Precision medicine using pharmacogenomic panel testing

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PART I

Generating Evidence for Pharmacogenomic Panel Testing

Chapter 2:

Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium

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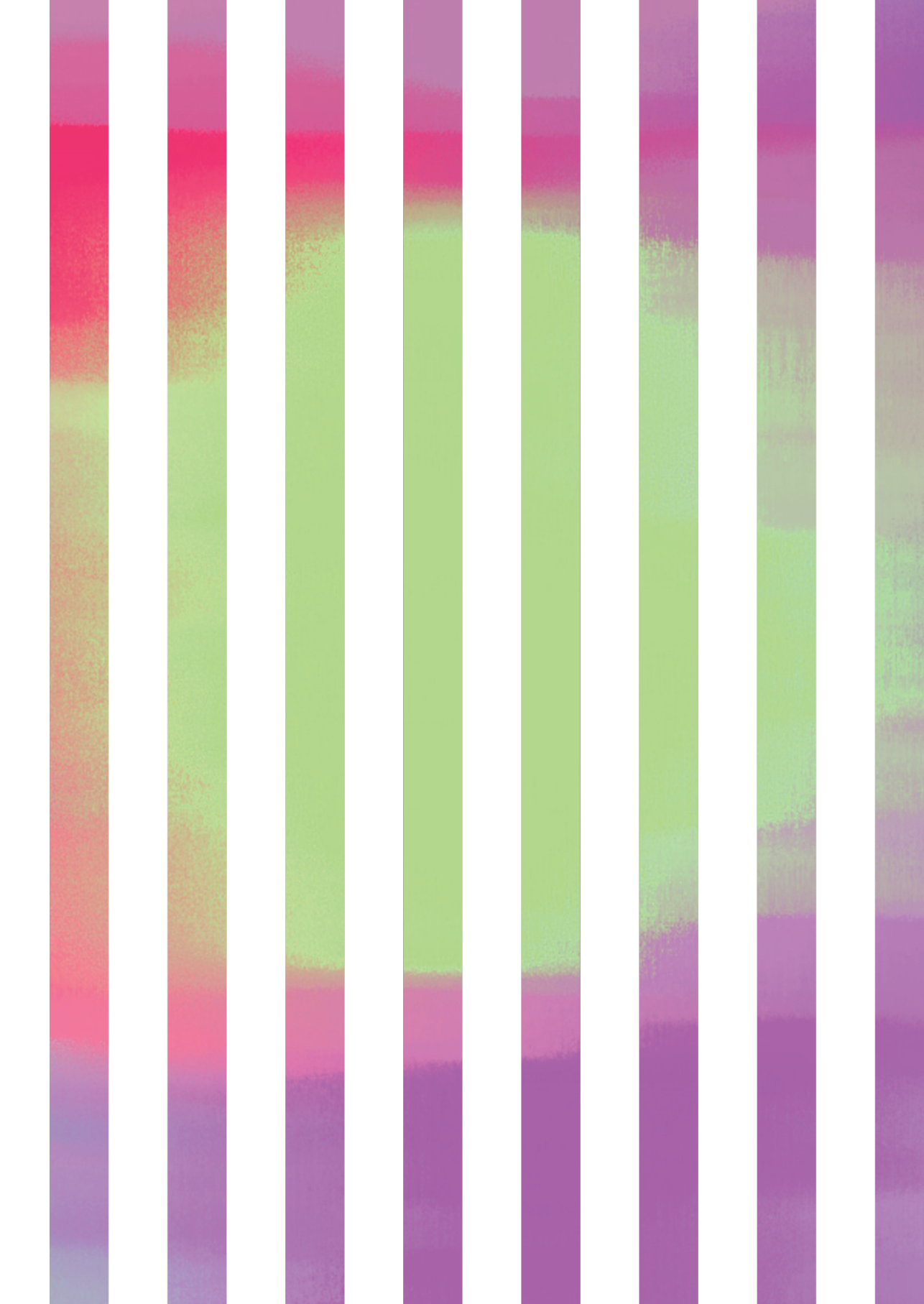

ABSTRACT

Despite scientific and clinical advances in the field of pharmacogenomics (PGx), application into routine care remains limited. Opportunely, several implementation studies and programmes have been initiated over recent years. This article presents an overview of these studies and identifies current research gaps. Importantly, one such gap is the undetermined collective clinical utility of implementing a panel of PGx-markers into routine care, because the evidence base is currently limited to specific, individual drug-gene pairs. The Ubiquitous Pharmacogenomics Consortium (U-PGx), which has been funded by the European Commission's Horizon-2020 programme, aims to address this unmet need. In a prospective, block-randomized, controlled clinical study (PREPARE), pre-emptive genotyping of a panel of clinically relevant PGx-markers, for which guidelines are available, will be implemented across healthcare institutions in seven European countries. The impact on patient outcomes and cost-effectiveness will be investigated. The program is unique in its multi-center, multi-gene, multi-drug, multi-ethnic, and multi-healthcare system approach.

INTRODUCTION

Pharmacogenomics in precision medicine

Pharmacogenomics (PGx) informed prescribing is one of the first applications of genomics in medicine (1, 2). It promises to personalize medicine by using an individual's genetic makeup, which predicts drug response, to guide optimal drug and dose selection (3, 4). This removes the traditional 'trial and error' approach of drug prescribing, thereby promising safer, more effective and cost-effective drug treatment (5, 6). The discrepancy between germline and somatic PGx is of importance with regard to PGx clinical implementation (7). Despite significant progress in the field of somatic precision medicine, it is outside the scope of this review. Several randomized controlled trials (RCTs) have provided gold-standard evidence for the clinical utility of single drug-gene PGx tests to: 1) guide dosing for warfarin, (8, 9), acenocoumarol, phencopromon (10), and thiopurines (11), and; 2) guide the drug selection of abacavir (12). Additionally, several prospective cohort studies have been performed indicating the clinical utility of single drug-gene PGx tests to guide drug selection of carbamazepine (13) and allopurinol (14). Many argue though that the perceived mandatory requirement for prospective evidence to support the clinical validity of a PGx test, prior to its implementation into routine care, is incongruous and excessive (15-18). The notion of "genetic exceptionalism" has been held responsible (19). Several recent studies estimate that 95% of the population carry at least one actionable genotype (20, 21). Since actionable PGx variants are ubiquitous and germline PGx results are life-long, we consider that quantifying the collective clinical utility of a panel of PGx-markers to be more relevant than providing evidence for individual drug-gene pairs. This will, however, still require the systematic implementation of a pre-emptive PGx strategy across multiple drugs, genes and ethnicities, and the robust assessment of this interventions impacts on both individual patient care and healthcare service processes. It is our expectation that the generation of such evidence will support the population-wide implementation of pre-emptive PGx testing.

Barriers preventing PGx implementation

There have been advances in PGx implementation, but significant barriers remain, including those preventing clinical implementation (22-26). The remaining hurdles include improving physician and pharmacist awareness and education about PGx (27, 28), the development of tools to implement PGx results into the workflow of physicians and pharmacists (29, 30) and the undecided reimbursement of PGx tests. Finally, and most importantly, evidence presenting the collective clinical utility of a panel of PGx-markers remains to be established. It is envisaged that surpassing these daunting barriers will provide the impetus for the widespread adoption of both the Dutch Pharmacogenomics Working Group (DPWG) guidelines (31, 32) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (33-46), which will help to realise the potential of PGx.

Current implementation projects are addressing these barriers

Several of the documented hurdles obstructing the implementation of PGx are currently being addressed by various initiatives, both in the United States and the European Union. A compact overview of these initiatives is provided in the following sections. From this overview, both trends and remaining research gaps have been identified. Various initiatives attempt to increase physician and pharmacist knowledge of PGx, and a diverse range of tools have been developed to integrate PGx testing results into their workflow. A significant research gap which, however, remains unmet is the absence of evidence presenting the collective clinical utility of a panel of PGx-markers. The Ubiquitous Pharmacogenomics Consortium (U-PGx), therefore, aims to provide this evidence in a large-scale, multi-drug, multi-gene, multi-center, multi-ethnic, approach to PGx testing.

The Ubiquitous Pharmacogenomics Consortium (U-PGx)

The U-PGx Consortium is an established network of European experts equipped to address the remaining challenges and obstacles for clinical implementation of PGx into patient care (16). Funded by a 15 million Euro Horizon 2020 grant from the European Commission, the U-PGx Consortium aims to make actionable PGx data and effective treatment optimization accessible to every European citizen. The U-PGx consortium will investigate the impact on adverse event incidence and healthcare costs following the widespread implementation of pre-emptive PGx testing using a panel of clinically relevant markers. As opposed to many other implementation initiatives, U-PGx will implement PGx through a pre-emptive panel strategy as opposed to implementing an individual drug-gene pair. For reasons stated above, this approach is designed to provide relevant evidence supporting the implementation of PGx in routine care. U-PGx uses a multifaceted approach consisting of four components to achieve this objective, as shown in **Figure 1**, and members of each component are mapped in **Figure 2**. The first component focuses on developing the enabling tools necessary to integrate PGx test results into the electronic health record (EHR) and clinical decision support system (CDSS), taking into account the differences in health care models, languages and laws across the EU. These enabling tools consist of information technology (IT) solutions, PGx testing infrastructure, educating healthcare professionals in PGx, and translating the existing DPWG guidelines, which were updated only in Dutch language, to six other local languages. This component will pave the way for the unobstructed operation of component two. This second component will implement pre-emptive genotyping of a panel of 50 variants in 13 pharmacogenes into clinical practice, in the context of a large prospective, international, block-randomised, controlled study (n=8,100). This study is called the PREPARE study (PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions). Primarily the study aims to assess the impact of PGx implementation on adverse event incidence. Additional outcomes include cost-effectiveness, process indicators for implementation and provider adoption of PGx. A third component applies innovative methodologies such as next-generation sequencing (NGS),

pharmacokinetic modelling and systems pharmacology to discover additional variants associated with drug response and to elucidate drug-drug-gene interactions. The final, fourth, component will focus on ethical issues of the project and implications for PGx, and spearheads outreach and educational activities to influential stakeholders. In comparison to the US, projects within the EU likely encounter even more challenges to achieve implementation because of the multi-linguistic settings, different legal environments and heterogeneous healthcare systems of EU countries. The specific approaches adopted by these components and the design of the PREPARE study are further elaborated in the following sections.

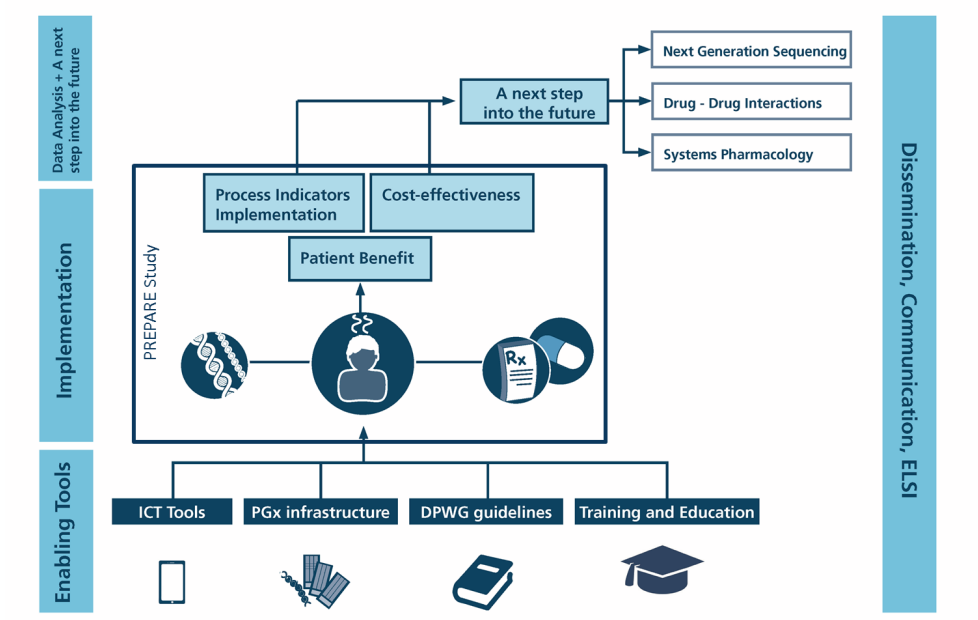

Figure 1 An overview of the Ubiquitous Pharmacogenomics (U-PGx) Project. Firstly, tools to enable the integration of PGx results into the CDSS will be developed, the DPWG guidelines will be translated and participating physicians and pharmacists will be educated in understanding and applying PGx during prescription and dispensing. Following this, the PREPARE study will evaluate the impact of PGx implementation on clinical outcomes, cost effectiveness and implementation process metrics. The PREPARE study will provide data collection for innovative projects, which aim to expand our understanding of PGx though next-generation sequencing and a systems pharmacology approach. In parallel, the final component supports the ethical proceeding of the project and spearheads outreaching and educational activities to influential stakeholders

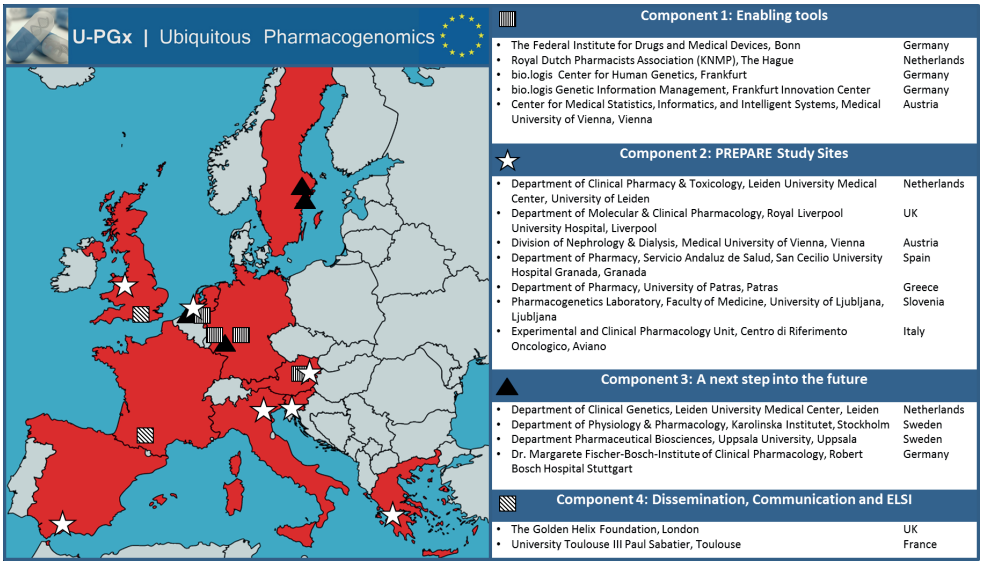

Figure 2 The established expert network of the Ubiquitous Pharmacogenomics (U-PGx) Consortium. The U-PGx Consortium consists of four components: 1) Enabling Tools, 2) The PREPARE Study, 3) A next step into the future, and 4) Dissemination, communication and ELSI (ethical, legal, and societal impact). The institutes listed below are members of the corresponding component

OVERVIEW OF CURRENT IMPLEMENTATION STUDIES

Several implementation studies have been initiated in the United States since 2010. An overview of published initiatives is given in **Table 1**. Additional, unpublished, initiatives may exist outside the scope of this table. A subsection of these studies has previously been summarized elsewhere (20). In the following sections the objectives and implementation strategies of these clinical implementation studies and programmes are summarized.

Cleveland Clinic's Personalized Medication Program

The Cleveland Clinic established the Center for Personalized Healthcare in 2011, to incorporate unique patient characteristics, including genetics, into the medical decision making process. The center has developed two programs, one of which is the Personalized Medication Program. This program was launched in 2012 aims to identify drug-gene pairs ready for integration into clinical practise and developing the tools needed to implement into the clinical workflow. The program has currently implemented *HLA-B*5701*-abacavir and *TPMT*-thiopurines into the clinical workflow and aims to implement two additional drug-gene pairs per year. An oversight committee selected these drug-gene pairs. Alerts and custom rules have been developed in the EHR to provide clinicians with point-of-care PGx decision support. A clinical pharmacogenomics specialist provides support for both patients and clinicians who require help with understanding the PGx results. Future goals also include development of an algorithm which identifies patients who are at high-risk of receiving a drug for which pre-emptive genotyping would be useful .

CLIPMERGE PGx

As part of the eMERGE-PGx project, Icahn School of Medicine at Mount Sinai has initiated the CLIPMERGE PGx Project for implementing PGx testing into the EHR and CDSS by using a biobank derived cohort, from the *BioMe* Biobank. Patients enrolled in the biobank, who are likely to receive a drug with genetic interactions and receive primary care at Mount Sinai Internal Medicine Associates, are eligible for inclusion. 1,500 pilot patients are being pre-emptively genotyped for known variants associated with drug response. CLIPMERGE-PGx aims to provide valuable insight into the mechanisms, tools and processes that will best support the use of PGx in clinical care. The investigators argue that before personalized medicine can be realized, tools and best practices to facilitate the delivery of PGx must be developed and evaluated so that the question of utility can be answered without the burden of a questionable process (47). As an initial result, a study among included physicians suggested they have a deficit in their familiarity and comfort in interpreting and using PGx (48).

Electronic Medical Records and Genomics Network-Pharmacogenomics (eMERGE-PGx)

The eMERGE-PGx is a partnership of the Electronic Medical Records and Genomics Network (eMERGE) (49) and the Pharmacogenomics Research Network (PGRN) (50, 51). eMERGE-PGx is a multi-center project which aims to implement targeted sequencing of 84 pharmacogenes and assess process and clinical outcomes of this implementation at ten academic medical centers across the United States. The goals of eMERGE-PGx are threefold: 1) to install a NGS sequencing platform to assess sequence variation in 9,000 patients likely to be prescribed a drug of interest in a one- to three-year timeframe across the ten clinical sites; 2) to integrate clinically validated genotypes into the EHR and CDSS and to measure the resulting clinical outcomes and assess the implementation process, and; 3) to develop a repository of variants of unknown significance linked to clinical phenotype data to expand PGx understanding (52).

Implementing Genomics in Practice (IGNITE)

IGNITE is a network of six sites and a coordinating center which aims to develop methods for, and evaluate the feasibility of, incorporating and individual patient's genomic information into their clinical care. The network was established in 2013 and supports the development and investigation of genomic practice models which are integrated into electronic medical records to inform decision making at the point of care. Three of these sites focus on implementing PGx testing in clinical care: Indiana University (INGENIOUS), University of Florida (Personalized Medicine Program), Vanderbilt University (I^3P) (53).

INdiana GENomics Implementation: an Opportunity for the Under Served (INGENIOUS)

Indiana University School of Medicine and the Indiana University Institute of Personalized Medicine, in collaboration with the Eskenazi Health System, are conducting an NIH funded trial, which started recruitment in March 2015. INGENOUS implements pre-emptive PGx genotyping of a panel of pharmacogenes through a randomized clinical trial. INGENIOUS is prospectively enrolling a total of 6,000 patients, with 2,000 patients assigned to the PGx testing arm and 4,000 to the control arm. Both arms will be followed for a year after being prescribed a targeted medication. Open Array genotyping will assess 43 variants in 14 genes known to affect the response of 28 drugs. Primary outcomes include adverse event incidence and annual healthcare cost. PGx results are integrated in the EHR and CDSS. Additionally, participating physicians are supported with provided consultations in using the PGx results in routine care (54, 55).

Personalized Medicine Program

The University of Florida and Shands Hospital launched the Personalized Medicine Program in 2011 to ensure the clinical implementation of PGx-based prescribing. The pilot implementation project focussed on implementation of clopidogrel-*CYP2C19* drug-gene pair and future plans include expansion to additional drug-gene pairs. The initiative developed a cost-effective PGx genotyping array (56). A specialized hospital regulatory body is responsible for regulating which clinically relevant PGx markers are migrated to the medical record and CDSS. As of March 2013, *CYP2C19* genotypes of 800 patients have been incorporated in their medical records (57).

PG4KDS

Through a research protocol St. Jude Children's Research Hospital's PG4KDS aims to selectively migrate PGx genotype tests into routine patient care so that results are available pre-emptively. Genotyping is performed using the DMET assay (58). The ultimate objective is to migrate all CPIC gene-drug pairs into the EHR, to facilitate PGx-based prescribing, and for it to ultimately become routine care. A PGx oversight committee evaluates whether drug-gene pairs are qualified for migration into the EHR. Interruptive pre-test alerts are fired when a drug linked to a drug-gene pair is prescribed, informing physicians that the patient does not yet have a documented genotype (29). Post-test alerts are fired when the genotype is available in the patient's EHR. Patients have the option to consent to individualized notification every time a new genetic test result is placed into their EHR. Additionally, educational efforts are focused at both patients and clinicians. As of August 2013, 1,559 patients had been enrolled and four genes and 12 drugs have migrated to the EHR (59).

Pharmacogenomics Research Network (PGRN) Translational Pharmacogenetics Program

In 2011 the PGRN established the Translational Pharmacogenetics Program to assess implementation within six diverse health-care systems. The project's aim is to assess the implementation of routine evidence-based pharmacogenetic testing .Each site will implement PGx testing of one or more drug-gene pairs, as per the CPIC guidelines, either through a clinical trial or through implementing into clinical practice. Implementation strategies include both through point-of-care and pre-emptive models. Process metrics for implementation are tracked among all sites, to assess the effectiveness of implementation (51).

Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment (PREDICT) Project

As part of the eMERGE-PGx project, Vanderbilt University has initiated the PREDICT Project. The aim is to develop the infrastructure and framework for incorporating PGx results into the EHR and making these available to healthcare professionals at the time of prescribing. Initially, the implementation focussed on *CYP2C19* genotyping for patients receiving antiplatelet therapy after having undergone cardiovascular stent insertion. The enrolment focus is on groups of patients with anticipated cardiac catheterization with coronary artery stenting, but providers are not limited to enrolling patients within this therapeutic area (21). As of November 2013, 10,000 patients had been genotyped and several other drug-gene pairs have been implemented (60).

Right Drug, Right Dose, Right Time (RIGHT)

As part of the eMERGE-PGx project, Mayo Clinic has initiated the RIGHT Project. The aims the project is to develop best practice for integrating both PGx results and CDSS into the EHR to make PGx results available to prescribers pre-emptively at the point of care. As of July 2013, 1,013 Mayo Clinic Biobank participants were included in the study and four gene-drug pairs were approved for implementation and several others were in under development for integration within the CDSS (20). Initially, patients were eligible for enrolment if they had a high risk of initiating statin therapy within three years, as this subset of patients would likely benefit from a PGx-driven intervention. These participants were identified through a multivariable prediction model (61). Pre-emptive PGx testing included targeted sequencing of 84 PGx genes and additional *CYP2D6* genotyping because of technical difficulties with sequencing *CYP2D6*. As an interim result, challenges have been identified which require multi-disciplinary and multi-institutional efforts to make PGx guided drug and dose selection routine care. (62)

The 1,200 Patients Project

The University of Chicago has initiated the 1,200 Patients Project and aims to determine the feasibility and utility of incorporating pre-emptive PGx testing into clinical care. This observational study involves the implementation of novel genomic prescribing system (GPS) to deliver a patient-specific interpretation of complex genomic data for a particular drug, distilled into a short summary (63). Outcomes of the study include, whether physicians take PGx information into consideration, and whether this results in altered prescribing patterns in patients at high risk for ADR or non-response. Future aims include an examination of the impact of providing PGx results on prescribing decisions and patient outcomes (64). Following recruitment of 821 patients, initial results of the project demonstrate a high level of patient interest in PGx testing, and physician adoption and utilization of PGx information through the GPS (65).

CURRENT PGX IMPLEMENTATION STUDIES: TRENDS AND REMAINING RESEARCH GAPS

From this overview, trends among initiatives and remaining knowledge gaps can be identified.

Trends Across Clinical Implementation Studies

Similarities across clinical implementation studies include: integrating the PGx test results into the EHR and CDSS at the point of care to guide healthcare providers in using results in patient care; implementation of the existing CPIC guidelines; implementing single drug-gene pairs one at a time and assessing their clinical utility; educating healthcare providers in PGx; and expanding the field of PGx by making use of NGS techniques. Individual initiatives have additionally addressed the utility of PGx in subpopulations such as paediatrics (59, 66) and polypharmacy (67, 68), where the impact of PGx may be greater.

Remaining Knowledge Gaps

Although many implementation studies are addressing the remaining barriers, important knowledge and research gaps remain. One remaining gap is demonstrating quantifiable patient and economic benefit from a PGx testing strategy that focuses, not on a single gene-drug pair, but rather on a panel of pharmacogenes across various therapeutic areas. This evidence could enable evidence-based decision making to shape policy. Further PGx investigations are also required to deepen our understanding of drug response phenotype-genotype associations. This deeper understanding of PGx is urgently needed to increase the predictive accuracy, benefits and impact of PGx. An important additional area for attention is the design of implementation models that are transferable and feasible for institutes not as highly specialized as the early adopting sites featured in **Table 1**.

The U-PGx Consortium was established to address these critical remaining research gaps in addition to observing the aforementioned state-of-the-art trends. The U-PGx

consortium strives to provide evidence regarding the clinical utility of PGx testing using a panel of pharmacogenes, provide evidence of cost-effectiveness, and to expand the field of PGx by both NGS and systems pharmacology approaches. U-PGx is one of the few implementation studies assessing the combined clinical utility of multiple drug-gene pairs and is therefore strategy specific as opposed to drug-gene pair specific. U-PGx is also the first to implement PGx across countries, and therefore across many ethnicities and healthcare systems. U-PGx is also not limited to implementing PGx in highly specialized institutions, and will therefore obtain different process metrics for implementation than early-adopting institutions, where providers may have more PGx know-how. U-PGx is also the first study implementing the DPWG guidelines as opposed to the CPIC guidelines. Similar to many implementation studies, U-PGx will integrate PGx results into the workflow of healthcare providers, aims to educate both physicians in pharmacists in PGx, and measure process metrics for implementation.

Table 1 An overview of current clinical implementation studies and programmes across the United States and Europe

Implementation Initiative	Objectives	Clinical sites (Country)	Strategy	N° PGx genes tested	Platform	Drug-gene combinations implemented in clinical care (clinical guidelines)	Population (n)
Cleveland Clinic's Personalized Medication Program (30, 47)	-Implementing a CDSS to guide pharmacogenetics test ordering and provide gene-based dosing recommendations at the point-of-care. In parallel a PGx consultation service is available	-Cleveland Clinic (USA)	-Implementing alerts which recommend ordering a PGx test at the point-of-care -Implementing drug-gene pairs one at a time	n/a	n/a	*HLA-B*57:01*/abacavir *TPMT*/thiopurines (as per the CPIC guidelines)	Patients treated in a tertiary care adult hospital, children's hospital regional hospitals or ambulatory locations across Ohio
CLIPMERGE PGx (48, 49)	-Provide insight into the mechanisms, tools and processes that will best support the use of PGx in clinical care -Contribute to the emerging body of data needed for forthcoming larger studies that will assess the utility of PGx in medication safety and efficacy	-Icahn School of Medicine at Mount Sinai (USA)	Implementing pre-emptive genotyping and real-time CDSS deployed through the EHR into routine care using a bio-bank derived cohort	36 (20)	Sequenom iPLEX ADME PGx (20)	*CYP2C19*/clopidogrel *CYP2C9*/warfarin *VKORC1*/warfarin *SLOCO1B1*/simvastatin *CYP2D6*/TCAs *CYP2C19*/TCAs *CYP2D6*/SSRIs (as per CPIC guidelines)	Pilot study: primary care patients who consented to Bio*ME* biobank (N=1,500). Eventual aim is to recruit all Bio*ME* participants
eMERGE-PGx (50-52)	-Install a NGS sequencing platform assessing sequence variation in patients likely to be prescribed a drug of interest in a 1 to 3 year time frame -Integrate clinically validated genotypes into the EHR and CDSS and to assess the impact on clinical outcomes and process of implementation -Develop a repository of variants of unknown significance linked to clinical phenotype data to expand PGx understanding	-Boston Children's Hospital -Children's Hospital of Philadelphia -Cincinnati Children's Hospital -Geisinger Health System -Group Health/University of Washington -Marshfield Clinic -Mayo Clinic (RIGHT) -Icahn School of Medicine at Mount Sinai (CLIPMERGE) -Northwestern University -Vanderbilt University Medical Center (PREDICT) (all above in USA)	Multi-center project evaluating pre-emptive sequencing and pre-emptive genotyping	84	PGRNseq	Varies across clinical sites (as per CPIC guidelines)	Individuals likely to be prescribed drugs of interest within a 1- to 3-year timeframe, specific therapeutic focus amongst all sites (N=9,000)

INGNITE (PGx initiatives) (54)	-To develop methods for, and evaluate the feasibility of, incorporating and individual patient's genomic information into their clinical care	-University of Florida (USA) -Vanderbilt University (USA) -Indiana University (USA)	A network of health-care systems who each implement PGx in their site	n/a	n/a	n/a	n/a
INGENIOUS (55, 56)	-To assess whether PGx testing for a panel of clinically relevant markers impacts annual healthcare costs and adverse event incidence	-Indiana Institute of Personalized Medicine at Indiana School of Medicine (USA)	Operational implementation of pre-emptive genotyping of a panel of clinically relevant markers in routine care, in a safety-net hospital	14	Open Array	Clinically relevant pharmacogenes associated with the response of 28 drugs (as per CPIC guidelines)	Adult patients receiving care at the Eskenazi Health System (n=6,000)
Personalized Medicine Program (57, 58)	-Developing a pre-emptive, chip-based genotyping approach that is cost-effective, initially for implementation of a single drug/gene pair but eventually expanding to many others	-University of Florida and Shands Hospital (USA)	Implementing pre-emptive genotyping in routine care	120 (20)	Life Technologi-es Quant Studio Open Array (20)	*CYP2C19*/clopidogrel (as per CPIC guidelines)	Patients receiving antiplatelet therapy and undergoing percutaneous coronary intervention (n=800)
PG4KDS (59, 60)	-Ultimately migrate all CPIC drug-pairs into the EHR and CDSS	-St. Jude Children's Research Hospital (USA)	Research protocol implementing pre-emptive genotyping	230	Affymetrix DMET Plus Array	*TPMT, CYP2D6, SLOC1B1* and *CYP2C19* coupled to 12 high-risk drugs (as per CPIC guidelines)	St. Jude (paediatric) patients with a primary medical record at St. Jude Hospital (n=1,559)
PGRN (52)	-To assess the implementation of routine evidence-based pharmacogenetic testing in six diverse healthcare systems	-University of Maryland (USA) -University of Florida (USA) -St. Jude Children's Research Hospital (USA) -Vanderbilt University (USA) -Mayo Clinic -Ohio State University	Each site has implemented pharmacogenomics testing of one or more drug-gene pairs, both through point-of-care and pre-emptive models.	n/a	n/a	Several drug-gene pairs as per the CPIC guidelines	n/a
PREDICT (21, 61)	-To establish a framework and infrastructure for pre-emptive incorporation of genomic information into the EHR.	-Vanderbilt University Medical Center (USA)	Operational implementation of pre-emptive genotyping in routine care	34	VeraCode ADME Core Panel	*CYP2C19*/clopidogrel *CYP2C9*/warfarin *VKORC1*/warfarin (as per CPIC guidelines)	Patients receiving antiplatelet therapy following placement of cardiovascular stent (N=10,000)

RIGHT (62, 63)	-Develop best practices for the implementation of genetic sequence data into clinical systems .	Mayo Clinic (USA)	Implementing pre-emptive sequencing and genotyping in routine care	84	PGRNseq and Luminex CYP2D6 ASPE kit	*SLOCO1B1*/simvastatin *CYP2C19*/clopidogrel *IFNL2*/interferon *CYP2D6*/tramadol *CYP2D6*/tamoxifen *CYP2D6*/codeine *HLA-B*1502*/carbamazepine *HLA-B*5701*/abacavir *TPMT*/thiopurines (as per CPIC guidelines)	Patients likely to receive statin therapy within 3 years, recruited from the Mayo Clinic Biobank (N=1,013) (20)
The 1200 Patients Project (64-66)	-To determine the feasibility and utility of incorporating pre-emptive pharmacogenomics testing in clinical care. -Future aims include examining the impact of providing PGx results on prescribing decisions and patient outcomes.	University of Chicago (USA)	Observational study implementing pre-emptive genotyping	n/a	Sequenom ADME and Sequenom custom panel	n/a	Adults receiving outpatient medical care and using 1-6 prescription medications (N=1,200)
U-PGx and the PREPARE Study	-Implementation of pre-emptive PGx testing, of a panel of clinically relevant markers -Assessing the impact on incidence of adverse event incidence and healthcare costs -Performing exploratory analyses to expand understanding of PGx	-Leiden University Medical Center (NLD) -Royal Liverpool University Hospital (UK) -University of Patras (GRC) -University of Ljubljana (SVN) -Medical University of Vienna (AUT) -National Cancer Institute Aviano (ITA) -University Hospital Granada (ESP)	Block-randomized clinical study to implement pre-emptive genotyping of a panel of clinically relevant markers. Additional NGS sequencing amongst those presenting extreme phenotypes	13	LGC Group SNPLine	Clinically relevant pharmacogenes associated with the response of 43 drugs (see Table 2 for actionable drug-gene combinations) (as per DPWG guidelines)	Individuals who receive a first prescription of a drug of interest. First line, oncology, renal and liver transplant, cardiology, and psychiatric patients (N=8,100)

EHR: Electronic health record; CDSS: Clinical decision support system; ADME: Absorption, distribution, metabolism, elimination; TCA: Tricyclic antidepressants; SSRI: Serotonin reuptake inhibitors; USA: United States of America; NLD: The Netherlands; UK: United Kingdom; GRC: Greece; SVN: Slovenia; AUT: Austria; ITA: Italy; ESP: Spain

UBIQUITOUS PHARMACOGENOMICS CONSORTIUM (UPGx)

Overcoming Implementation Barriers

Enabling tools

As of October 2016, a variety of enabling tools have been developed to facilitate implementation of PGx testing in a wide range of healthcare systems across the European Union. A detailed analysis of existing data management systems (both electronic and paper-based) at clinical sites has been conducted to guide the development of CDSS implementation strategies in U-PGx. To accommodate the widely varying capabilities and needs of data management systems at different implementation sites, a spectrum of complementary CDSS solutions were developed . Specifically, to make PGx data and CDSS available in health care systems where an EHR is unavailable, the "Safety-Code card" has been adopted (69). This card is part of a mobile-based CDSS called the Medication Safety Code (MSC) system that is independent of existing IT infrastructures, and enables quick retrieval of patient-relevant PGx drug dosing guidelines (**Figure 3**). The MSC system does not require central patient data storage. Instead, the "Safety-Code card" contains a QR code that stores the patient's encoded PGx results. It can be decoded and interpreted by common smartphones and other devices. After scanning the QR code, the medical professional is led to a website that provides drug dosing recommendations customized to the PGx profile of the patient. In the context of PREPARE, the MSC system is aimed to serve as an auxiliary tool to maximize the accessibility and sharing of PGx results within and between different health care settings and health care professionals. Patients will be asked to show their "Safety-Code card" to physicians and pharmacists who prescribe or dispense drugs to them during the follow-up period of the study. These physicians and pharmacists can thus use the patient's PGx results to guide drug and dose selection. Concomitantly, patients will be asked to report prescriptions of additional newly started drugs to research nurses during the follow-up period.

Knowledge base curation and the automated translation of genetic data to associated phenotypes and recommendations will be handled by the Genetic Information Management Suite (GIMS) created by the U-PGx partner bio.logis Genetic Information Management (70). The GIMS Diagnostic Report Module holds the CE Mark according to according to EEC 93/42, EC 2007/47. The CE mark for a medical device not only certifies the product's quality according to valid European guidelines but also confirms its fitness to be used for the intended medical purpose. The authorities responsible for monitoring the manufacturer's compliance with the relevant European regulations are the German Institute of Medical Documentation and Information (DIMDI) as well as the Federal Institute for Drugs and Medical Devices (BfArM). In addition the Diagnostic Report Module has been certified as an "Internet medicine quality product" by the Federal Association for Internet Medicine (BiM).

Figure 3 The front (top) and back (bottom) of the "Safety-Code card". This is a plastic card, akin to a credit card, carrying an individual's pharmacogenomic information and a QR code which is connected to the individual's personalized dosing recommendations as per the Dutch Pharmacogenomics Working Group

The Dutch Pharmacogenomics Working Group Guidelines

In 2005, the Royal Dutch Pharmacists Association (KNMP) established the DPWG with the objective to develop pharmacogenetics-based therapeutic recommendations based on a systematic review of the literature. The DPWG consists of 14 members including clinical pharmacists, community pharmacists, general practitioners, physicians, clinical chemists, epidemiologists and a toxicologist. Currently, the database consists of 84 drug-gene combinations comprising 13 genes. DPWG guidelines are integrated in the "G-Standaard" (the Dutch national drug database) and are incorporated into all electronic systems for drug prescribing and dispensing in the Netherlands. As part of U-PGx, the DPWG guidelines (31, 32) have been translated into all local languages (from Dutch to English, German, Greek, Slovenian, Spanish and Italian) by certified professionals.

Genotyping platform and variant selection

The LGC Group SNPline™ platform will be deployed at all implementation sites, ensuring homogenous genotyping across the project. The SNPline platform is a flexible and scalable solution for PCR-based genotyping. It is comprising a workflow that enables the user to generate up to more than 1,000 ,000 data points per day. Additionally, it retains the flexibility to run individual repeats without consuming arrays and producing far more data than needed. The variants included in the panel were selected systematically by pre-specified criteria. The criteria for variant selection are listed in **Supplemental Table S1**. The selection yielded 50 variants in 13 pharmacogenes. Variants included in the panel and their associated phenotypes are listed in **Supplemental Table S2**.

Pharmacogenomics education

Provider and patient education and support are crucial for successful implementation of PGx. E-Learning programs will be prepared with the aim of developing an e-learning based knowledge platform for the participating countries and partners. This e-learning platform will be used to distribute the PGx knowledge required by physicians and pharmacists to make use of PGx in patient care. Using electronic education methods, lectures will cover the main themes that are regarded necessary for the use and implementation of PGx and will be offered to schools of medicine, schools of pharmacy and post-academics. These will cover the basics of PGx, drug metabolism, drug dosing, targeted therapies, regulation and guidelines for PGx diagnostics in drug development and pharmacovigilance, companion diagnostics, obligatory genetic tests, good genomic practice and PGx information in drug labels. The level of knowledge and opinion on PGx among physicians and pharmacists at the start and at the end of the project will be investigated through surveys. The aim is to assess the level of knowledge about PGx among healthcare professionals to identify knowledge gaps which may hinder the implementation of PGx testing in routine care.

The PREPARE Study

Overall study design

PREPARE is an international prospective, multi-center, open, block-randomized, study. **Figure 4** illustrates the PREPARE study design. The PREPARE study (Clinicaltrials.gov: NCT03093818) will investigate the impact of pre-emptive genotyping of a panel of clinically relevant PGx-markers on patient outcomes. It is unique in its multi-center, multi-gene, multi-drug, multi-ethnic, and multi-healthcare system approach. It is hypothesized that implementing PGx guided drug and dose selection will decrease clinically relevant ADRs by 30% (from 4% to 2.8%). Pre-emptive PGx testing will be implemented in clinical sites across seven European countries (United Kingdom, The Netherlands, Austria, Greece, Slovenia, Italy and Spain). The PREPRARE protocol has been submitted for ethical approval, locally, in all seven countries. The study will be performed in accordance with the Helsinki Declaration of

1975 (as revised in 1983). The 36-month study is split into two 18-month blocks. The participating countries are randomized to start with either implementing PGx guided prescribing or with standard of care for the first block. After this 18-month block, the countries switch to implementing the opposite strategy and will recruit new patients (i.e. patients recruited into one of the arms cannot be re-recruited into the other arm). Both patients and research teams cannot be blinded; the PGx results will be used to guide drug and dose selection, and patients will receive their PGx results on a "Safety-Code card". In total, 8,100 patients will be recruited; 4,050 patients in the intervention arm and 4,050 patients in the control arm. Each implementation site will concentrate on, but is not limited to, recruiting patients within a specific therapeutic area. Therapeutic areas include primary care, general medicine, cardiology, oncology, psychiatry, neurology, and transplantation. The PREPARE study schema is illustrated in **Figure 5**.

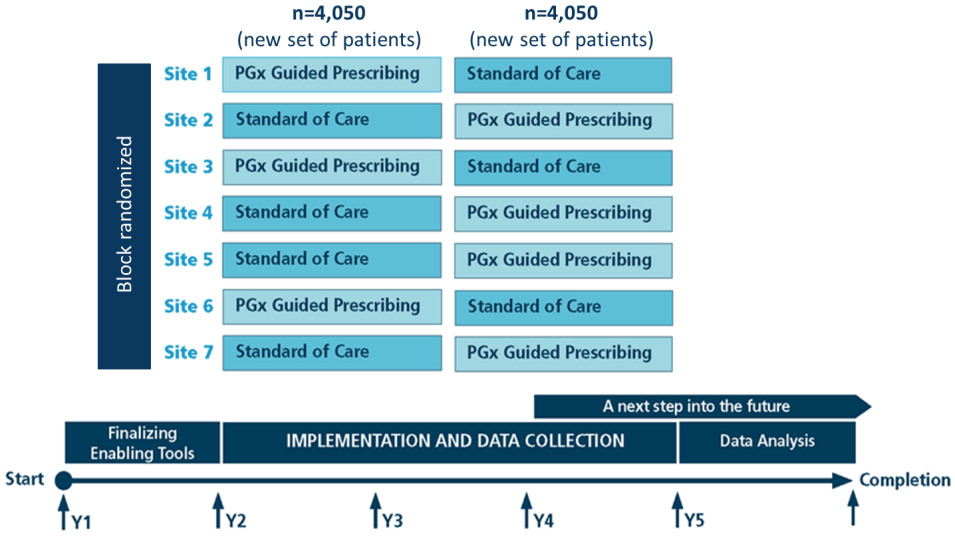

Figure 4 Timeline of the PREPARE study: in the first year all tools enabling pre-emptive PGx testing (IT, genotyping technology, education, translation and sharing of guidelines) will be prepared and finalized. In years 2 to 4 the impact of pre-emptive PGx testing will be evaluated in the PREPARE study. Sites (countries where the study is performed) are block-randomized to either implement PGx guided prescribing or standard of care for an 18-month block. After this 18-month block, the opposite strategy will be implemented, with a new set of recruited patients. 4,050 new patients will be recruited in each block. Each site will function as its own control. In parallel, data will be collected for innovative projects, which aim to expand the understanding of pharmacogenomics though next-generation sequencing and systems pharmacology approaches

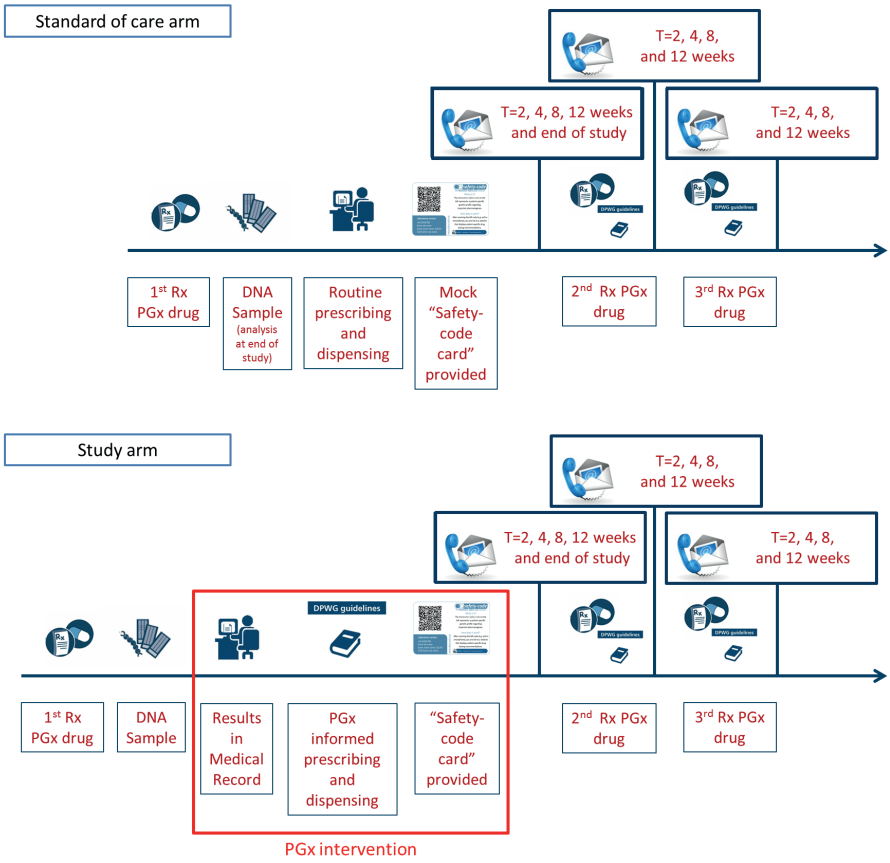

Figure 5 Study logistics in the PREPARE study. Adult patients receiving a first prescription for one of the 42 included drugs will be identified and are eligible for inclusion. At recruitment a DNA sample is collected for genotyping of a panel of 50 variants in 13 pharmacogenes. The PGx results of patients in the intervention arm only will be used to guide drug and dose selection as per the DPWG guidelines. Patients in the intervention arm will receive a "Safety-Code card" containing their personal PGx results, which can be used by other physicians or pharmacists to guide subsequent prescriptions. Patients in the standard of care arm will receive a mock "Safety-Code card", not containing any PGx results but listing the U-PGx eligible drugs. There are two consecutive 18-month blocks for recruitment of participants. In one block, participants will receive standard of care; in the other block, other participants will receive the PGx intervention. The order of these blocks is randomized at each study site. Following recruitment, all patients will be followed-up for three months, both by the research nurse (at baseline, 4 weeks and 12 weeks after initiating the index drug) and by an online patient reported outcomes survey (at two weeks and eight weeks). In addition, a final cross-sectional survey will be performed by the research nurse, at the end of the study arm. Follow-up will assess for incident adverse drug events, drug modifications, drug adherence, quality of life, healthcare costs, co-medication and attitudes towards PGx. Assessment of adverse drug reactions will be performed by the research team and involves a causality, severity and genotype correlation assessment. Patients are requested to report if they newly start any of the 43 drugs (including oestrogen containing drugs) of interest during follow-up in addition to the index drug. This will trigger an identical three month follow-up

Patient recruitment

Adult patients who receive a first prescription for a drug listed in **Table 2** (drugs for which a DPWG dosing recommendation is available), within routine care, will be identified and are eligible for inclusion. Inclusion and exclusion criteria are listed in **Supplemental Table S3**. This first drug that is included is referred to as the "index drug". To ensure that there is a balanced patient and drug population among intervention and control arms, inclusion of any given index drug is limited to 10% in both the intervention (n=405) and control arms (n=405).

Drug selection

DPWG guidelines to guide dose and drug selection are available for more drugs than are included in the PREPARE study. **Table 2** includes all drugs for which an actionable drug-gene interaction is present according to the DPWG recommendations with the exception of abacavir, omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. Abacavir is excluded because PGx-guided prescribing is mandatory in routine care. Proton pump inhibitors are excluded because the DPWG recommendations are only associated with differences in efficacy, rather than ADR frequency, amongst aberrant genotypes (where ultra-rapid metabolisers are recommended a higher dose to ensure sufficient blood levels for an efficacious pharmacotherapy). Oestrogen containing drugs will not serve as an index drug, but are incorporated into the study if newly started in a patient already recruited onto PREPARE during study follow (see below 'subsequent drugs').

The PGx intervention

A DNA sample is collected at recruitment for genotyping of a panel of 50 variants in 13 pharmacogenes. The PGx results of patients in the study arm only will be used to guide drug and dose selection as per the DPWG guidelines. These results will be provided to the prescribing physician or dispensing pharmacist with a maximum turnover time of three-working days.

Table 2 Actionable drug-gene pairs implemented in routine care in the PREPARE Study as per the Dutch Pharmacogenomics Working Group guidelines

Drug Class	Drug (n=43)	DGI	Actionable Phenotype/Genotypes
Antiarrhythmic	Flecainide	*CYP2D6*	PM, IM, UM
	Propafenon	*CYP2D6*	PM, IM, UM
Analgesic	Codeine	*CYP2D6*	PM, IM, UM
	Oxycodone	*CYP2D6*	PM, IM, UM
	Tramadol	*CYP2D6*	PM, IM, UM
Anticancer	Capecitabine	*DPYD*	Gene activity score 0, 0.5, 1, 1.5
	Fluorouracil	*DPYD*	Gene activity score 0, 0.5, 1, 1.5
	Irinotecan	*UGT1A1*	PM, *28/*28
	Tamoxifen	*CYP2D6*	PM, IM
	Tegafur	*DPYD*	Gene activity score 0, 0.5, 1, 1.5
Anticoagulation	Acenocoumarol	*VKORC1*	*VKORC1*TT
	Clopidrogel	*CYP2C19*	PM, IM
	Phenprocoumon	*VKORC1*	*VKORC1*TT
	Warfarin	*CYP2C9* *VKORC1*	*1/*3, *2/*2, *2/*3, *3/*3, IM, PM TT
Antidepressant	Citalopram	*CYP2C19*	PM, IM
	Escitalopram	*CYP2C19*	PM, IM
	Paroxetine	*CYP2D6*	UM
	Sertraline	*CYP2C19*	PM, IM
	Venlafaxine	*CYP2D6*	PM, IM, UM
Antidepressant (TCA)	Amitriptyline	*CYP2D6*	PM, IM, UM
	Clomipramine	*CYP2D6*	PM, IM, UM
	Doxepine	*CYP2D6*	PM, IM, UM
	Imipramine	*CYP2D6* *CYP2C19*	PM, IM, UM PM
	Nortryptiline	*CYP2D6*	PM, IM, UM
Antiepileptic	Carbamazepine	*HLA B*1502*	-
	Phenytoin	*CYP2C9*	IM, PM, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3
Antihypertensive	Metoprolol	*CYP2D6*	PM, IM, UM
Anti-infective	Efavirenz	*CYP2B6*	PM, IM
	Flucloxacillin	*HLA B*5701*	-
	Voriconazole	*CYP2C19*	PM, IM
Antipsychotic	Aripiprazole	*CYP2D6*	PM
	Clozapine	*CYP1A2*	*1C heterozygote, *1C/*1C
	Haloperidol	*CYP2D6*	PM, UM
	Pimozide	*CYP2D6*	PM, IM
	Zuclopenthixol	*CYP2D6*	PM, IM, UM
Cholesterol-lowering	Atorvastatin	*SLCO1B1*	521TC, 521CC
	Simvastatin	*SLCO1B1*	521TC, 521CC
Immunosuppressant	Azathioprine	*TPMT*	PM, IM
	Mercaptopurine	*TPMT*	PM, IM
	Tacrolimus	*CYP3A5*	homozygote or heterozygote expressers

	Thioguanine	*TPMT*	PM, IM
Other	Atomoxetine	*CYP2D6*	PM, UM
	Oestrogen containing drugs*	*F5*	homozygote expresser, heterozygote expresser

DGI: Drug-Gene Interaction; CYP: Cytochrome P450; DPYD: Dihydropyrimidinedehydrogenase; UGT: UDP-glucuronosyltransferase; VKORC: Vitamin K epOxide Reductase Complex; HLA: Human Leucocyte Antigen; SLCO: Solute Carrier Organic Anion Transporter; TPMT: Thiopurine S-methyltransferase; FVL: Factor Five Leiden *Only included for follow-up as a subsequent prescription, not for a drug of inclusion

Follow-up

Follow-up by the research team will assess incident adverse drug events, (index) drug modifications, drug adherence, quality of life, costs, co-medication and attitudes towards PGx. Assessment of adverse drug reactions will be performed by the research team and will involve causality, severity and genotype correlation assessments. Incident adverse drug reactions collected by the research team will contribute to the primary composite endpoint (see primary composite endpoint). The research team will contact patients at four weeks, twelve weeks and at the end of the study arm by telephone (out patients) or in person (in patients). Various open questions will be posed to identify adverse events experienced by the patient, followed by a series of closed questions to identify specific adverse events associated with the drug of interest.

In parallel, patient reported outcomes will be monitored through an established web-based platform developed by the Netherlands Pharmacovigilance Center Lareb, and will only be used as a secondary outcome. This web-based intensive monitoring system has been validated in several clinical trials as a feasible and accurate method for collecting adverse drug event data (71). This aspect of the study is important as patient reported adverse events may differ from those collected by the research team (72). Reporting patients will provide assessments of severity and causality of their own adverse event. Patient reported severity will be measured by using a scale based on the Patient-Reported Outcome-Common Toxicity Criteria (PRO-CTCAE) (73).

Subsequent prescriptions of drugs of interest

Patients are requested to notify the research team every time they receive a prescription for one of the 43 drugs of interest (as listed in **Table 2**) during follow-up. These drugs are referred to as "subsequent drugs". This will trigger an identical three-month follow-up, as for the index drug (as illustrated in **Figure 5**). Patients are requested to provide their (mock) "Safety-Code card" to physicians that manage them or dispensing pharmacists. Healthcare providers will have the ability to make use of the PGx results to guide drug and dose selection at the point of consultation; in the contrast to the index drug, where a thee working day lag-time is unavoidable. There is recognition for the fact that the research team is fully reliant on patient report of subsequent prescriptions, in order to trigger follow-up for this subsequent prescription. This could introduce selection bias. Therefore, incident adverse drug reactions resulting from subsequent prescriptions will only be used as a secondary outcome.

Primary composite outcome

All adverse events are monitored during follow-up by the research team are classified according to causality, severity and drug-genotype association. Causality will be classified using the Liverpool Causality Assessment Tool (74). Severity will be classified using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) scale. The drug-genotype association will be assessed using the DPWG guidelines (31, 32). To ensure homogenous assessment across all sites, the Netherlands Pharmacovigilance Center Lareb will blindly reassess a random selection of adverse drug events. Adverse drug events contributing to the composite primary endpoint are illustrated in **Figure 6**. All ADRs which contribute to the primary endpoint, contribute equally; regardless of their severity.

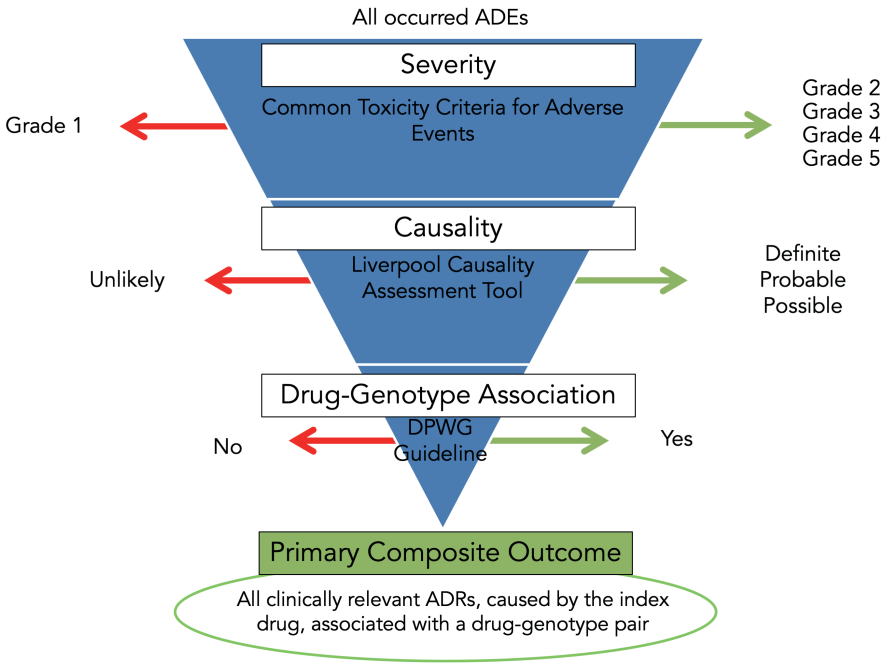

Figure 6 The primary endpoint is the frequency of clinically relevant adverse drug reactions within three months of initiating the index drug. All incident adverse drug events will be assessed regarding causality (using the Liverpool Causality Assessment Tool), severity (using the NCI-CTCAE scale), and association to genotype (using the DPWG guidelines). Only adverse drug events defined as definitely, probably or possibly adverse drug reactions according to the Liverpool causality assessment tool, classified as severe (defined as NCI-CTCAE Grade 2,3,4 or 5), and associated with a drug-genotype pair contribute to the primary endpoint

Primary analysis

A gatekeeping analysis will be performed for the primary analysis only amongst patients who had an actionable drug-genotype combination for the index drug. This first analysis will compare the fraction of patients who experienced at least one clinically relevant ADR within the 12-week follow-up, attributable to the index drug, between the standard of care and the intervention arm. If this is statistically significant, a second analysis will be performed, including all patients in the study. This second analysis will compare the fraction of patients who experienced at least one clinically relevant ADR within the 12-week follow-up, attributable to the index drug, between the standard of care and the intervention arm. All sites will act as their own controls. The first analysis will quantify the absolute impact of PGx based prescribing on the frequency of clinically relevant ADRs, the second will quantify the impact of PGx intervention when it is implemented population-wide.

Secondary Outcomes

Drug efficacy is not an outcome measure in the PREPARE study. It is not anticipated that PGx guided prescribing will have a negative impact on drug efficacy. To provide evidence for this statement, two proxy-measures of efficacy will be collected. Firstly, the frequency of drug discontinuation due to lack of efficacy will be compared in the standard of care arm to the intervention arm. Secondly, routine index drug levels of patients who received a dose alteration as a result of an actionable drug/gene combination will be compared to the routine index drug levels of patients who did not receive a dose alteration. It is hypothesized that the drug exposures are similar in both arms, and that efficacy must therefore also be similar. Data on costs associated with ADRs will be collected to perform a country-specific cost-effectiveness analyses. Adherence to PGx guidelines will also be collected following every index drug and subsequent drug prescription within the PREPARE study. This will yield data on DPWG guideline adherence by both the health care professionals who recruit to the PREPARE study and the health care professionals outside the scope of the PREPARE study but who manage an episode of routine care for a participant during the study follow up period. The research team will contact health care professionals after they have received their patient's PGx results to ask whether or not they complied with the DPWG recommendation. When health care professionals do not comply with the recommendation, they are asked to report reasons for not doing so. Patient knowledge of and attitudes towards PGx will also collected at baseline and at the end of the study.

A Step into the Future

PGx is still an evolving discipline and will undoubtedly be further developed over the years to increase the applicability and subsequent impact of PGx on patient outcomes. Our incomplete understanding of the genetic impact on drug responses limits the benefits of PGx in clinical care; possibly up to 50% of ADRs may be predicted by common genetic determinants. Rare variants may also be associated with drug responses or ADRs; using NGS

(75-78) and systems pharmacology approaches, we may be able to increase our understanding of the role of PGx and thereby potentially increase its benefits and impact. The U-PGx consortium will achieve this by using two approaches: 1) NGS techniques to identify rare variants that are associated with drug response in the extreme phenotype sub-study and 2) through a systems pharmacology approach, non-genetic determinants of drug response (such as gender, age, drug-drug interaction) will be integrated to create novel, powerful and practice-oriented models of personalized medicine in pharmacokinetic sub-studies. Inclusion and exclusion criteria for the sub-studies are listed in **Supplemental Table S4**.

Extreme Phenotype Sub-Study

Patients included in the PREPARE study who either 1) experience a serious ADR which is not expected on the basis of the pre-emptive PGx testing results in the PGx intervention arm, or 2) experience a serious ADR (already known to be associated with the drug in the DPWG guidelines) even though the patient has received an altered drug or dose selection as a result of an actionable genotype or 3) experience a serious ADR in the PGx control arm. These "extreme phenotype" patients will be flagged and contacted by the research nurse to obtain a blood sample, for drug level monitoring, at the time of the ADR for NGS sequencing and detection of plasma levels of the drug of interest including relevant metabolites. NGS sequencing will be performed to search for novel variants associated with the extreme phenotype. To identify a possible genetic origin of the extreme phenotype, all patients included in the study will be asked to provide informed consent for NGS. This data will only be used anonymously for exploratory analysis and not be implemented in clinical care or returned to the patient, thereby no potential secondary genetic findings will be returned to the patients. Plasma samples of drugs of interest will be detected by previously established methods (e.g. HPLC, LC-MS/MS) to perform additionally phenotype (plasma level)-genotype correlation analysis.

Pharmacokinetic Sub-Study

Patients included in the study after a first prescription of voriconazole, metoprolol, simvastatin, atorvastatin, fluorouracil or capecitabine will be asked to provide additional blood samples (see **Supplemental Table S5**) to quantify levels of the parent drug and respective metabolites . Through a systems pharmacology approach, non-genetic determinants of drug response (such as gender, age, disease related factors, drug-drug interaction) will be integrated to create novel, powerful and practice-oriented models of personalized medicine. This work will strive toward assessing the relative contribution of PGx to variability in drug response by utilizing pharmacometric models that integrate PGx with other sources of variability. The models will describe the events from dose to drug response, thus including effects of PGx on pharmacokinetics and pharmacodynamics. Physiologically based pharmacokinetic models and(or population pharmacokinetic models will be utilised.

Clinical endpoint data as well as clinically relevant drug-drug interactions will be extracted from PREPARE to be used for adjustment and qualification of model-based analyses.

CONCLUSIONS

In conclusion, the U-PGx Consortium will implement pre-emptive PGx testing involving a panel of pharmacogenes into routine care to guide drug and dose selection for 43 drugs, through a multi-center, block-randomized controlled study. PREPARE aims to assess the impact of implementation on ADR incidence and healthcare costs. In parallel, innovative approaches such as pharmacometric modelling, NGS and systems pharmacology will be used to expand our understanding of PGx and thereby increase its potential benefits and impact.

We hypothesize successful PGx implementation could drastically decrease the incidence of ADRs and could increase the benefit: risk profile of pharmacotherapy. Currently, unacceptable levels of ADRs, poor adherence and ineffectiveness are associated with pharmacotherapies for many conditions. Each year, adverse drug events are responsible for 5% of hospitalizations, but crucially, PGx implementation has the potential to alleviate this. The impact of PGx testing will be maximized when implemented population-wide. Since actionable PGx variants are ubiquitous and the results of PGx testing are life-long, we foresee a future where everyone undergoes PGx testing. Physicians and pharmacists can use these results pre-emptively to optimize drug and dose selection throughout a patient's lifetime. This could ultimately decrease (but not abolish) the incidence of ADRs and their associated healthcare service and societal burdens.

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SUPPLEMENTARY MATERIAL

Supplemental Table S1 The pre-emptive PGx test consists of a panel of 50 PGx variants within 13 pharmacogenes. The criteria for variant inclusion were:

	UPGx Panel Selection
Criteria	• A DPWG guideline with therapeutic recommendations for the specific genotype exists • The effect of the variant on the gene is established (e.g. Is *CYP2C9* inactive if the variant is present?) • Is the overall MAF[1] ≥ 1%? • If not, is the MAF in selected populations (European/Asian/African) [2] ≥ 1%? • If the MAF is below 1% in all cases, selection of certain variants is possible if at least one of the implementation sites already determines the allele in patient care.

1. MAF: Minor Allele Frequency. For the determination of the MAF we used www.ensembl.org and received input from Karolinksa Institutet and the Dutch Pharmacogenomics Working Group. A MAF of 1% or greater is considered to be common. We restricted allele selection above this selected MAF cut off.
2. The selected populations are the most common populations in Europe. Besides the Europeans, Asians and Africans are present in Europe due to migration.

Supplemental Table S2 Genotype to phenotype translation in the PREPARE Study.

Genes	Allele	Major Nucleotide Variation	dbSNP RS ID	Effect on protein	Functional Status
CYP1A2	*1C	-3860G>A	rs2069514	X	Decreased
CYP1A2	*1F	-163C>A	rs762551	X	Higher inducibility
CYP2B6	*6	516G>T	rs3745274	Q172H	Decreased or Inactive
CYP2B6	*16	785G>A	rs2279343	K252R	Decreased or Inactive
CYP2B6	*18	983T>C	rs28399499	I328T	Decreased or Inactive
CYP2C9	*2	430C>T	rs1799853	R144C	Decreased
CYP2C9	*3	1075A>C	rs1057910	I359L	Decreased
CYP2C9	*5	1081C>G	rs28371686	D360E	Decreased
CYP2C9	*8	449G>A	rs7900194	R150H	Increased
CYP2C9	*11	1003C>T	rs28371685	R335W	Decreased
CYP2C19	*2	19154G>A*	rs4244285	Splicing defect/ P227P	Inactive
CYP2C19	*3	17948G>A*	rs4986893	W212X	Inactive
CYP2C19	*4A/B	1A>G*	rs28399504	M1V	Inactive
CYP2C19	*5	90033C>T*	rs56337013	R433W	Inactive
CYP2C19	*6	12748G>A*	rs72552267	R132Q	Inactive
CYP2C19	*7	19294T>A*	rs72558186	Splicing defect	Inactive
CYP2C19	*8	12711T>C*	rs41291556	W120R	Inactive or Decreased
CYP2C19	*9	12784G>A*	rs17884712	R144H	Decreased
CYP2C19	*10	19153C>T*	rs6413438	P227L	Decreased
CYP2C19	*17	-806C>T*	rs12248560	X	Increased
CYP2D6	*xN	Gene duplication or multiplication	X	X	Increased
CYP2D6	*3	2549delA	rs35742686	Frameshift	Inactive
CYP2D6	*4	1846G>A	rs3892097	Splicing defect	Inactive
CYP2D6	*5	Gene deletion	X	Gene deletion	Inactive
CYP2D6	*6	1707delT	rs5030655	Frameshift	Inactive
CYP2D6	*8	1758G>T	rs5030865	G169X	Inactive
CYP2D6	*9	2615delAAG	rs5030656	K281 deletion	Decreased
CYP2D6	*10	100C>T	rs1065852	P34S	Decreased
CYP2D6	*14A/B	1758G>A	rs5030865	G169R	Decreased
CYP2D6	*17	1023C>T	rs28371706	T107I	Decreased
CYP2D6	*29	1659G>A; 1661G>C	rs61736512	V136I	Decreased
CYP2D6	*29	3183G>A	rs59421388	V338M	Decreased
CYP2D6	*41	2988G>A	rs28371725	Splicing	Decreased
CYP3A5	*3	6986A>G	rs776746	SpliceDefect	Inactive
CYP3A5	*6	14690G>A	rs10264272	SpliceDefect	Inactive
CYP3A5	*7	27131_27132insT	rs41303343	346Frameshift	Inactive
DPYD	*2A	IVS14 + 1G>A (1905+1G>A)	rs3918290	X	Inactive
DPYD	*13	1679T>G	rs55886062	I560S	Inactive
DPYD	X	2846A>T	rs67376798	D949V	Decreased

DPYD	X	1236G>A	rs56038477	Glu412Glu	Decreased
F5	X	1691G>A	rs6025	A506G	Decreased
*HLA-B*5701*	X	rs2395029			tagging SNP for HLA-B*5701
SLCO1B1	*5/*15/*17	521T>C	rs4149056	V174A	Decreased
TPMT	*2	238G>C	rs1800462	Ala80Pro	Inactive
TPMT	*3B	460G>A	rs1800460	Ala154Thr	Inactive
TPMT	*3C	719A>G	rs1142345	Tyr240Cys	Inactive
UGT1A1	*6	211(G>A)	rs4148323	Gly71Arg	Decreased
UGT1A1	*27	686(C>A)	rs35350960	P229Q	Decreased
UGT1A1	*28/*37	A(TA)6TAA>A(TA)7TAA/A(TA)8TAA	rs8175347	X	Decreased
VKORC1	X	1173C>T (C6484T)	rs9934438		Increased sensitivity

CYP: Cytochrome P450; DPYD: Dihydropyrimidinedehydrogenase; UGT: UDP-glucuronosyltransferase; VKORC: Vitamin K epOxide Reductase Complex; HLA: Human Leucocyte Antigen; SLOC: Solute Carrier Organic Anion Transporter; TPMT: Thiopurine S-methyltransferase; FVL: Factor Five Leiden

Supplemental Table S3 Overall inclusion and exclusion criteria for the PREPARE study patient participants

	PREPARE Study Participants
Inclusion Criteria	• Subject must be ≥ 18 years old • Subject must receive a 1st prescription (meaning no known prescription for this drug in the preceding 12 months) for a drug included in Table 2, which is prescribed to them in routine care. • The study limit of enrolment (200 per arm, per 18-month block) for that drug has not been reached
Exclusion Criteria	• Previous (direct-to-consumer, or clinical) genetic testing for a gene important to the index drug • Pregnancy or lactating • Life expectancy estimated to be less than three months by treating clinical team • Duration of index drug total treatment length is planned to be less than seven consecutive days. A drug whose route of administration changes during the first seven days (e.g. intravenous to oral flucloxacillin) but whose total treatment duration is seven days or longer, is still eligible. • For inpatients: hospital admission is expected to be less than 72 hours (to facilitate acting upon the PGX results) • Patient has existing impaired hepatic or renal function for which a lower dose or alternate drug selection are already part of current routine care. This would not apply to any drugs specifically given to manage liver/renal impairment/transplantation. • Estimated glomerular filtration rate (MDRD) of less than 15 ml/min per 1,73m^2 in a subject with a functioning graft • Patients with advanced liver failure (stage Child-Pugh C)

Supplemental Table S4 Overall inclusion and exclusion criteria for the extreme phenotype and drug-drug-gene interaction sub-studies

	Extreme phenotype sub-study	Drug-drug-gene interaction sub-study
Inclusion Criteria	• Experience a serious ADR which is not expected on the basis of the pre-emptive PGx testing results in the PGx intervention arm. • Experience a serious ADR (already known to be associated with the drug in the DPWG guidelines) even though the patient had received an altered drug or dose selection as a result of an actionable genotype. • Experience a serious ADR in the PGx control arm	• Patients included in the study for a first prescription of voriconazole, metoprolol, simvastatin, atorvastatin, fluorouracil or capecitabine • Patients who provide informed consent for this sub-study

Supplemental Table S5 Clinical endpoints for the pharmacokinetic sub-study

Drug for inclusion to sub-study	Endpoints
Voriconazole	-Clinical symptoms and signs (e.g., body temperature, CT scans, MRI findings), -Microbiological response, (e.g. -microscopic examination, the cultivation result) -Serological tests (b-D-glucan test, galactomannan test
Metoprolol	-Resting blood pressure -Heart rate
Atorvastatin	-Lipid panels (TC, HDL-C, LDL-C, and TG)
Simvastatin	-Lipid panels (TC, HDL-C, LDL-C, and TG)
Capecitabine	-5-FU related ADRs, e.g. hand-and-foot syndrome; leucopenia, neutropenia, thrombocytopenia (tumor response)
Fluorouracil	-5-FU related ADRs, e.g. hand-and-foot syndrome; leucopenia, neutropenia, thrombocytopenia (tumor response)