# Improving acceptance of pharmacogenetic testing in patient care

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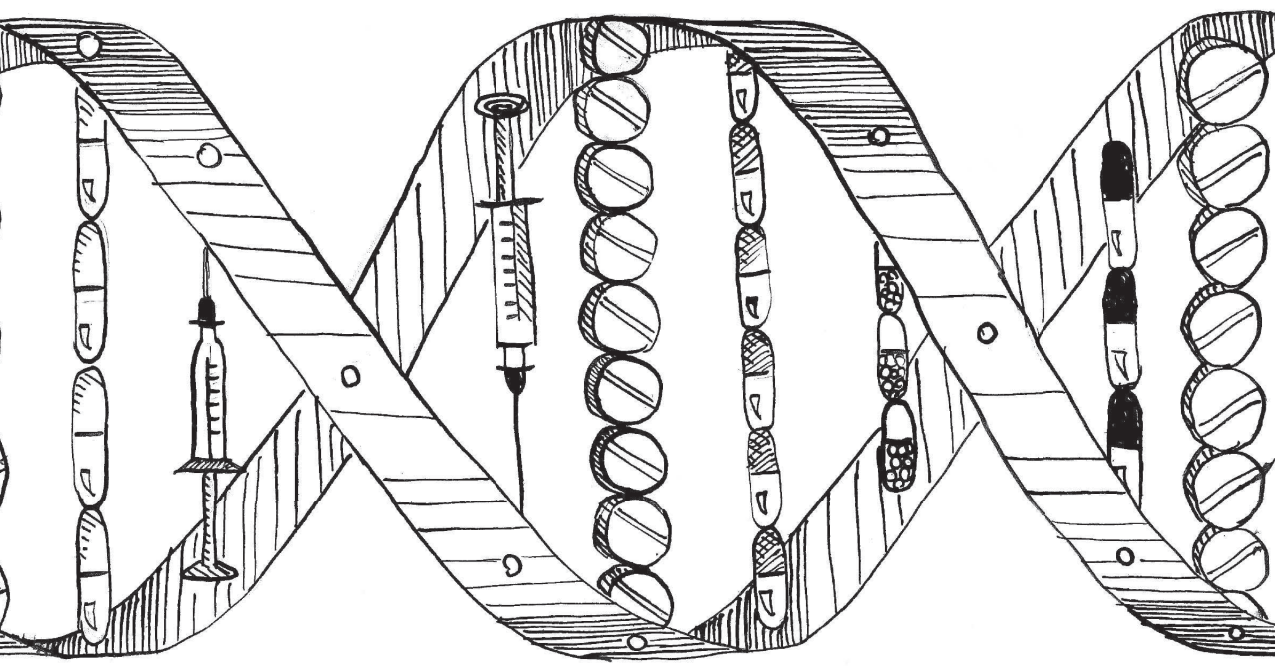
# Chapter 11

## English summary



## Introduction

This thesis covers scientific research with the overall aim to improve clinical acceptance of pharmacogenetics in clinical care. **Chapter 1** describes how in the last decades clinical studies have generated evidence that a one-size-fits-all approach to drug therapy is often not applicable and large inter-patient variability exists in both risk of side effects and efficacy of pharmaceuticals. By aid of the advancements made in biotechnology, proof was delivered that absorption, distribution, metabolism and excretion of pharmaceuticals (and endogenous substrates) is in part under control by the genome. Recent clinical studies have indeed shown that the use of genetic information can improve drug efficacy and toxicity. Additionally, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have provided clinicians with evidence-based therapeutic recommendations and in The Netherlands guidelines of the DPWG are incorporated in the electronic drug-prescribing and -dispensing systems. Currently, pharmacogenetics (PGx) is routinely used to adjust pharmacotherapy with high risk medication in some secondary and tertiary centers. However, in primary care PGx is still scarcely used, while a large majority of the drugs that are reviewed by CPIC and the DPWG are (primarily) prescribed and dispensed in primary healthcare centers. Moreover, small pilot studies and large PGx implementation projects have shown that a large majority of individuals carry at least one actionable phenotype. This portrays the need to implement a pre-emptive panel based pharmacogenetic screening in primary healthcare centers.

The first part of this thesis provides answers to frequently asked questions by clinicians regarding PGx. The second part describes the clinical implementation of PGx in clinical practice and its impact on primary care on a national level. Harmonization of PGx guidelines and therapeutic recommendations are described in the third part of the thesis. In the fourth part knowledge, experience and attitudes towards PGx of pharmacists and pharmacy students are described. The final part contains the general discussion.

## Part I: Answers to frequently asked question by clinicians regarding PGx

In **Chapter 2**, six frequently asked questions by clinicians are answered which can be applied to the implementation of PGx in clinical practice.

### Q1: Do we need pharmacogenetic markers to improve pharmacotherapy? Yes!

As randomized clinical trials that are required for registration purposes generally include highly selected individuals, the efficacy and safety of prescription drugs is often lower than found in the clinical studies. Safety of pharmacotherapy can be increased by slowly titrating patients to a tolerable dose with sufficient efficacy. Using predictive pharmacogenetic biomarkers at the start of therapy, healthcare professionals can potentially use drugs in a more efficacious manner without requiring the so called 'trial-and-error prescribing'.

### Q2: What are the sources of genetic variation that influence drug response?

**Pharmacokinetics:** Genetic variations come in form of single nucleotide polymorphisms, insertions and deletions that occur in the encoding genes, which can have consequences for the activity of the protein. Increased enzyme activity, by duplication of the encoding gene, can also occur.

**Pharmacodynamics:** When genetic variation occur in the genes that encode for a receptor or enzymes involved in the signal-transduction this can lead to altered downstream signaling and associated processes and ultimately can lead to altered pharmacodynamics of a drug.

**Idiosyncratic drug reactions:** In some cases, genetic variation can lead to altered drug response that does not appear to be related to exposure to the drug. These mutations are often found in the genetic regions that code for the Human Leukocyte Antigen (HLA) and seem to modulate immune-responses to drugs.

### Q3: To what extent is variability in drug response explained by pharmacogenetics? Variable!

Using the $R^2$ parameter, the contribution of pharmacogenetic biomarkers to an outcome can be compared to conventional clinical factors used to adjust therapy. Dependent on the studied phenotype PGx biomarkers should be combined with clinical factors, rather than used standalone.

### Q4: Are pharmacogenetic test results actionable? Yes!

However, the majority of drug labels do not yet contain information on how to adjust therapy based on genetic biomarkers, although this is increasing. If genetic biomarkers are to be used by clinicians as part of routine care the results form clinical studies have to be translated to therapeutic recommendations, scoring systems or decision trees.

### Q5: What level of evidence is required for implementation? Still debated!

From the evidence-based paradigm the best supporting evidence for implementation of pharmacogenetics in clinical practice would be obtained from randomized clinical trials (RCT's). However, when gene-drug interactions are considered in the same way as drug-drug interactions or dose-adjustment for clinical factors as impaired renal or liver function, observational evidence should be sufficient to support implementation. In case proof of principle is established with a number of RCT's investigating PGx markers providing positive results, additional evidence in the form of well replicated observational studies should be sufficient to justify implementation of PGx markers into clinical care.

### Q6: Where can I find sources for up-to-date information regarding interpretation of PGx test results? PharmGKB!

The DPWG and CPIC both have provided clinicians with dosing recommendations based on systematic reviews of the literature since 2008 and 2011 respectively. With this information these two consortia have provided tools which facilitate physicians and pharmacists with the interpretation of PGx tests and adjustment of pharmacotherapy based on genotypes. The guidelines of both consortia can be found on pharmgkb.org.

## Part II: Implementation of PGx in clinical practice and its impact on a national level

To ensure clinical acceptance of PGx-testing healthcare professionals should be able to order clinical grade tests for clinically relevant genes. One pharmacogene particularly relevant in pharmacotherapy is *CYP2D6*. At the start of this thesis the gold standard in *CYP2D6* testing in clinical practice was the Roche AmpliChip. In **Chapter 3** the concordance between the novel GenoChip CYP2D6 macroarray and the AmpliChip was investigated. The study was performed by genotyping 200 samples with germline DNA samples from the CYPTAM study, a prospective multicenter study performed in the Netherlands and Belgium which includes 671 female patients with breast cancer which were screened with the Roche AmpliChip. Of the tested samples 99% (n = 198) of the results of the GenoChip were concordance with the results of the AmpliChip. In two samples the genotyping results from the GenoChip CYP2D6 macroarray were discordant from the results from the AmpliChip as the Amplichip identified a *41 allele, while the GenoChip did not. Sanger sequencing of the two discordant samples revealed that the 2988G>A mutation, considered by The Human Cytochrome P450 Allele Nomenclature Committee as the key mutation for *41, was not present. Based on the results of this comparison it was concluded that

the CYP2D6 GenoChip Macroarray is a valid method for detecting 13 genetic variants in the *CYP2D6* gene.

In addition to the development of clinical grade assays adoption of PGx test by healthcare professionals is an important factor in its implementation in clinical practice. At the start of this thesis PGx was increasingly used in hospitals, while the adoption of PGx tests by general practitioners and community pharmacists remained low. To further improve adoption of PGx-testing in primary care the **I**mplementation of **P**harmacogenetics in **P**rimary care **P**roject (IP3) was initiated. **Chapter 4** describes the IP3-study in which general practitioners and community pharmacists could implement PGx testing in their own practice. Patients with an incident prescription for a drug with known gene-drug interactions (amitriptyline, atomoxetine, atorvastatin, (es)citalopram, clomipramine, doxepin, nortriptyline, simvastatin or venlafaxine) were eligible for inclusion. The patients were screened for 40 genetic variants in the genes *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, *TPMT* and *VKORC1* using the DMET platform in combination with a qPCR Taqman to detect copy-number variation in the *CYP2D6* gene. The genotypes were translated to predicted phenotypes and combined with a therapeutic recommendation from the DPWG guidelines in a written report. This report was then transferred to the treating general practitioner and pharmacist with the request to archive the results in their electronic drug prescribing and -dispensing systems in order to perform medication surveillance using clinical decision support (CDS). A total of 200 patients were included by clinicians in the period from November 2014 to July 2016, accounting to an adoption of PGx-testing in 18.0% of the eligible patients. The majority of the patients was included on an incident prescription of a statin, being atorvastatin (57.5%) or simvastatin (14.5%). The remainder of the patients (28.0%) was included on an antidepressant (amitriptyline, (es)citalopram, nortriptyline, or venlafaxine). In 90% of the patients at least one actionable genotype in the selected panel was found. More importantly, in 31.0% of the incident prescriptions a combination of one of the selected drugs of inclusion with the associated actionable genotype was present and a therapeutic recommendation was provided based on the DPWG guidelines to the clinicians to change the regimen and/or monitor the patient more closely for ineffective or unsafe therapy. The study showed that genotype guided dosing in primary care is feasible and allowed general practitioners and community pharmacists to gain experience with PGx in the context of their own practice. Additionally, it demonstrated that actionable genotypes in the selected panel are common among the population. In **Chapter 5** an estimate was made of the national clinical impact of implementing a preemptive panel based PGx consisting of *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, *TPMT* and *VKORC1* in primary care throughout The Netherlands. The frequencies of the actionable genotypes for the selection of 8 genes

from the IP3-study were used a representative sample for the Dutch population and were combined with national prescription data in primary care obtained from the Foundation of Pharmaceutical Statistics (SFK). Our estimate shows that for 45 drugs associated with the 8 genes a gene-drug interaction as described in the guidelines of the DPWG is present in 23.6% of all incident prescriptions (n = 856,002 prescriptions/year). Additionally, in one in every 19 (= 5.4%) incident prescriptions this would result in an adjustment of the dose or switch to an alternate drug at the start of therapy. Based on this estimation we predict that in a near future where clinicians will be confronted with patients with a known PGx profile, general practitioners and community pharmacists will routinely have to adjust pharmacotherapy based on actionable genotypes.

## Part III: Harmonization of PGx-test interpretation and therapeutic recommendations

An important goal is to achieve a worldwide uniform interpretation of PGx-test results and clinical actions based on actionable pharmacogenes. However, due to of differences in size of studies, study population, chosen methodology and chance investigators might find differences in effect size of studied genotype-phenotype relationships. **Chapter 6** provides a response to Magnani et al. who proposed a further reduction of the starting dose of fluoropyrimidine regimens in patients who are heterozygous carriers of the *DPYD* IVS14+1G>A variant. This proposal was based on a single prospective study with 180 patients that were candidate for therapy with a fluoropyrimidine-based regimen. Patients were screened for the *DPYD* IVS14+1G>A splice site variant as part of the study and were routinely evaluated for fluoropyrimidine-related toxicities. In our response, based on literature reviews performed by the CPIC and the DPWG and pharmacokinetic study performed by Deenen et al, we argue that a 50% dose reduction followed by dose titration based upon toxicity is the best approach to fluoropyrimidine dosing in patients who are heterozygous carriers of the IVS14+1G>A variant.

Despite the global availability of scientific literature different research groups interpret the available evidence slightly differently resulting in differences in interpretation of PGx test results and therapeutic recommendations. **Chapter 7** describes the initiative to harmonize the guidelines released by the CPIC and DPWG by an inventory of existing differences. This was executed by a review of the methodologies incorporated by these two consortia, a systematic comparison of the genotype to phenotype translations and therapeutic recommendations for gene-drug interactions shared between the guidelines of both groups. The comparison shows that there is a substantial agreement between

the therapeutic recommendations provided in the guidelines of the two consortia. The discordances in dosing advices or recommendations to switch to alternate drugs can be explained by differences in applied methodologies, the differences at which literature search for the recommendations for the drug-gene pairs were carried out or differences in clinical practices between countries. An important difference between the guidelines of the two consortia is the translation of genotype to phenotype in case of the gene *CYP2D6*. CPIC classifies the combination of a normal *CYP2D6* allele with a null allele as a normal metabolizer, while according to the DWPG this is an intermediate metabolizer. Currently, an international group of experts in the field, including members of CPIC and DPWG is trying to find consensus on how *CYP2D6* genotypes should be translated.

## Part IV: Knowledge, experience and attitudes towards PGx of pharmacists and pharmacy students

The fourth part of this thesis is dedicated to the mindset of (future) healthcare professionals toward PGx.

In addition to evidence, the opinion of clinicians of a new laboratory test is also of major importance for its implementation in routine care. Available research done among USA physicians and Canadian pharmacists has shown that clinicians have found themselves unprepared by the swift pace of evolution of (pharmaco)genetic research driven by the advances in biotechnology. The adoption of PGx by clinicians can be hampered if they do not believe in the concept of (partially) heritable drug response, do not know where to apply for PGx testing or are not comfortable in their abilities to interpret PGx test results and act on (pharmaco)genetic data. In **Chapter 8** the results of a nationwide survey among 667 Dutch pharmacists in the context of a national CDS system are described. In this survey participants were asked a total of 41 questions divided among 7 themes. The results show that virtually all pharmacists (99.7%) believe in the concept of (partially) heritable drug response and have high expectations of PGx in relation to pharmacotherapy. In contrast, the adoption of PGx among the surveyed pharmacists was low as only 14.7% had ordered or recommended a PGx test in the previous 6 months. Additionally, 14.1% of the participants felt adequately informed about PGx testing and 88.8% would like additional training on the subject. Moreover, being aware of the existence of the therapeutic recommendations created by the DPWG or the incorporation of the DPWG guidelines in electronic medication surveillance systems did not have any significant effect on knowledge how to apply PGx or adoption of PGx-testing. From the results of this study we concluded that Dutch pharmacists are generally very positive toward PGx, but perceive a lack in knowledge on

the subject and are need of extra training. **Chapter 9** provides insight in the knowledge and perceived abilities of pharmacy students regarding PGx testing. A survey consisting of 28 questions performed among 148 pharmacy students revealed that like their practicing colleagues they all believe in the concept of PGx and have high expectations that PGx will lead to safer and more effective pharmacotherapy. Virtually all surveyed students had received some sort of education on PGx, but only 12.8% felt adequately informed on how to apply PGx in pharmacotherapy indicating a knowledge gap on this subject among future pharmacists. A comparison with the cohort of 667 surveyed pharmacists using a multivariate analysis revealed that there are significant differences between the students and their practicing colleagues. Compared to pharmacist, the students feel more qualified to recommend PGx testing to predict drug efficacy, would use extra information to support the use of PGx testing in pharmacotherapy more often and other kind of sources of information to support the use of PGx within pharmacotherapy and to support changes in dose and drug when a patients' genotype is known. Additional research should investigate which type of education can reduce the PGx knowledge gap among pharmacy students.

## Part V: General discussion & Summary

This dissertation is concluded with a general discussion in **Chapter 10** on the implementation of pharmacogenetics in everyday clinical settings. The chapter provides an overview of the current players in the field who are involved with the integration of PGx into routine clinical care. Additionally, several challenges which currently still hinder the implementation are identified such as selecting of clinically relevant pharmacogenes, providing data on diagnostic criteria of PGx testing, guidelines directing the clinical use of PGx test results, the evidence supporting improve of clinical care, information on cost-effectiveness and cost-consequences of PGx testing and the improvement of acceptance of PGx testing. The chapter closes with the conclusion that clinical grade assays have been developed, guidelines with therapeutic recommendation for actionable gene-drug pairs have been created and several RCT's have delivered evidence for implementation. One remaining barrier still hindering implementation is currently the knowledge gap on PGx among healthcare professionals and future clinicians which can potentially by resolved by a change in the current curriculum and post-academic education.