thus making them equally easy and/or difficult statements. Statement 7 (concerns guidelines of genetic variation) and 8 (concerns what impaired biological function may have for the effect on drug treatment) are similar in the same way as previously mentioned. The second statement concerns genes that are affected by PGx, statement 5 concerns EMA's requirements about PGx testing, and statement 6 concerns alleles and their effect on the metabolic pattern. These three statements all had the most answers on the 'I do not know' option, thus making them similar among themselves. The most difficult statement was number 10, with 0 correct answers. This statement concerned the degree of polymorphism among the Finnish population.

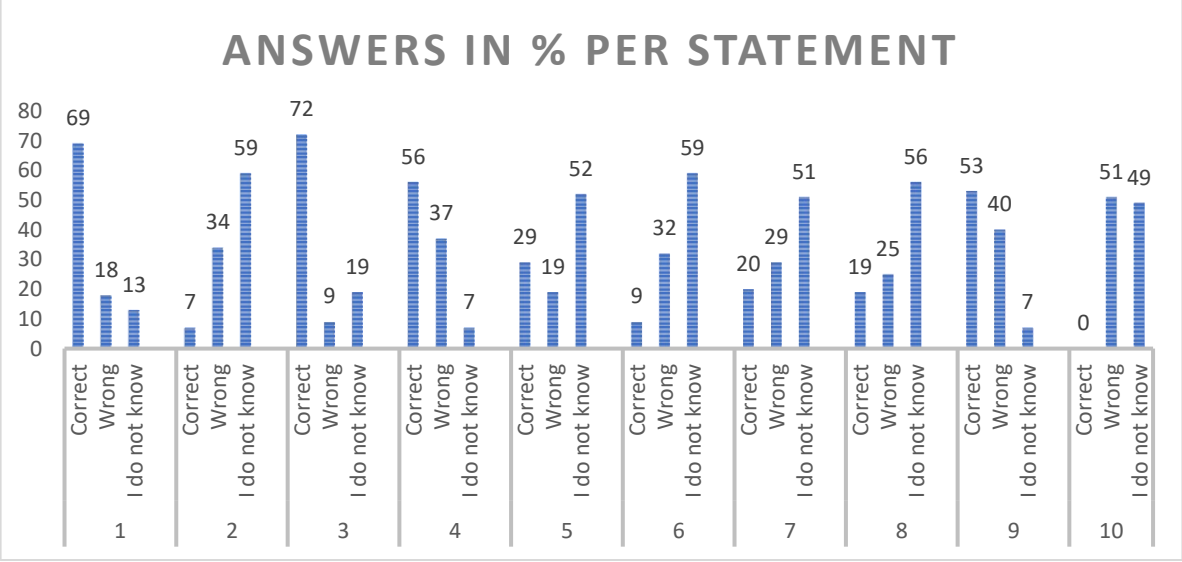

Figure 7. The proportion of correct, incorrect, and uncertain answers to each statement. The statements 1-10 are listed in 'Materials and Methods' section of the study.

9. Further education

The question, regarding how the participants would prefer further education in pharmacogenetics, was a multiple-choice question. Online lecture was the most popular learning method of all participants (see Table 7). The two following learning methods had approximately same level of popularity: lecture and online courses for self-studies. Learning by listening to podcasts, searching the internet and by reading a book were the least popular learning methods. Even this time, 5 participants showed no interest in learning more about PGx, all of which being pharmacists. Apart from the learning methods in table 7, there were participants that were interested in receiving more education from a competent PGx person and various types of practical exercises. Some, by reading an article and others, as a course with assignments. Almost 40% of all participants chose to enter their email address at the end of the survey to get more information about pharmacogenetics.

Table 7. The proportion of responders per learning method

Learning method	**Proportion of responders**
Lecture	69
Online lecture	101
Book	14
Online courses for self-studies	66
Via internet	28
Podcasts	31
Not interested in receiving more PGx education	5

10. Comparison with different countries

Part 2 of this thesis was to compare the results with different countries. Similar studies have been conducted in e.g. the Netherlands (in 2021) and the USA (in 2020), thus making a comparison with those countries possible. The Dutch study was more like the Finnish one, resulting in a more accurate comparison.

The Dutch study involved 100 pharmacists (50%), 73 physicians (36%) and 28 students (14%) (Edris, et al., 2021). In percentage, this does not differ much from the Finnish study: 58%; 30%; 12%. The study consisted of two parts, the first one including information about participants' characteristics, and the second one about deeper PGx knowledge. Only 3% of all participants from the Dutch study did not continue to the second part, whereas the percentage of the Finnish participants is higher, 55%.

In part 1, 62% of all participants in the Dutch study had under 10 years of experience, 33% of whom being physicians, and 49% pharmacists. Students in the Dutch study were counted as a student and not as a student with part-time work, as in the Finnish study. When compared to the Finnish study, 40% had under 10 years of experience. Of the 40%, 28.3% were physicians, 63.3% pharmacists, and 8.3% students. Fifty-eight percent of all participants in the Dutch study did not have any prior education in pharmacogenetics, whilst the corresponding number in Finland was 31 percent. In contrast, among students the percentage is 64% in the Dutch study for having a prior education and 82% in the Finnish study. Nine percent of the participants in the Dutch study have had prior education during postgraduate education, whilst 8 percent of the Finnish participants had prior education during postgraduate education. A small proportion of the Dutch participants, 9%, had counseled patients regarding the answers from their PGx test. Among the Finnish participants, this percentage was even lower, 5%. However, this study showed that more Finnish participants, 10% versus 3%, were aware of the availability of PGx tests at their workplace.

Fifty-three percent of the Dutch participants agreed with the statement '*I have general knowledge with the basics of genetics'*, whereas 34 percent of the Finnish participants agreed. However, the number of participants who strongly agreed was 7% in the Dutch study and 23% in the Finnish study. Twenty-one percent of the Dutch participants agreed

with the statement '*I have knowledge with the basics of* pharmacogenetics' and 34 percent Finnish participants agreed. Fifty-four percent of the Dutch participants agreed with the statement '*I believe that pharmacogenetic testing can both increase safety and efficacy of drugs'*, whilst 45 percent of the Finnish participants agreed. In contrast, 22% versus 42% strongly agreed.

In part 2, assessing the deeper knowledge regarding pharmacogenetics, 29% of the Finnish participants had answered correctly to which drugs may require PGx testing according to EMA (see Table 8), whereas 25% of the Dutch participants had answered correctly on the same statement. The proportion of correct answers by the Dutch to the statement regarding metabolic pattern of a CYP2C19*2/*2 genotype, was 13%, compared to 9% of the Finnish. Twenty-seven percent of the Dutch participants answered correctly on the statement regarding the main metabolic CYP enzyme of voriconazole, whereas 20 percent of the Finnish participants answered correctly. As for the statement regarding DPD deficiency and the resulting side effects, 21% of the Dutch participants answered correctly, whereas nearly the same proportion of the Finnish participants answered correctly, 19%. When asked about the side effects of codeine in patients with genetic variation in CYP2D6, 57% of the Dutch study answered correctly, while 53% correct answers were given from the Finnish participants.

Table 8. The proportion of correct, incorrect, and uncertain answers in the Dutch study versus the Finnish study

	% Dutch study/ Finnish study		
	Correct answer	Incorrect answer	I do not know
Identifying drugs requiring pharmacogenetic testing according to EMA	25/29	10/19	65/52
Interpretation of CYP2C19 genotype results for a patient taking clopidogrel	13/9	10/32	78/59

Voriconazole main metabolizing pharmacogene	27/20	13/29	60/51
Dihydropyrimidine dehydrogenase association with side effects	21/19	24/25	55/56
CYP2D6 association with side effects of codeine	57/53	18/40	25/7

The study conducted in USA was distributed to 349 healthcare workers, of which 55 responses were collected (15.8%) (Johengen, et al., 2020). Most of the participants were physicians (n=46), which left a small number of pharmacists left (n=5). There were 2 nurses among the participants and 2 physician assistants, but these are not considered in this comparison. Many participants worked in general medicine or family medicine, whilst the largest group of Finnish participants worked at a pharmacy. A larger percentage, 7.3%, of the Finnish participants could interpret the results of a PGx test compared to the study conducted in USA, 3.6%. Twenty-one participants (38%) from the American study had interacted with results from a PGx test before, whereas only 7 Finnish participants (5%) had experienced the same situation. Almost the same number of Finnish participants (n=4) and American participants (n=5) had ordered a PGx test, but as percentage, 2.8% versus 9.1%. Approximately 93% of the American participants indicated that they were interested in receiving further PGx education, while approximately 97% of the Finnish participants were interested. The largest group (70%) of the American participants preferred live learning activities as a learning method, when the most chosen learning method for the Finnish participants was online learning activities. The second most popular learning method was online learning activities by American participants and live learning activities by Finnish.

11. Discussion

This was the first study conducted in Finland to assess the knowledge and perceptions of pharmacogenetics among Finnish physicians and pharmacists. Studies conducted in the

Netherlands and in the USA, had used the same research method. The results in each and every country was for the most part similar, indicating that the applied method was sufficiently suitable for this purpose. The method obtains the results of the desired questions and/or statements. However, this study had few exceptions.

There is no guarantee that those who responded to the survey were in fact physicians or pharmacists. In addition, external factors, such as stress, can be the cause of misleading responses. Participants' own interest in PGx and PGx tests, and their readiness to answer the survey, may also affect their responses. The low number of students in this study limits the actual knowledge of PGx in training. Additionally, a greater number of participants would have given more accurate results. On the contrary, the advantages of an online survey are that it is a cheap and fast way to get answers to desired questions. The participants are anonymous and can whenever answer the questions. In addition, the survey has enabled simultaneous analysis of several different variables. An online survey was well suited to this type of research, as, for example, the questioner's tone of voice during an oral examination can affect the respondents. Additionally, an online survey can be distributed to a larger geographical area.

Amongst 151 participants, 34% agreed to having self-assessed general knowledge of genetics and pharmacogenetics. Only 11% stated they were able to interpret the results of a PGx test. The results were unexpected based on that 34% agreed to knowing the basics of PGx. There is room for different interpretive possibilities, as some may be able to interpret the results but not to the extent that they feel confident to present them to others or make medication decision based on the results. Another theory could be that those who have taken a PGx test, such as pharmacists and/or physicians, can interpret the results themselves. After all, results from previous statements do not fully support that theory. The statement about identifying which drugs may require a PGx test, can be correlated to the previous statement, thus making the results quite similar, in this case 19% of the participants agreed. These results may be due to the low proportion of participants who actually used pharmacogenetic databases. If the use of databases had been higher among participants, the answers would have most likely been different. Among those who used databases, Duodecim Drug Database for Pharmacogenetics, and

more specifically the Abomics GeneRx database, was the most used database among participants. This was expected, since it is the main database used at pharmacies to evaluate drug interactions.

Regarding the participants' deeper knowledge of PGx many participants had answered incorrectly. On the one hand, it may be a sign of a lack of knowledge, but on the other hand, the questions may have been unclear. For example, no one answered correctly to statement 10 (see Chapter 4), as 5% is only the ratio of CYP2C19 and/or CYP2D6 impacted medications that are approved for sale in Finland. However, if the consumption statistics are considered, and all significant pharmacogenetic recommendations are included, the corresponding ratio is 19.2% (Kelasto, 2022).

No one really felt it was their responsibility to inform patients about the availability of PGx tests. Only 14% of all participants agreed to the statement. These results were alarming since both pharmacists and physicians have a responsibility to inform the patient about serious drug interactions. Either they do not know that it may be on their responsibility, they do not master the subject, have a dissenting opinion, or pharmacists think it is the role of physicians and vice versa. The fact that students did not feel that it is their responsibility to inform patients about the availability of PGx tests, is not surprising. Students may feel that those who have more experience in the industry should carry that responsibility. However, this study showed that the majority of participants with over 10 years of experience, strongly disagreed to the statement. The high percentage of prior PGx training among participants does not go hand in hand with the low percentages of participants who stated that they could interpret the results of a PGx test (11%), participants who could identify with drugs may require a PGx test (19%), and participants who felt it is their responsibility to inform patients about the availability of a PGx test (14%). Despite the low percentage, 62% of all participants were interested in applying PGx in practice, excluded those ones who are strongly interested. Prior education in PGx was correlated to a higher percentage of general knowledge about PGx, especially among students. These findings are similar to findings conducted by Edris et al. To sum up, an increased dissemination of information about PGx and PGx testing between professions could result in a higher percentage of PGx testing in clinical praxis. Universities seem to have done a great job in teaching about PGx, as the study showed that a large proportion of the participants had gained knowledge during their basic education. A large proportion

are still interested in learning more about PGx and PGx testing. Given future education, online lectures would be preferable, also online courses for self-studies and normal lectures.

A great percentage of participants (45%) agreed that PGx testing can both increase safety and efficacy of drugs. A similar percentage (42%) agreed that PGx testing is helpful for predicting the risk of side effects for the patient. This means that the participants knew that PGx testing can improve the patients' health, but still, they do not feel it is their responsibility to inform patients about PGx tests. Since the majority were pharmacists in this study, and they do not have the right to write a referral to a PGx test in Finland, the percentage was expected to be low. However, it is alarming that 47% of the participants had no idea if a PGx test were offered at their workplace. PGx tests (B-Farm-L and B-Farma-D) have been available for several years in all major private health care clinics and all major public healthcare districts, except for East Savo, Essote, Helsinki and Uusimaa, North Savo, and Siun Sote (Tarkiainen, et al., 2021). The hospital district of Helsinki and Uusimaa was the last hospital district to make PGx testing available to its physicians starting in 2022. The results seem to suggest that although PGx testing was in practice available to all physicians and patients in Finland, most physicians were unaware of the availability. Better education on and advertising for PGx testing and PGx education, especially the financial benefits of a PGx test, could change participants' views on the price of the test and thus increase the use of PGx testing.

As for the question if the participant ever prescribed or ordered a PGx test for a patient (e.g. B-FarmL-D, B-Farma-D), the results is not applicable due to the fact that only physicians in Finland can prescribe a referral to a PGx test. The proportion of physicians that prescribed a PGx tests, is not directly linked to their years of experience, as would be expected. Of the two physicians who prescribed a PGx test 6-15 times, one physician had 4-6 years of experience and the other 30+ years of experience. The third physician had 21-30 years of experience and had prescribed a PGx test 1-5 times. The low number of respondents who had ordered a test somewhat arbitrary. Pharmacists are able to sell a PGx test for the patient, but based on the previous results, they do not have the knowledge on how to proceed with it and most pharmacies do not offer a PGx test to their customers.

The fact that PGx tests have not earlier been widely used in Helsinki and Uusimaa (see Figure 3) may be the reason why only 5% of participants have ever had a patient visit them in their clinic with the results of a PGx test. If a greater number of participants from western Finland and central Finland had participated in the study, results regarding clinical praxis and deeper knowledge of PGx could have been higher. The majority of this proportion were physicians (n=5), the remaining were pharmacists (n=2). This was not unusual, as the physician prescribes a referral to a PGx test for the patient, after which the patient makes a return visit to the same physician who then interpret the results.

This study showed also differences in results between countries. In general, there were not large differences between the countries. However, a clear difference was regarding prior PGx education, where a higher proportion of the Finnish participants had received PGx education compared with the Dutch participants. The reason for this may be that Finnish universities' curriculums cover PGx to a greater extent than Dutch university curriculums. The number of courses offered, and which of these are mandatory, can also be assumed as one reason for the differences. The difference may potentially depend also on the time when the questionnaires were distributed, as the Dutch study was conducted several years earlier.

The participants with under 10 years of experience were more enthusiastic about learning more about PGx and more knowledgeable about PGx than the participant with over 10 years of experience. This result was expected as PGx is a growing new area.

It is worth mentioning that the majority of the participants in the study were pharmacists working in pharmacies. If the proportion of pharmacists working with other tasks, such as pharmacotherapy, had been higher, the results could have been different. The same goes for higher proportion of physicians. For more reliable results, the survey could have several multiple-choice questions and/or statements and more 'Other, what?' options. This could be something to consider in further research.

12. Conclusions

The survey was open for 41 days, resulting in 151 answers. The survey was available in 3 different languages, and this benefited the participants. Most participants worked at a hospital district located in Southern Finland. The largest proportion of all participants worked at the hospital district of Helsinki and Uusimaa. Apart from that, the remaining participants were evenly distributed from the whole of Finland. Most of the participants were women. Pharmacists were the largest group of participants, while the smallest were students. Among participants, most had 21-30 years of experience, fewest had 7-10 years of experience. There was no major difference between higher and lower degree education among participants, students excluded. Most physicians had a specialty, while this was extremely rare among pharmacists. Most pharmacists worked at a pharmacy, while most physicians worked with clinical tasks. A few students worked part-time with various tasks. It was common that the participants had received prior training or education in pharmacogenetics, since most of the participants had. However, it was uncommon for a participant to have prescribed/ordered a PGx test for a patient. Further education in pharmacogenetics was mostly wanted as an online lecture and least wanted by reading a book. Only pharmacists did not want any further education in pharmacogenetics.

Participants with under 10 years of experience had more general knowledge regarding pharmacogenetics than participants with over 10 years of experience. Students were very knowledgeable, as 94% strongly agreed or agreed. The same goes for the second statement, where participants with over 10 years of experience knew least of all participants about the basics of pharmacogenetics. Again, students were the group that knew the most, 79% strongly agreed or agreed. Only a small number of participants could really interpret the results of a PGx test, all in all 3.3%. This time it was not a remarkable difference between years of experience. Participants with over 10 years of experience had least knowledge regarding identifying which drugs may require a PGx test. Participants with under 10 years of experience had slightly more knowledge, but the margin is certainly small. However, most students were knowledgeable and could identify which drugs may require a PGx test. None of the participants really felt that it was their responsibility to inform patients about the availability of the PGx test. Only 5.3% of all participants strongly

agreed to the statement. Despite lack of self-assessed responsibility, many participants (62%) were interested in applying PGx testing to patient care. However, three hundred euros for a PGx test was too expensive according to most participants. Almost all participants either strongly agreed or agreed to the statement that they believe that PGx testing can both increase safety and efficacy of drugs. Students were the group of participants that mostly strongly agreed, followed by participants with under 10 years of experience and, lastly, participants with over 10 years of experience. The largest group of students thought that PGx testing is helpful for predicting the risk of side effects for the patient (see Figure 6). Physicians and pharmacists with over 10 years of experience mostly agreed to the statement. The group, in which all participants either strongly agreed or agreed, was the participants with under 10 years of experience with a Master's degree in pharmacy.

Most of the participants were, to some extent, knowledgeable about pharmacogenetics. Students showed the most self-knowledge about pharmacogenetics. Participants with under 10 years of experience have more general knowledge than participants with over 10 years of experience. This could be expected, given that PGx testing is quite a new method. Participants with over 10 years of experience must become knowledgeable on their own initiative, while participants with under 10 years of experience receive the information during their education. The topic 'drug metabolism' is greatly discussed within master's degree programs in Finland, thus resulting in knowledgeable participants (see Figure 6). Even though pharmacogenetics was a new topic for some, many participants were still interested in receiving more education.

There were more participants with over 10 years of experience in the Finnish study compared to the Dutch study. This could reflect on the number of correct answers given in table 8. However, it is remarkable that a higher proportion of participants in the Dutch study did not receive any prior education in pharmacogenetics. Finnish students were more knowledgeable about pharmacogenetics than Dutch students. More Dutch participants agreed to the statement about having general knowledge about the basics of genetics than Finnish participants. On the contrary, more Finnish participants strongly agreed to the same statement, making Finnish participants more knowledgeable. Finnish participants were more knowledgeable regarding the basics of pharmacogenetics than

Dutch participants. A larger proportion of Dutch participants agreed that PGx testing could increase both the safety and efficacy of drugs than Finnish participants. However, a larger proportion of Finnish participants strongly agreed to the same statement. About deeper knowledge about pharmacogenetics, the Finnish participants had more correct answers than the Dutch participants when regarding which drugs may require PGx testing according to EMA. Overall, the largest number of answers were at the 'I do not know' option, except from the statement regarding codeine, making it the easiest statement for both the Dutch participants and Finnish participants. Otherwise, Dutch participants had more correct answers.

Being able to interpret the results from a PGx test was more common among Finnish participants than among participants of the American study. However, interaction with a patient at a clinic regarding their PGx results as well as prescribing/ordering a PGx test for a patient was more common among American participants. Since the American study had more physicians, there were more people working in family medicine or general medicine, compared to Finnish participants. Participants from both countries were highly interested in receiving further education. Among the most chosen learning methods were live learning activities and online learning activities.

As a summary, students were more knowledgeable about the basics of genetics, basics of pharmacogenetics, and at identifying which drugs may require a PGx test. They had also the highest percentage in believing that PGx testing can both increase safety and efficacy of drugs. Finnish participants were more knowledgeable regarding the basics of pharmacogenetics, whilst Dutch participants had deeper knowledge about pharmacogenetics. American participants had more experience in patient care, compared to Finnish participants. Finnish participants could better interpret results from a PGx test, compared to participants in the American study.

Lastly, one can say with certainty that we are heading towards a new era of personalized medicine. Although, PGx and PGx testing have been shown to have a significant clinical benefit, the knowledge of PGx and PGx testing is deficient. However, in spite of that, the field of PGx is widely discussed and developed. Academia, among others, play an important role in the dissemination of knowledge of PGx and PGx testing.

One of the goals of this study was to give participants a deeper insight into the importance of PGx and PGx tests. The future is unpredictable, but all we can do is hope that PGx is becoming more and more common from generation to generation.

13. Summary in Swedish – Svensk sammanfattning

Enkätbaserad utvärdering av farmakogenetisk kunskap bland finska läkare, farmaceuter och studerande i respektive område.

13.1. Introduktion

Farmakogenetiska tester utförs för att utvärdera en persons potentiella respons på en läkemedelsbehandling. Dessa tester ökar sannolikheten för patienten att få rätt medicinering och rätt dos för en specifik sjukdom vid det första läkarbesöket. Studier har också visat att patienter är nöjdare och med större sannolikhet följer doseringsanvisningar ifall ett farmakogenetiskt test har blivit utfört (Brixner, et. al., 2016). Syftet med denna studie var att kartlägga finska läkares, farmaceuters och studerandes kunskap om farmakogenetik. Dessutom gjordes en jämförelse mellan resultaten från den finska studien med resultaten från studier gjorda av Edris et al. och Johengen et al, där liknande studier utfördes i Nederländerna respektive USA. Det allmänna målet var att väcka mera intresse för farmakogenetik och öka kunskapsspridningen.

13.2. Material och metoder

En tvådelad webbaserad enkät med totalt 28 frågor och/eller påståenden, skickades ut till finska läkare och farmaceuter (se Appendix 15.1. och 15.2.). Frågorna och/eller påståendena var starkt inspirerade av liknande studierna som utfördes av Edris med kollegor och Johengen med kollegor. Enkäten var öppen från den 27 januari 2022 till den

8 mars 2022. Enkäten var fritt översatt till 3 språk: engelska, finska och svenska, för att få pålitligare svar. Den första delen har 18 frågor och/eller påståenden som mäter deltagarnas allmänna egenskaper, såsom kön, år av arbetserfarenhet och utbildning. I stort sett var alla frågor flervalsfrågor med ett 'Jag vet inte'-alternativ och ett 'Välj alla som passar in'-alternativ. Endast ett fåtal av frågorna var obligatoriska att svara på, exempelvis frågor om kön och utbildning. Den andra delen hade 10 rätt/fel-flervalsfrågor som mätte deltagarnas djupare kunskap om farmakogenetik. Alla delar var frivilliga att svara på, och resultaten användes endast i forskningssyfte. Det publicerades även en artikel till Duodecims läkemedelsdatabas om farmakogenetik, för att öka spridningen av enkäten (se Appendix 15.3.).

13.3. Resultat

Enkäten fick 151 svar av 88 farmaceuter, 46 läkare och 17 studerande. Majoriteten av alla deltagare valde att svara på enkäten på finska, en tredjedel valde svenska och två deltagare valde engelska. De flesta hade 21–30 år av arbetserfarenhet, följt efter den näst största gruppen med 0–3 år av arbetserfarenhet. Gruppen med minst antal deltagare hade 7–10 år av arbetserfarenhet. Trettiosex procent hade högre högskoleutbildning, femtiotre procent hade lägre högskoleutbildning. Elva procent var fortfarande studeranden. De allra flesta läkare hade kliniska arbetsuppgifter, samtidigt som de allra flesta farmaceuter jobbade på apotek. Den största andelen av deltagare jobbade i södra delen av Finland, i Helsingfors och Nylands sjukvårdsdistrikt. Flera än hälften av alla deltagare hade haft tidigare någon form av utbildning om farmakogenetik. Största delen av deltagarna hade fått sin farmakogenetiska kunskap från grundutbildningen och/eller från andra utbildningar. Den mest populära databasen för sökinformation var Duodecims läkemedelsdatabas för farmakogenetik (Abomics PGx). Med tanke på fortsatt utbildning, var online-kurser och föreläsningar att föredra (se tabell 7).

De deltagare med under 10 år av erfarenhet kunde mera allmänt om genetik än de med över 10 år av erfarenhet. I stort sett alla studerande höll endera starkt med eller höll med samma fråga. Det samma gällde den allmänna kunskapen om farmakogenetik, vilka läkemedel som kan kräva ett farmakogenetiskt test och att farmakogenetiska tester kan

både öka säkerheten och verkan av läkemedlet. Endast ett fåtal kunde tolka resultaten från ett farmakogenetiskt test. Det var inte någon märkvärdig skillnad på arbetserfarenhetsåren. Ingen kände starkt att det var deras uppgift att informera patienterna om möjligheten till farmakogenetiska tester, men trots det, var över häften intresserade av att tillämpa farmakogenetiska tester i klinisk praxis. Majoriteten av alla deltagare ansåg att farmakogenetiska tester kan vara till hjälp för att förutspå risken för biverkningar för patienten. Dock upplevdes 300€ för ett farmakogenetiskt test vara rätt högt av de flesta deltagare.

Endast 68 av alla deltagare valde att fortsätta till andra delen som bestod av 10 rätt/fel-frågor. Denna del mätte deltagarnas djupare kunskap om farmakogenetik. Det påståendet som nästan alla fick rätt på var det tredje påståendet, som gällde hur genetisk variation kan påverka effekten av läkemedelsbehandlingen (se figur 7). Det första påståendet, som var ett påstående om rätt terminologi, var även ett lätt påstående. Däremot var det fjärde och nionde påståendena sinsemellan lika lätta eller svåra, med i stort sett samma rätt svar som fel svar. Det samma gällde för det sjunde och åttonde påståendet. Det andra, femte och sjätte påståendena hade allra flest valt ’Jag vet inte’ alternativet. Det svåraste påståendet var tionde påståendet, med 0 rätt svar, som gällde hur den genetiska polymorfismen är bland den finska populationen.

Den nederländska studien hade 201 svar, därav 100 farmaceuter, 73 läkaren, och 28 studenter. Procentuellt är detta inte så stor skillnad från den finska studien. En större skillnad sågs bland antal deltagare i den andra delen, där endast 3 % av de nederländska deltagarna deltog. I den finska studien var procenten avsevärt högre, 55 %. Det fanns flera deltagare i den nederländska studien med under 10 år av erfarenhet än i den finska. Femtioåtta procent av de nederländska deltagarna hade inte fått någon tidigare utbildning i farmakogenetik, medan denna siffra i den finska studien endast var trettioett procent. När det gällde studeranden i respektive studie, hade större andel av de finska studerandena fått tidigare utbildning i farmakogenetik. Andelen som starkt höll med påståendet om allmän kunskap om farmakogenetik var 23 % i den finska studien och 7 % i den nederländska. Finska deltagaren var även mera kunniga i grunderna i farmakogenetik. Andelen som starkt höll med påståendet ’*Jag tror att farmakogenetiska tester kan både öka säkerheten och verkan av läkemedlet’* var 42 % i den finska studien medan 22 % i den

nederländska. Angående djupare kunskap om farmakogenetik, var de finska deltagarna endast bättre på att identifiera vilka läkemedel som kan kräva ett farmakogenetiskt test enligt EMA, de resterande frågorna var deltagare från den nederländska studien bättre på (se tabell 8). En större andel av de finska deltagarna kunde tolka ett farmakogenetiskt test jämfört med de amerikanska deltagarna. Däremot hade de amerikanska deltagarna bättre kunskap om farmakogenetiska tester i praktiken än de finska. Flera finska deltagaren var intresserade av vidare utbildning än de amerikanska deltagarna.

13.4. Slutsats

Sammanfattningsvis kan man säga att alla deltagare var till viss mån kunniga om farmakogenetik. Trots att kunskapsspridningen om farmakogenetik är bristfällig, visade denna studie att det ändå finns ett ökat intresse av att lära sig mera. Eftersom farmakogenetik är ett relativt nytt område, kunde en tydlig skillnad i den farmakogenetiska kunskapen mellan erfarenhetsåren observeras. De facto att studenter var väldigt kunniga om farmakogenetik, och att de dessutom var intresserade av att implementera farmakogenetiska tester mer i klinisk praxis, kan vara precis det som farmakogenetiken behöver för att växa i framtiden.

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15. Appendix

15.1. Questions/statements that measure participants' general knowledge

1. Choose the language
    a. English
    b. Finnish
    c. Swedish
2. Sex
    a. Male
    b. Female
    c. Prefer not to say
3. What is your education?
    a. Specialist (physician)
    b. Specializing physician
    c. Physician
    d. Master's degree in Pharmacy
    e. Master of Bioscience (Specialization in Pharmacy)
    f. Bachelor's degree in Pharmacy
    g. Student
4. Employer? (Select all that apply)
    a. Physician
        i. District hospital
        ii. Central hospital
        iii. University hospital
        iv. Municipal Healthcare center
        v. Publicly listed company

vi. Government agencies
vii. Private
viii. Pharmaceutical industry
ix. Still being trained to be a physician
x. Other

b. Master's degree in Pharmacy
    i. Hospital
    ii. University hospital
    iii. Pharmacy
    iv. Pharmaceutical industry
    v. Still being trained to be a physician/pharmacist
    vi. Other
c. Master of Bioscience (Specialization in Pharmacy)
    i. Hospital
    ii. University hospital
    iii. Pharmacy
    iv. Pharmaceutical industry
    v. Still being trained to be a physician/pharmacist
    vi. Other
d. Pharmacist
    i. Hospital
    ii. University hospital
    iii. Pharmacy
    iv. Pharmaceutical industry
    v. Still being trained to be a physician/pharmacist
    vi. Other

5. Job description? (Select all that apply)
    a. Clinical
    b. Administrative
    c. Research
    d. Pharmacy
    e. Teaching
    f. Student
    g. None of the above
    h. Other, what?
6. In which hospital district do you work?
    a. South Karelia Social and Health Care District (Eksote)
    b. South Ostrobothnia Hospital District
    c. South Savo Social and Health Care Authority (Essote)
    d. Hospital District of Helsinki and Uusimaa
    e. East Savo Hospital District Joint Municipal Authority (Sosteri)
    f. Kainuu Social and Health Care Joint Municipal Authority
    g. Kanta-Häme Hospital District

    h. Central Ostrobothnia's Joint Municipal Authority for Specialized Medical Care and Basic Services
    i. Central Finland Hospital District
    j. Social and Health Services in Kymenlaakso (Kymsote)
    k. Lapland Hospital District
    l. Länsi-Pohja Healthcare District
    m. Pirkanmaa Hospital District
    n. Siun sote – Joint municipal authority for North Karelia social and health services
    o. Northern Ostrobothnia Hospital District
    p. North Savo Hospital District
    q. Päijät-Häme Hospital District
    r. Satakunta Hospital District
    s. Vaasa Hospital District
    t. Hospital District of Southwest Finland
    u. Ålands hälso- och sjukvård, ÅHS
    v. None of the above
7. What is your specialty? (Select all that apply)
    a. Surgical specialties
    b. Other operational specialties (e.g. anesthesiology, ear, nose, and throat diseases, gynecology, obstetrics)
    c. Internal medicine specialties (e.g. endocrinology, infectious disease, cardiology)
    d. Other conservative specialties (e.g. dermatology, lung diseases, child neurology, oncology)
    e. Psychiatric specialties (e.g. child psychiatry, adolescent psychiatry)
    f. Diagnostic specialties (e.g. Clinical Pharmacology and Pharmacotherapy, pathology, radiology)
    g. Other specialties (e.g. sports medicine, occupational health care, general practice)
    h. I do not have a specialty
8. Years of experience
    a. 0–3 years
    b. 4–6 years
    c. 7–10 years
    d. 11–20 years
    e. 21–30 years
    f. 30+ years
9. Have you received any education in pharmacogenetics? (Select all that apply)
    a. Yes, during my basic education
    b. Yes, during postgraduate education
    c. Yes, as a trainee/intern
    d. Yes, as continuing education or courses arranged by employer
    e. No, but interested in receiving any education

    f. No, not interested in receiving any education
10. Please select your level of interest (1-5) on learning more about applying pharmacogenetic testing to patient care.
    a. From very uninterested (1) to very interested (5)
11. How would you prefer education in pharmacogenetics? (Select all that apply)
    a. Lecture
    b. Online lecture
    c. Book
    d. Online courses for self-studies
    e. Via internet
    f. Podcasts
    g. I am not interested in learning more about pharmacogenetics
12. Is it possible to get a referral for a pharmacogenetic test at your workplace (e.g. B-Farma-D, B-FarmL-D, B-PGX-D)?
    a. Yes
    b. No
    c. I do not know
13. Have you ever prescribed/ordered a pharmacogenetic test for a patient (e.g. B-FarmL-D, B-Farma-D and/or B-PGX-D)?
    a. Yes
        i. 1–5 times
        ii. 6–15 times
        iii. 16–50 times
        iv. 50+ times
    b. No
14. If you ordered a pharmacogenetic test, what medications did you check up? (Select all that apply)
    a. Antidepressants (e.g. Escitalopram)
    b. Cardiovascular medications (e.g. Clopidogrel)
    c. Pain medications (e.g. Codeine)
    d. Polypharmacy
    e. Cancer medications (e.g. Irinotecan)
    f. I have not ordered a pharmacogenetic test
15. Has a patient ever visited you in your clinic with the results of a pharmacogenetic test?
    a. 1 time
    b. 2–3 times
    c. 4–5 times
    d. 5+ times
    e. No
16. Have you used pharmacogenetic databases? (Select all that apply)
    a. Duodecim Drug Database for Pharmacogenetics (https://www.terveysportti.fi/apps/laake/)
    b. GeneRx (https://www.terveysportti.fi/apps/generx/)

c. tietoEVRY Lifecare: the pharmacogenetic section
d. CPIC (https://cpicpgx.org/)
e. PharmGKB (https://www.pharmgkb.org)
f. FDA (https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations)
g. EMA (https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/pharmacogenomics-working-party)
h. No, I have not used
i. Other, what?

17. Indicate to what degree you do agree/disagree with the following statements:
    a. I have general knowledge with the basics of genetics
    b. I have knowledge with the basics of pharmacogenetics
    c. I consider myself able to interpret the results of a pharmacogenetic test
    d. I can identify which drugs may require a pharmacogenetic test
    e. I feel it is my responsibility to inform patients about the availability of pharmacogenetic test
    f. I believe that pharmacogenetic testing can both increase safety and efficacy of drugs
    g. I believe that pharmacogenetic testing is helpful for predicting the risk of side effects for the patient
18. A pharmacogenetic blood test costs approximately 300€ (https://www.epshp.fi/files/8990/Kliinisen_kemian_ja_mikrobiologian_hinnasto_2021.pdf). Is this according to you:
    a. Very inexpensive
    b. Inexpensive
    c. Reasonable
    d. Expensive
    e. Very expensive

15.2. Questions/statements that measure participants' deeper knowledge

1. Single nucleotide polymorphisms (SNPs) are:
    a. Duplications of pieces of DNA
    b. Variations of a single nucleotide
    c. The removal of pieces of DNA
    d. Variation of the structure of DNA, e.g. by adding a functional group
    e. I do not know
2. In pharmacogenetics, allelic variations are generally referred to as star alleles. Mostly *1 refers to one specific allele that is:
    a. Mutant
    b. Least common

c. Non-functional
d. Wild-type
e. I do not know

3. Genetic variation can also occur in drug targets, leading to an impact on the:
    a. Drug's half life
    b. Drug's clearance
    c. Area under the plasma concentration curve (AUC)
    d. Therapeutic response
    e. I do not know
4. With a poor metabolizer due to a genetic polymorphism, a prodrug always has:
    a. A higher therapeutic effect
    b. More side effects
    c. A limited therapeutic effect
    d. Less side effects
    e. I do not know
5. According to your knowledge, which of the following drugs require pharmacogenetic testing according to European Medicines Agency (EMA)?
    a. Abacavir
    b. Olanzapine
    c. Isoniazid
    d. Terbinafine
    e. I do not know
6. A pharmacogenetic test for clopidogrel was conducted and the results showed that the patient has a CYP2C19*2/*2 genotype. According to this, we can estimate that the patient has a metabolic pattern that is:
    a. Ultrarapid
    b. Normal
    c. Poor
    d. I do not know
7. According to the guidelines of Clinical Pharmacogenetics Implementation Consortium (CPIC), it is recommended that slow metabolizers avoid the use of voriconazole due to genetic variation in gene encoding:
    a. CYP1A2
    b. CYP3A5
    c. CYP2C19
    d. CYP2D6
    e. I do not know
8. Dihydropyrimidine dehydrogenase (DPD) is an enzyme that metabolizes pyrimidines in the human body. DPD deficiency can cause serious side effects when using drugs such as:
    a. Fluorouracil
    b. The prodrugs tegafur and capecitabine
    c. All the above
    d. None of the above

e. I do not know

9. Codeine is metabolized by CYP2D6 to morphine. Side effects such as drowsiness, superficial breathing and nausea can occur, even with a standard dose of codeine, if the patient is CYP2D6:
    a. Poor metabolizer
    b. Intermediate metabolizer
    c. Normal metabolizer
    d. Ultrarapid metabolizer
    e. I do not know
10. According to the most recent studies, only 40% of the Finnish population have normal CYP2C19 metabolism (1; 2). As for CYP2D6, about 63% of the Finnish population have normal metabolism (1). Do you know what proportion of the drugs used in Finland are metabolized by CYP2C19 and/or CYP2D6?
    1: doi: 10.1038/s41397-022-00270-y
    2: https://youtu.be/m9lWYTEnoMw?t=2440)
    a. 5%
    b. 9%
    c. 13%
    d. 17%
    e. I do not know

15.3. Article published on Duodecim Drug Database for Pharmacogenetics

The article was originally in Finnish and is freely translated to English.

<u>One of Finland's most widely used antithrombotic drugs is effective in less than 70% of the population.</u>

Clopidogrel was one of the most widely used antithrombotic drugs in Finland in 2020 (10.34 DDD/1000 people/day), after acetylsalicylic acid (62.33 DDD/1000 inhabitants/day) (FIMEA & KELA, 2020).

Clopidogrel is a prodrug that is metabolized by the liver enzyme CYP2C19 to its active metabolite. Ticagrelor and prasugrel are both platelet inhibitors, like clopidogrel, but they do not require a metabolic change to function. Patients that are intermediate metabolizers (IM) or poor metabolizers (PM) of the CYP2C19 enzyme will receive a lower proportion of

the active metabolite of clopidogrel, which in turn results in a lower antithrombotic effect (Feske, 2021).

Lee et al. showed in their study that IMs and PMs of clopidogrel had a significantly higher risk of atherothrombotic events compared to patients treated with prasugrel or ticagrelor (Lee, 2012). In addition, Wang et al. showed in his study that the combination of ticagrelor and acetylsalicylic acid in IMs and PMs may significantly reduce the risk of cerebrovascular accidents than the combination of clopidogrel and acetylsalicylic acid, especially in patients with transient ischemic attack (TIA) (see Figure 1) (Wang, et al., 2021).

According to HUSLAB guidelines, clopidogrel should be avoided in patients with poor or partially reduced CYP2C19 metabolism due to a lack of efficacy (Tarkiainen & Niemi, 2022). Alternative medicines, such as ticagrelor or prasugrel, should be considered in these patients.

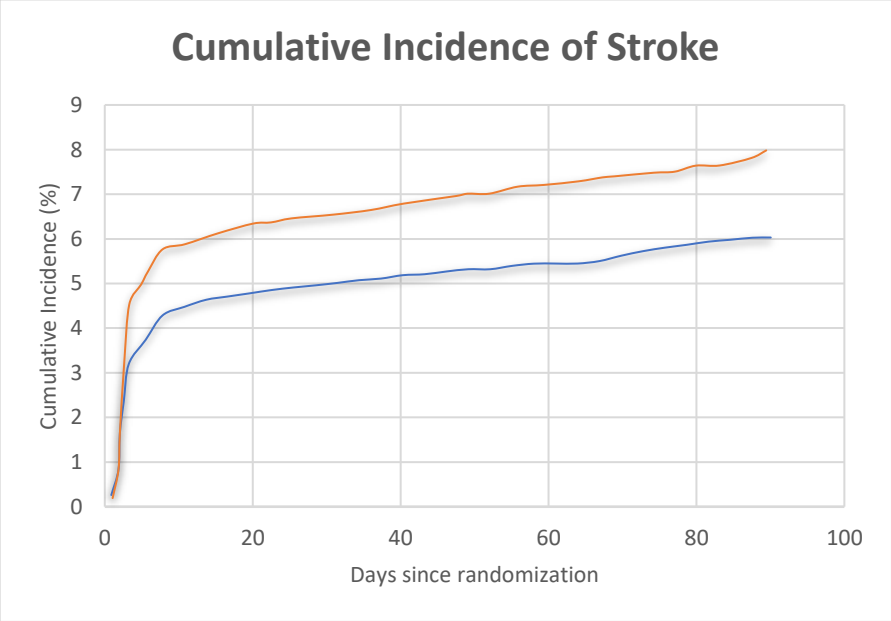

Figure 1. The cumulative incidence of stroke with a combination of ticagrelor-aspirin (blue) and a combination of clopidogrel-aspirin (orange). Intermediate metabolizers and poor metabolizers of CYP2C19, all of which had previously suffered from cerebrovascular events, were randomized to two groups (Wang, et al., 2021). Approximately 6.0% of the ticagrelor-aspirin group (n=3205) and approximately 7.6% of the clopidogrel-aspirin group (n=3207) suffered a cerebral infarction or bleeding during the 90-day follow-up period. Hazard ratio 0.77 (95% CI, 0.64-0.94; P=0.008) (figure adapted from Wang, et al., 2021).

In 2020, 77,389 prescriptions of clopidogrel were prescribed in Finland and distributed to 20,095 patients (Kelasto, 2022). The use of clopidogrel had increased by 9% from the previous year (FIMEA & KELA, 2020). The proportion of prescriptions for both ticagrelor (23,824 prescriptions, n: 6918) and prasugrel (678 prescriptions, n: 172) in Finland had also increased from the previous year: 2% for ticagrelor and 60% for prasugrel (Kelasto, 2022; FIMEA & KELA, 2020). Approximately 32% of the Finnish population are either PM (3.36%) or IM (28.74%) of the CYP2C19 enzyme (Häkkinen, et al., 2022). This means that of these 20,095 patients, approximately 723 patients (60 patients/month) have a decreased metabolic rate and approximately 5,775 patients (481 patients/month) have a partially decreased metabolic rate.

A pharmacogenetic test can be used to determine whether a drug is suitable for a patient or not. CYP2C19 activity can be detected, for example, by the B-Farma-D, B-FarmL-D or B-PGX-D test (Mehiläinen, 2022; Terveystalo, 2022; Tarkiainen, et al., 2021).

Test your knowledge of pharmacogenetics by clicking on the link below:

https://docs.google.com/forms/d/e/1FAIpQLSdkio8t9XpKRkjKgETG5ZacfvM3_21sdct-ai5okvISVeEXgg/viewform?usp=sf_link