# Precision medicine using pharmacogenomic panel testing

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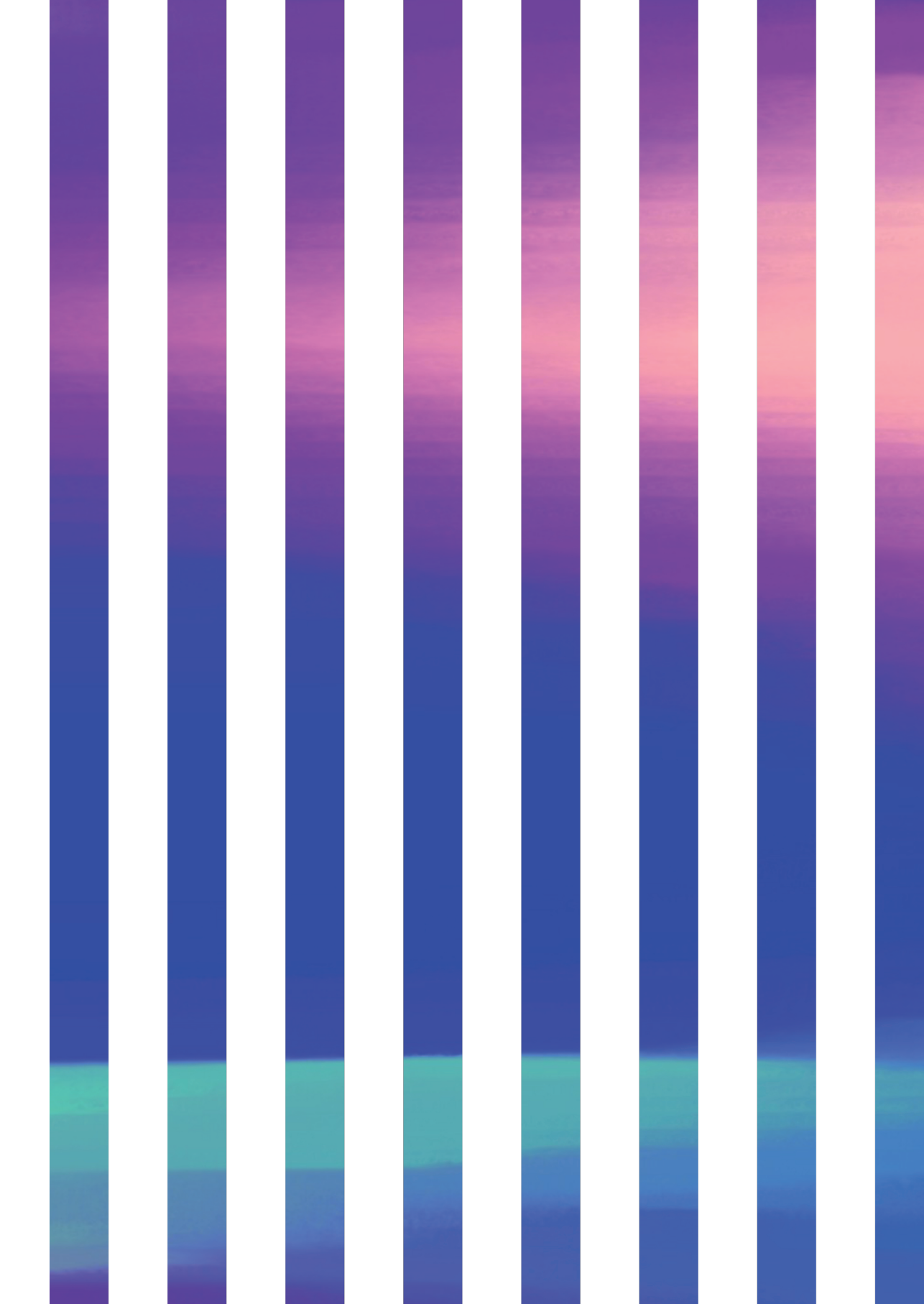
# Chapter 11:

Summary



## Precision Medicine Using Pharmacogenomic Panel Testing

While drug treatment is often successful, the presentation of adverse drug reactions (ADRs) and the lack of efficacy as a result of unsuccessful pharmacotherapy is a significant burden for patients and society. As introduced in **Chapter 1**, pharmacogenomics (PGx) utilizes an individual's germline genetic profile to identify those who are at higher risk for ADRs or lack of efficacy. This information can be used by healthcare professionals (HCPs) to guide dose and drug selection before drug initiation in an effort to optimize drug therapy through precision medicine. To date, several randomized controlled trials support the clinical utility of PGx-guided pharmacotherapy for a number of individual drug-gene interactions (DGIs). In addition, further literature regarding other DGIs is available. Based on systematic review of available literature, the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) develop clear guidelines for HCPs on how to interpret and apply PGx test results. Additionally, the labels of 15% of European Medicines Agency drugs include PGx information to inform prescribing. Since 95% of the population carries at least one PGx variant for which guidelines are available, and individuals are expected to initiate a number of PGx drugs throughout their lifetime, it has been suggested that delivering PGx through a pre-emptive panel-based approach as opposed to reactive single-gene approach is more cost-effective and practical. In a pre-emptive panel approach, variants in multiple pharmacogenes are tested simultaneously and used when a potentially interacting drug is prescribed.

Despite both the promise of and the progress in the field of PGx to achieve precision medicine, it is still not routinely applied in patient care. As such, a number of barriers preventing implementation have been identified. These include the undetermined model for delivering PGx, the lack of evidence supporting a PGx panel approach and the lack of tools supporting implementation. Therefore, the work of this thesis aims to support the implementation of precision medicine using PGx panel testing. It reports on generating evidence for PGx panel testing (**Part I**) and the development of tools facilitating implementation (**Part II**), evaluates the implementation process utilizing these tools (**Part III**) and quantifies the impact of PGx implementation on patient outcomes and cost-effectiveness (**Part IV**).

## Part I: Generating Evidence for Pharmacogenomic Panel Testing

Although several implementation studies and programs have been initiated over recent years (**Chapter 2**), an identified evidence gap is the undetermined collective clinical utility of a PGx panel test. Therefore, the U-PGx Consortium aims to fill the identified evidence gap by quantifying the (cost-) effectiveness of PGx panel testing in the PREPARE study. **Chapter 2** provides an overview of the design and implementation strategy of the U-PGx consortium and the PREPARE study. In brief, the PREPARE study aims to collectively quantify the impact PGx-guided dose and drug selection of 39 commonly prescribed drugs,

by a pre-emptive PGx panel test covering twelve pharmacogenes, on the occurrence of clinically relevant ADRs through a randomized controlled trial across seven European countries (n=8,100). **Chapter 3** provides an overview of considerations made to mitigate multiple methodological challenges that emerged during the design and operationalization of the PREPARE study. Challenges and respective solutions included: i) defining and operationalizing a composite primary endpoint enabling measurement of the anticipated effect, by including only severe, causal and drug-genotype associated adverse drug reactions; ii) avoiding overrepresentation of frequently prescribed drugs within the patient sample while maintaining external validity, by capping drugs of enrolment; iii) designing the PGx intervention strategy to be applicable across ethnicities and healthcare settings; iv) designing a statistical analysis plan to avoid dilution of effect by initially excluding patients without a DGI in a gatekeeping analysis.

**Part II: Developing Tools Facilitating Implementation**

An important barrier, which has now been surmounted, was the lack of clear guidelines on how to interpret and apply PGx test results. In **Chapter 4**, the DPWG guideline for the *DPYD*-fluoropyrimidine interaction is presented. It aims to optimize the starting dose of three anti-cancer drugs (5-fluorouracil, capecitabine, and tegafur) based on an individual's *DPYD* predicted phenotype to decrease the risk of severe, potentially fatal, toxicity. Fluoropyrimidine-induced toxicity may be caused by dihydropyrimidine dehydrogenase (DPD, encoded by the *DPYD* gene) enzyme deficiency. When treated with standard fluoropyrimidine doses, DPD-deficient patients have higher exposure to active 5-Fluorouracil (5-FU) metabolites and are therefore at higher risk for developing toxicity. Variants in the *DPYD* gene are the main cause of DPD-deficiency and genotyping is used to identify DPD-deficient patients. The *DPYD*-gene activity score, determined by four DPYD variants, predicts DPD activity and can be used to optimize an individual's starting dose.

Another reported barrier preventing implementation, exchange, and continuity of PGx testing is the lack of a standardized PGx panel. Clinical impact of PGx testing is maximized when all variant alleles for which actionable clinical guidelines are available, are included in a test panel. Therefore we have developed such a standardized panel (the "PGx-Passport"), based on the DPWG guidelines, which is presented in **Chapter 5**. Germline variant alleles were systematically selected using pre-defined criteria regarding allele population frequencies, effect on protein functionality and association with drug response. A PGx-Passport of 58 germline variant alleles, located within 14 genes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1,* and *VKORC1*) was composed. This PGx-Passport can be used in combination with the DPWG guidelines to optimize drug prescribing for 49 commonly prescribed drugs.

**Part III: Evaluating the Implementation Process**

A suggested route for requesting personal genomic testing is through a direct-to-consumer (DTC) model. Here, consumers are able to request personal genetic results, including their genetic risk for diseases and their PGx profile, without the involvement of an HCP. In **Chapter 6** we explore consumer perceptions of interactions with primary care providers. More specifically, we report on the incidence of consumer sharing of genetic results with HCPs and their satisfaction with the interaction. We found that 63% of consumers planned to share their results with a primary care provider. However, at 6-month follow-up, only 27% reported having done so, and 8% reported sharing with another HCP. Among participants who discussed results with their primary care provider, 35% were very satisfied with the encounter, and 18% were not at all satisfied.

A suggested route for delivering PGx test results to clinicians is through a pre-emptive panel-based approach within a clinical decision support system (CDSS). Here, clinical recommendations are automatically deployed by the CDSS when a drug-gene interaction is encountered. However, this requires record of PGx panel results as contra-indications in the electronic medical record (EMR). In **Chapter 7** we quantify both feasibility and real-world impact of this approach in primary care, within a side-study of a prospective pilot study (the IP3 study). We found that both pharmacists and GPs are very able to record PGx results in their EMRs as contra-indications (96% and 33% of pharmacists and GPs, respectively). As a result, 97% of patients to re-used PGx panel results for at least one, and 33% for up to four newly initiated prescriptions with possible DGIs within a 2.5-year follow-up. In this case, 24% were actionable DGIs, requiring pharmacotherapy adjustment. This high rate of re-use indicates this may be a promising model for delivering PGx panel-based testing.

The implementation barriers and enablers encountered by community pharmacists who have actual experience with PGx panel-based testing are yet undetermined. Therefore, in **Chapter 8,** we studied pharmacist reported barriers and enablers of pharmacist-initiated PGx in primary care utilizing mixed-methods, including qualitative investigation using theoretical frameworks. By conducting 15 semi-structured interviews we identified five barrier themes: 1) unclear procedures, 2) undetermined reimbursement for PGx test and consult 3) insufficient evidence of clinical utility for PGx panel testing, 4) infrastructure inefficiencies, and 5) HCP PGx knowledge and awareness; and two enabler themes: 1) pharmacist perceived role in delivering PGx, and 2) believed clinical utility of PGx. Despite a strong belief in the beneficial effects of PGx pharmacists report barriers that hinder the implementation in primary care.

### Part IV: Quantifying the Impact on Patient Outcomes and Cost-Effectiveness

The impact of PGx panel testing on patient outcomes and cost-effectiveness will primarily be generated by the PREPARE study, as presented in **Chapters 2 and 3**. In the meantime, to stimulate PGx testing of the highest priority interactions, we assessed the collective cost-effectiveness of PGx-guided pharmacotherapy of "essential" DGIs to prevent gene-drug-related deaths in The Netherlands (**Chapter 9**). 148,128 patients initiate at least one of seven drugs per year. The corresponding PGx testing, HCP interpretation and drugs would cost €21.4 million. Of these drug initiators, 24.1% would require an alternative dose or drug. PGx-guided initial dose and drug selection would reduce the overall risk of gene-drug-related death with 10.6% (range per DGI: 8.1% – 14.5%) and prevent 419 (0.3% of initiators) deaths a year. The mean cost of preventing one gene-drug-related death is €51,000 (range per DGI: €-752,000 – €633,000).

### Future Perspectives on Precision Medicine

In **Chapter 10** we provide future perspectives on precision medicine with PGx panel testing. In the future, the utility of precision medicine using PGx guided pharmacotherapy will be further optimized as a result of technological developments improving the predictive utility of genetic variation to predict drug response and developments improving our ability to adjust pharmacotherapy to reduce risk of unwanted effects among high-risk individuals. Additionally, the utility of precision medicine will be further improved by combining other determinants of drug response in prediction models. In parallel, implementation and evidence generation supporting improved precision medicine approaches can be generated concomitantly by combining digital medicine and innovative study designs within learning health care systems. In conclusion, these developments will revolutionize current stratified medicine to enable true personalized medicine.