Precision medicine using pharmacogenomic panel testing

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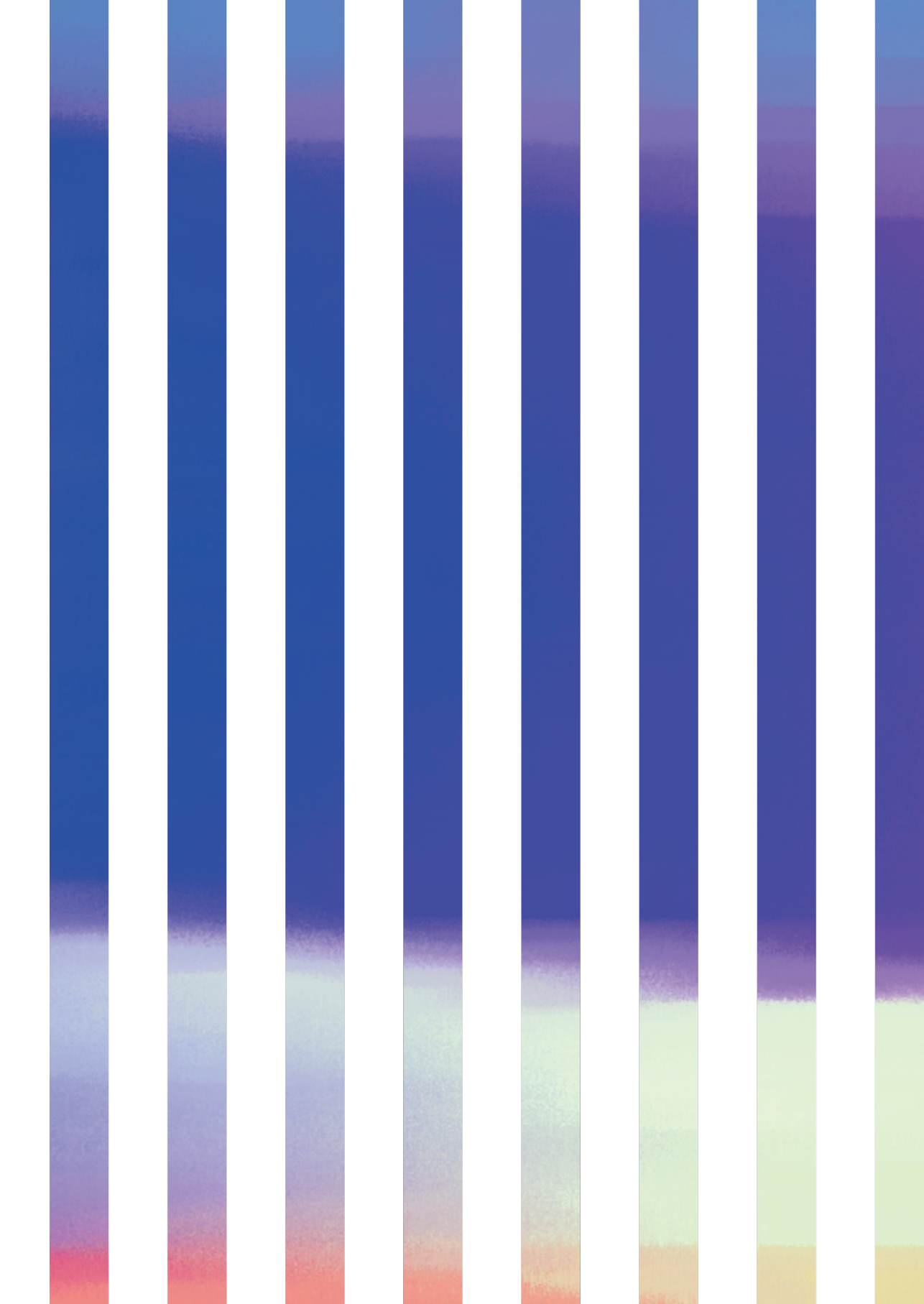
Chapter 1:

General Introduction



Benefit and Burden of Pharmacotherapy

Given the complexity of human and disease biology, medicine has come a long way in treating certain diseases. In a historical context, innovations in pharmacotherapy have been revolutionary in increasing life expectancy and improving quality of life (1). However, while drug treatment is often successful, the presentation of adverse drug reactions (ADRs) and the lack of efficacy as a result of unsuccessful or inappropriate pharmacotherapy is a significant burden for individual patients and society as a whole. ADRs are an important cause of emergency department visits and hospital admissions. A study in two large UK hospitals showed that 6.5% of hospital admissions were attributable to ADRs (2). Among hospitalized patients, ADRs comprise about 19% of all injuries; the largest single category of events experienced by hospitalized patients (3). In the Netherlands, it was estimated 5.6% of hospital admissions were medication-related of which half were potentially preventable (4). A meta-analysis of prospective studies concluded that one-fourth to one-sixth of all US in-hospital mortality was due to ADRs (5). In the Netherlands, the resulting economic burden has been estimated to be €6,009 per potentially preventable, medication-related hospital admission (6). In the United States estimated ADR-related morbidity and mortality have been estimated at $30 billion to $136 billion annually (7). In parallel, lack of efficacy also results in a significant burden. However, data quantifying patient and societal burden is scarce. Nevertheless, one can conclude its magnitude by inspecting the number needed to treat (NNT) of commonly used drugs (8). NNTs lower than five are rare and more commonly above 10. This implies that the large majority of patients will not benefit from drug treatment and may experience harm from untreated disease. An example illustrating the potential harm inflicted is the increased risk for suicide as a result of ineffective antidepressant therapy (9). It has been estimated that $100 billion a year are wasted on ineffective drug treatment (10).

Precision Medicine

In medicine, as it is performed today, we apply the optimal population dose, as determined in clinical trials, on all individuals. However, since the population is heterogeneous, the optimal individual dose is not equal to the optimal population dose for all individuals and therefore leads to variability in drug response. Precision medicine aims to individualize or stratify application of pharmacotherapy, as opposed to population-based application, in an effort to optimize benefit/risk ratio (11, 12). By enabling identification of individuals who are at higher risk for ADRs or lack of efficacy, before drug initiation and potential harm, we may apply an individualized dose and drug selection to reduce this risk. The term precision medicine may be used interchangeably with personalized medicine. While the term precision infers application of drugs with more precision, such as genetic variation of pre-specified variants present in multiple individuals, the term personalized infers use of a single or combination of determinants uniquely present in a specific individual.

Determinants of Drug Response

Inconveniently, drug response is difficult to predict since it is affected by multiple determinants including the competence of the treating healthcare system and both exogenous and endogenous patient factors. Healthcare system factors that may affect drug response include unintended medication errors (13, 14) and misdiagnosis of the treated disease (15). Exogenous factors that may affect drug response include co-medication (16, 17), food (18), smoking (19), the microbiome (20), compliance (21) and exogenous disease factors. Endogenous factors that may affect drug response include age, gender (16, 22), endogenous disease factors, organ function, ethnicity (23), and the placebo effect (24, 25). The functionality (and dysfunctionality) of endogenous proteins involved in drug response may be reflected in the metabolome (26), transcriptome, epigenome (27), and genome (28, 29). To further complicate prediction, these factors may affect one another, and their interactions may vary across drugs.

Genetic Prediction of Drug Response

Although the biological mechanism underlying drug response may be downstream of genetic variation, genetics is considered the causal anchor (30). Therefore, an individuals' germline genetic variation is a particularly promising predictive factor that can enable drug response prediction. This is supported by its pharmacological plausibility and has been demonstrated in various studies. Pharmacokinetically, the intended drug response is expected when plasma drug concentrations are above the therapeutic and below the toxic thresholds. An individuals' plasma blood concentration at a particular dose is determined by proteins involved in the absorption, distribution, metabolism, and elimination (ADME) of the drug, which are encoded in DNA. Genetic variation within these ADME genes may cause variation in protein functionality and therefore cause variation in plasma blood level resulting in variation in drug response. Current evidence suggests 91% of metoprolol and 86% of torsemide area under the curve (AUC) variations are due to genetic variation in *CYP2D6* and *CYP2C9/OATP1B1*, respectively (31). Similar studies have shown comparable genetic contributions for nortriptyline (32), phenylbutazone (33) and metformin (34) pharmacokinetics. From an evolutionary perspective, it is also plausible to expect strong variation in ADME genes across individuals as a result of ancestral adaptation to diverse environments and exposure to diverse exogenous molecules. Pharmacodynamically, genetic variation in drug receptors or enzyme active sites may alter drug potency for its effector protein, and therefore affect its efficacy. Additionally, idiosyncratic drug response may also be determined by genetic variation in immunological processes (35).

Additionally, applying germline genetics to predict drug response has a number of practical advantages, over other predictors, as a tool for enabling precision medicine. First, since the genome in healthy cells is static, it only needs to be determined once in a lifetime. Secondly, it enables prediction before drug initiation and potential drug-induced harm.

Thirdly, the rise of novel technologies enables the determination of an individual's genetic profile relatively quickly and at reasonable costs.

Precision Medicine Using Pharmacogenomics

Pharmacogenomics (PGx) utilizes an individual's germline genetic profile to identify those who are at higher risk for ADRs or lack of efficacy (36-38). 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 (39). PGx can potentially optimize the 'trial and error' approach to medicine and thereby improve both the benefit and safety of pharmacotherapy by initiating drug therapy on an individualized dose as opposed to the default population dose. The discrepancy between germline and somatic PGx is of importance with regard to PGx implementation (40). Somatic variation is acquired in non-germline cells and therefore is not passed on to the next generation. Somatic variation may lead to malignancies and in these cases somatic variation can identify which types of malignancy are likely to respond to various anticancer agents (41, 42). Despite significant progress in the field of somatic precision medicine, it is outside the scope of this thesis. Within germline PGx, the focus lies on inherited variation in genes which play a role in drug ADME. To date, several randomized controlled trials support the clinical utility of individual gene-drug pairs to either optimize dosing (43-46) or drug selection (47, 48). Following the completion of the Human Genome Project (29), the Royal Dutch Pharmacists Association (KNMP) anticipated a proximate future were patients would present themselves in the pharmacy with their genetic information. As a result, the Dutch Pharmacogenetics Working Group (DPWG) was established in 2005 to develop clear guidelines for HCPs on how to interpret and apply PGx test results (49, 50). In parallel, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was initiated in 2008 and devises similar guidelines (51). Additionally, the labels of 15% of European Medicines Agency drugs include PGx information to inform prescribing (52). Since 95% of the population carries at least one PGx variant for which guidelines are available (53), and individuals are expected to initiate a number of PGx drugs throughout their lifetime (54, 55), 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 (56, 57). In a pre-emptive panel approach, variants in multiple pharmacogenes are tested simultaneously and used when a potentially interacting drug is prescribed. When PGx is adopted in such a model, it has been estimated that 23.6% of all incident prescriptions will have a relevant drug-gene interaction (58).

Despite the promise of and 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 (59-61). These include the undetermined model for delivering PGx, the lack of evidence supporting a PGx panel approach and the lack of tools supporting implementation. The work of this thesis aims to support the implementation of

precision medicine using PGx panel testing. Therefore, it reports on generating evidence for PGx panel testing (Part I) and the development of tools facilitating implementation (Part II). Furthermore, it reports on evaluation of the implementation process utilizing these tools (Part III) and quantifies the impact of PGx implementation on patient outcomes and cost-effectiveness (Part IV). This research is part of a large European collaborative project, The Ubiquitous Pharmacogenomics (U-PGx) Consortium, funded by the European Commission's Horizon 2020 Program under grant agreement No.668353.

Precision Medicine Using Pharmacogenomic Panel Testing: Aims and Outline

Part I: Generating Evidence for Pharmacogenomic Panel Testing

Despite scientific and clinical advances in the field of PGx, application into routine care remains limited. Opportunely, several implementation studies and programs have been initiated over recent years. **Chapter 2** firstly presents an overview of these studies, to identify a current evidence gap preventing implementation; namely the lack of clinical utility of a pre-emptive panel of PGx-markers. Secondly, it describes the design and implementation strategy of the U-PGx Consortium, which includes a randomized controlled trial across seven European countries (n=8,100) and referred to as the PREemptive Pharmacogenomic testing for prevention of Adverse drug Reactions (PREPARE) study. It aims to fill the identified evidence gap by quantifying the (cost-) effectiveness of guiding drug and dose selection using a PGx panel. More specifically, it aims to quantify the impact of implementation on the occurrence of clinically relevant ADRs. **Chapter 3** provides an overview of considerations made to mitigate multiple methodological challenges that emerged during the design and operationalization of the PREPARE study.

Part II: Developing Tools Facilitating Implementation

A number of barriers preventing implementation have been reported. This thesis presents solutions and tools for overcoming these barriers.

An important barrier is 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.

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 actionable DPWG guidelines, which is presented in **Chapter 5**.

Part III: Evaluating the Implementation Process

It is of importance to assess and evaluate the implementation process when implementing genomic medicine in practice. This part investigates several process indicators.

A suggested route for requesting PGx testing is through a direct-to-consumer 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 aim to explore the consumer perceptions of interactions with primary care providers when discussing their results. More specifically, we report on the incidence of consumer sharing of genetic results with HCPs and their satisfaction with the interaction.

A suggested route for delivering pre-emptive panel-based PGx results is through 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 the record of PGx-panel results in the electronic medical record (EMR). In **Chapter 7** we aim to quantify both feasibility and real-world impact of this approach in primary care, within a side-study of the prospective Implementation of Pharmacogenetics in Primary Care (IP3) pilot study. More specifically, regarding feasibility, we investigate whether the PGx panel results were recorded as a contra-indication in both general practitioner and pharmacist EMRs. Regarding real-world impact, we report on the frequency at which patients receive newly initiated prescriptions with possible drug-gene interactions and their downstream impact on healthcare utilization. Furthermore, we investigate both pharmacist reported enablers and barriers of pharmacist-initiated panel-based testing in primary care. Additionally, we investigate pharmacist-reported barriers and process indicators for implementation such as shared decision making, report of results to patients, and time allocation in **Chapter 8**.

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

In addition to assessing process indications, it is of prime importance to assess the impact of implementation on patient outcomes and cost-effectiveness both to practice evidence-based medicine and to convince stakeholders. This will primarily be generated by the PREPARE study, as presented in **Chapters 2 and 3**. Currently, over 6,500 patients have been enrolled and the trial is aiming to report by the end of 2020. In the meantime, we report on the cost-effectiveness of single-gene testing for drug-gene interactions with a clinical implication score "essential" to prevent gene-drug-related deaths when adopted nation-wide in **Chapter 9**.

General Discussion

This thesis concludes with a general discussion and future perspectives on precision medicine in **Chapter 10**. Summaries of this thesis in both English and Dutch are presented in **Chapters 11 and 12**.

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