

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

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Despite scientific and clinical advances in the field of pharmacogenomics (PGx), application into routine care remains limited. Opportunely, several implementation studies and programs 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 (U-PGx) Consortium, which has been funded by the European Commission's Horizon-2020 program, aims to address this unmet need. In a prospective, block-randomized, controlled clinical study (PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions [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 multicenter, multigene, multidrug, multi-ethnic, and multi-healthcare system approach.

## Pharmacogenomics in precision medicine

Pharmacogenomics (PGx) informed prescribing is one of the first applications of genomics in medicine.<sup>1,2</sup> It promises to personalize

medicine by using an individual's genetic makeup, which predicts drug response, to guide optimal drug and dose selection.<sup>3,4</sup> This removes the traditional "trial and error" approach of drug

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prescribing, thereby promising safer, more effective, and cost-effective drug treatment.<sup>5,6</sup> The discrepancy between germline and somatic PGx is of importance with regard to PGx clinical implementation.<sup>7</sup> Despite significant progress in the field of somatic precision medicine, it is outside the scope of this review. Several randomized controlled trials have provided gold-standard evidence for the clinical utility of single drug-gene PGx tests to: (1) guide dosing for warfarin,<sup>8,9</sup> acenocoumarol, phencopromon,<sup>10</sup> and thiopurines<sup>11</sup>; and (2) guide the drug selection of abacavir.<sup>12</sup> Additionally, several prospective cohort studies have been performed indicating the clinical utility of single drug-gene PGx tests to guide drug selection of carbamazepine<sup>13</sup> and allopurinol.<sup>14</sup> However, many argue 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.<sup>15–18</sup> The notion of “genetic exceptionalism” has been held responsible.<sup>19</sup> Several recent studies estimate that 95% of the population carry at least one actionable genotype.<sup>20,21</sup> Because 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. However, this will still require the systematic implementation of a pre-emptive PGx strategy across multiple drugs, genes, and ethnicities, and the robust assessment of this intervention 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 pharmacogenomics implementation

There have been advances in PGx implementation, but significant barriers remain, including those preventing clinical implementation.<sup>22–26</sup> The remaining hurdles include improving physician and pharmacist awareness and education about PGx,<sup>27,28</sup> the development of tools to implement PGx results into the workflow of physicians and pharmacists,<sup>29,30</sup> 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<sup>31,32</sup> and the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines,<sup>33–46</sup> which will help to realize the potential of PGx.

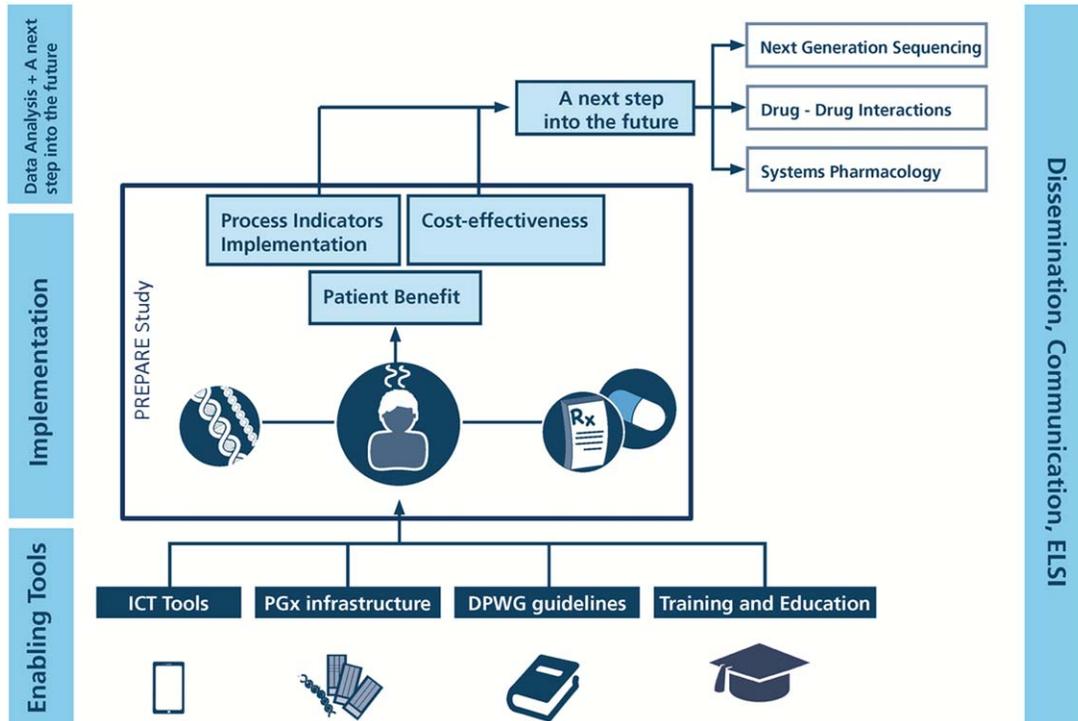
### Current implementation projects are addressing these barriers

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. However, a significant research gap, which 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, multidrug, multigene, multi-center, multi-ethnic approach to PGx testing.

### The Ubiquitous Pharmacogenomics Consortium

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.<sup>16</sup> 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 European Union. These enabling tools consist of information technology solutions, PGx testing infrastructure, educating healthcare professionals in PGx, and translating the existing DPWG guidelines, which were updated only in the 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-randomized, controlled study ( $n = 8,100$ ). This study is called the PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study. 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 modeling, 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 United States, projects within the European Union likely encounter even more challenges to achieve implementation because of the multilingual 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. First, tools to enable the integration of pharmacogenomics (PGx) results into the clinical decision support system will be developed, the Dutch Pharmacogenomics Working Group (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 PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (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 aims to expand our understanding of PGx through next-generation sequencing and a systems pharmacology approach. In parallel, the final component supports the ethical proceeding of the project and spearheads outreach and educational activities to influential stakeholders. ELSI, ethical, legal, and societal impact; ICT, information communication technology; PGx, pharmacogenomics.

U-PGx   Ubiquitous Pharmacogenomics	
	<b>Component 1: Enabling tools</b> <ul style="list-style-type: none"> <li>The Federal Institute for Drugs and Medical Devices, Bonn <span style="float: right;">Germany</span></li> <li>Royal Dutch Pharmacists Association (KNMP), The Hague <span style="float: right;">Netherlands</span></li> <li>bio.logis Center for Human Genetics, Frankfurt <span style="float: right;">Germany</span></li> <li>bio.logis Genetic Information Management, Frankfurt Innovation Center <span style="float: right;">Germany</span></li> <li>Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna <span style="float: right;">Austria</span></li> </ul>
	<b>Component 2: PREPARE Study Sites</b> <ul style="list-style-type: none"> <li>Department of Clinical Pharmacy &amp; Toxicology, Leiden University Medical Center, University of Leiden <span style="float: right;">Netherlands</span></li> <li>Department of Molecular &amp; Clinical Pharmacology, Royal Liverpool University Hospital, Liverpool <span style="float: right;">UK</span></li> <li>Division of Nephrology &amp; Dialysis, Medical University of Vienna, Vienna <span style="float: right;">Austria</span></li> <li>Department of Pharmacy, Servicio Andaluz de Salud, San Cecilio University Hospital Granada, Granada <span style="float: right;">Spain</span></li> <li>Department of Pharmacy, University of Patras, Patras <span style="float: right;">Greece</span></li> <li>Pharmacogenetics Laboratory, Faculty of Medicine, University of Ljubljana, Ljubljana <span style="float: right;">Slovenia</span></li> <li>Experimental and Clinical Pharmacology Unit, Centro di Riferimento Oncologico, Aviano <span style="float: right;">Italy</span></li> </ul>
	<b>Component 3: A next step into the future</b> <ul style="list-style-type: none"> <li>Department of Clinical Genetics, Leiden University Medical Center, Leiden <span style="float: right;">Netherlands</span></li> <li>Department of Physiology &amp; Pharmacology, Karolinska Institutet, Stockholm <span style="float: right;">Sweden</span></li> <li>Department Pharmaceutical Biosciences, Uppsala University, Uppsala <span style="float: right;">Sweden</span></li> <li>Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Robert Bosch Hospital Stuttgart <span style="float: right;">Germany</span></li> </ul>
	<b>Component 4: Dissemination, Communication and ELSI</b> <ul style="list-style-type: none"> <li>The Golden Helix Foundation, London <span style="float: right;">UK</span></li> <li>University Toulouse III Paul Sabatier, Toulouse <span style="float: right;">France</span></li> </ul>

**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 PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study; (3) a next step into the future; and (4) dissemination, communication, and ethical, legal, and societal impact (ELSI). The institutes listed above 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**.<sup>21,30,47–65</sup> Additional, unpublished, initiatives may exist outside the scope of this table. A subsection of these studies has previously been summarized elsewhere.<sup>20</sup> In the following sections, the objectives and implementation strategies of these clinical implementation studies and programs 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 and aims to identify drug-gene pairs ready for integration into clinical practice and developing the tools needed to implement into the clinical workflow. The program has currently implemented *HLA-B\*1502*-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 that identifies patients who are at high-risk of receiving a drug for which pre-emptive genotyping would be useful.

### CLIPMERGE pharmacogenomics

As part of the Electronic Medical Records and Genomics (eMERGE)-PGx project, the 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. The 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.<sup>48</sup> As an initial result, a study among included physicians suggested they have a deficit in their familiarity and comfort in interpreting and using PGx.<sup>49</sup>

### Electronic Medical Records and Genomics Network-Pharmacogenomics

The eMERGE-PGx is a partnership of the Electronic Medical Records and Genomics Network<sup>50</sup> and the Pharmacogenomics Research Network (PGRN).<sup>51,52</sup> The eMERGE-PGx is a multi-center project that aims to implement targeted sequencing of 84 pharmacogenes and assess process and clinical outcomes of this

implementation at 10 academic medical centers across the United States. The goals of eMERGE-PGx are threefold: (1) to install an NGS sequencing platform to assess sequence variation in 9,000 patients likely to be prescribed a drug of interest in a 1–3-year timeframe across the 10 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.<sup>66</sup>

### Implementing Genomics in Practice

Implementing Genomics in Practice (IGNITE) is a network of six sites and a coordinating center that aims to develop methods for, and evaluate the feasibility of, incorporating 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 the EHRs 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<sup>3</sup>P).<sup>53</sup>

### Indiana GENomics Implementation: an Opportunity for the UnderServed

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. INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS) implements pre-emptive PGx genotyping of a panel of pharmacogenes through a randomized clinical trial. INGENIOUS is prospectively enrolling 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.<sup>54,55</sup>

### 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 focused 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.<sup>56</sup> 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.<sup>57</sup>

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

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
Cleveland Clinic's Personalized Medication Program <sup>30,47</sup>	-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 that 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 hospital, or ambulatory locations across Ohio
CLIPMERGE PGx <sup>48,49</sup>	-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 preemptive genotyping and real-time CDSS deployed through the EHR into routine care using a bio-bank derived cohort	36 <sup>20</sup>	Sequenom IPLEX ADME PGx <sup>20</sup>	CYP2C19/clopidogrel CYP2C9/warfarin VKORC1/warfarin SLO-CO1B1/simvastatin CYP2D6/TCAs CYP2C19/TCAs CYP2D6/SSRIs (as per CPIC guidelines)	Pilot study: primary care patients who consented to BioME biobank (N = 1,500). Eventual aim is to recruit all BioME participants
eMERGE-PGx <sup>50-52</sup>	-Install an NGS sequencing platform assessing sequence variation in patients likely to be prescribed a drug of interest in a 1-3-year timeframe -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)	Multicenter project evaluating preemptive sequencing and preemptive genotyping	84	PGRNseq	Varies across clinical sites (as per CPIC guidelines)	Individuals likely to be prescribed drugs of interest within a 1-3-year timeframe, specific therapeutic focus among all sites (N = 9,000)
IGNITE (PGx initiatives) <sup>53</sup>	-To develop methods for, and evaluate the feasibility of, incorporating an individual patient's genomic information into their clinical care	-University of Florida (USA) -Vanderbilt University (USA) -Indiana University (USA)	A network of healthcare systems who each implement PGx in their site	N/A	N/A	N/A	N/A

Table 1 Continued on next page

Table 1 Continued

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
INGENIOUS <sup>54,55</sup>	-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 <sup>56,57</sup>	-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 <sup>20</sup>	Life Technologies Quant Studio Open Array <sup>20</sup>	CYP2C19/clopidogrel (as per CPIC guidelines)	Patients receiving anti-platelet therapy and undergoing percutaneous coronary intervention (N = 800)
PG4KDS <sup>58,59</sup>	-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, SLOCLB1, and CYP2C19 coupled to 12 high-risk drugs (as per CPIC guidelines)	St. Jude (pediatric) patients with a primary medical record at St. Jude Hospital (N = 1,559)
PGRN <sup>62</sup>	-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 (USA) -Ohio State University (USA)	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 <sup>21,60</sup>	-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 anti-platelet therapy following placement of cardiovascular stent (N = 10,000)

Table 1 Continued on next page

**Table 1 Continued**

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
RIGHT <sup>61,62</sup>	-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*1501/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) <sup>20</sup>
The 1,200 Patients Project <sup>63-65</sup>	-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 among those presenting extreme phenotypes	13	LGC Group SNPline	Clinically relevant pharmacogenes associated with the response of 43 drugs (see <b>Table 2</b> 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)

ADME, absorption, distribution, metabolism, elimination; AUT, Austria; CDSS, clinical decision support system; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group; EHR, electronic health record; ESP, Spain; GRC, Greece; HLA, human leucocyte antigen; IGNITE, Implementing Genomics in Practice; INGENIOUS, Indiana GENomics Implementation: an Opportunity for the UnderServed; ITA, Italy; N/A, not applicable; NGS, next-generation sequencing; NLD, The Netherlands; PGRN, Pharmacogenomics Research Network; PGRNseq, Pharmacogenomics Research Network sequencing; PGx, pharmacogenetic; PRE-DICT, Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment; RIGHTS, Right Drug, Right Dose, Right Time study; SSRI, serotonin reuptake inhibitor; SVN, Slovenia; TCA, tricyclic antidepressant; TPMT, thiopurine S-methyltransferase; UK, United Kingdom; U-PGx, Ubiquitous Pharmacogenomics Consortium; USA, United States of America.

### 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.<sup>58</sup> The ultimate objective is to migrate all CPIC drug-gene 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 pretest 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.<sup>29</sup> 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 4 genes and 12 drugs have migrated to the EHR.<sup>59</sup>

### Pharmacogenomics Research Network Translational Pharmacogenetics Program

In 2011, the PGRN established the Translational Pharmacogenetics Program to assess implementation within six diverse healthcare 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.<sup>52</sup>

### Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment Project

As part of the eMERGE-PGx project, Vanderbilt University has initiated the Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment (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 focused on *CYP2C19* genotyping for patients receiving antiplatelet therapy after having undergone cardiovascular stent insertion. The enrollment 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.<sup>21</sup> As of November 2013, 10,000 patients had been genotyped and several other drug-gene pairs have been implemented.<sup>60</sup>

### Right drug, right dose, right time

As part of the eMERGE-PGx project, the Mayo Clinic has initiated the Right Drug, Right Dose, Right Time (RIGHT) project. The aim of 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, four drug-gene pairs were approved for implementation, and several others were under development for integration within the CDSS.<sup>20</sup> Initially, patients were eligible for enrollment if they had a high risk of initiating statin therapy within 3 years, as this subset of patients would likely benefit from a PGx-driven intervention. These participants were identified through a multivariable prediction model.<sup>61</sup> 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 that require multidisciplinary and multi-institutional efforts to make PGx-guided drug and dose selection routine care.<sup>62</sup>

### 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 a novel genomic prescribing system to deliver a patient-specific interpretation of complex genomic data for a particular drug distilled into a short summary.<sup>63</sup> 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 adverse drug reactions (ADRs) or nonresponse. Future aims include an examination of the impact of providing PGx results on prescribing decisions and patient outcomes.<sup>64</sup> 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 genomic prescribing system.<sup>65</sup>

### CURRENT PHARMACOGENOMICS 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 pediatrics<sup>59,67</sup> and polypharmacy,<sup>68,69</sup> in which 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 drug-gene 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**.<sup>21,30,47–65</sup>

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 therefore, will obtain different process metrics for implementation than early adopting institutions, in which providers may have more PGx knowledge. 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 and pharmacists in PGx, and measure process metrics for implementation.

## UBIQUITOUS PHARMACOGENOMICS CONSORTIUM

### 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 in which an EHR is unavailable, the “Safety-Code card” has been adopted.<sup>70</sup> This card is part of a mobile-based CDSS called the Medication Safety Code system that is independent of existing information technology infrastructures, and enables quick retrieval of patient-relevant PGx drug dosing guidelines (**Figure 3**). The Medication Safety Code system does not require central patient data storage. Instead, the “Safety-Code card” contains a quick response code that stores the patient’s encoded PGx results. It can be decoded and interpreted by common smartphones and other devices. After scanning the quick response 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 Medication Safety Code system is aimed to serve as an auxiliary tool to maximize the accessibility and sharing of PGx results within and

between different healthcare settings and healthcare 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. Thus, these physicians and pharmacists can 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 created by the U-PGx partner bio.logis Genetic Information Management.<sup>71</sup> The Genetic Information Management Suite Diagnostic Report Module holds the CE mark 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 as well as the Federal Institute for Drugs and Medical Devices. In addition, the Diagnostic Report Module has been certified as an “internet medicine quality product” by the Federal Association for Internet Medicine.

**The Dutch Pharmacogenomics Working Group guidelines.** In 2005, the Royal Dutch Pharmacists Association established the DPWG with the objective to develop pharmacogenetic-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 pairs 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<sup>31,32</sup> 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 polymerase chain reaction-based genotyping. It comprises 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 prespecified criteria. The criteria for variant selection are listed in **Supplementary Table S1** online. The selection yielded 50 variants in 13 pharmacogenes. Variants included in the panel and their associated phenotypes are listed in **Supplementary Table S2** online.



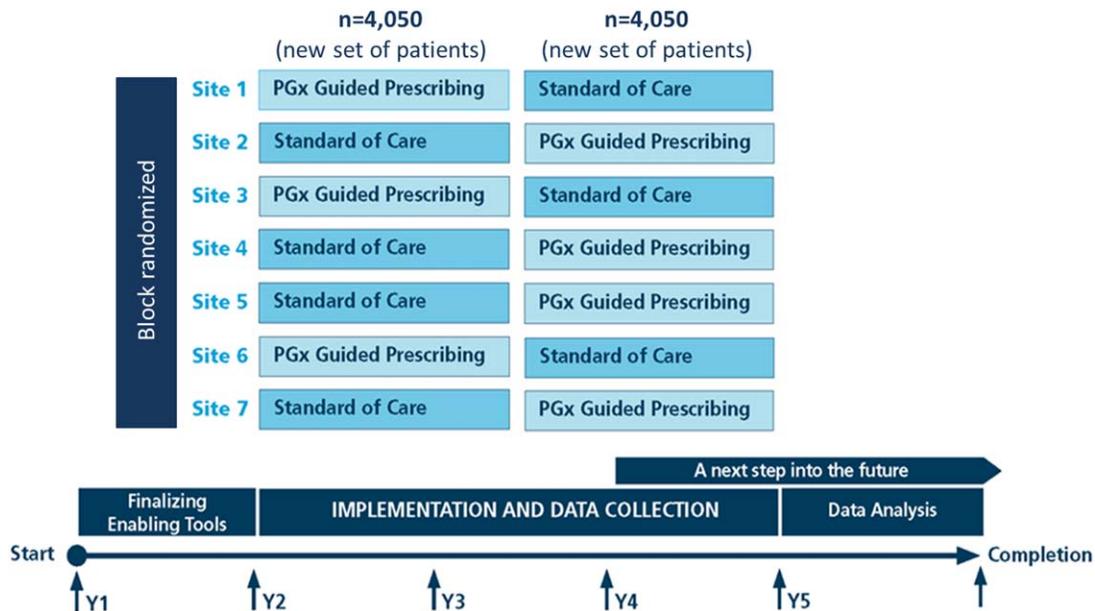
**Figure 3** The front (top) and back (bottom) of the “Safety-Code card.” This is a plastic card, akin to a credit card, carrying an individual’s pharmacogenomic information and a quick response (QR) code, which is connected to the individual’s personalized dosing recommendations, as per the Dutch Pharmacogenomics Working Group. TPMT, thiopurine S-methyltransferase; U-PGx, Ubiquitous Pharmacogenomics (U-PGx) Consortium.

**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, regulations 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 that may hinder the implementation of PGx testing in routine care.

**The PREPARE study**

**Overall study design.** PREPARE is an international prospective, multicenter, open, block-randomized study. **Figure 4** illustrates the PREPARE study design. The PREPARE study (Clinicaltrials.gov Number – registration pending) will investigate the impact of pre-emptive genotyping of a panel of clinically relevant PGx-markers on patient outcomes. It is unique in its multicenter, multi-gene, multidrug, multi-ethnic, and multihealthcare system approach. It is hypothesized that implementing PGx-guided drug and dose selection will decrease clinically relevant ADRs by 30%



**Figure 4** Timeline of the PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study: in the first year all tools enabling pre-emptive pharmacogenomics (PGx) testing (information technology, genotyping technology, education, translation, and sharing of guidelines) will be prepared and finalized. In years 2–4, 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. A total of 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 through next-generation sequencing and systems pharmacology approaches.

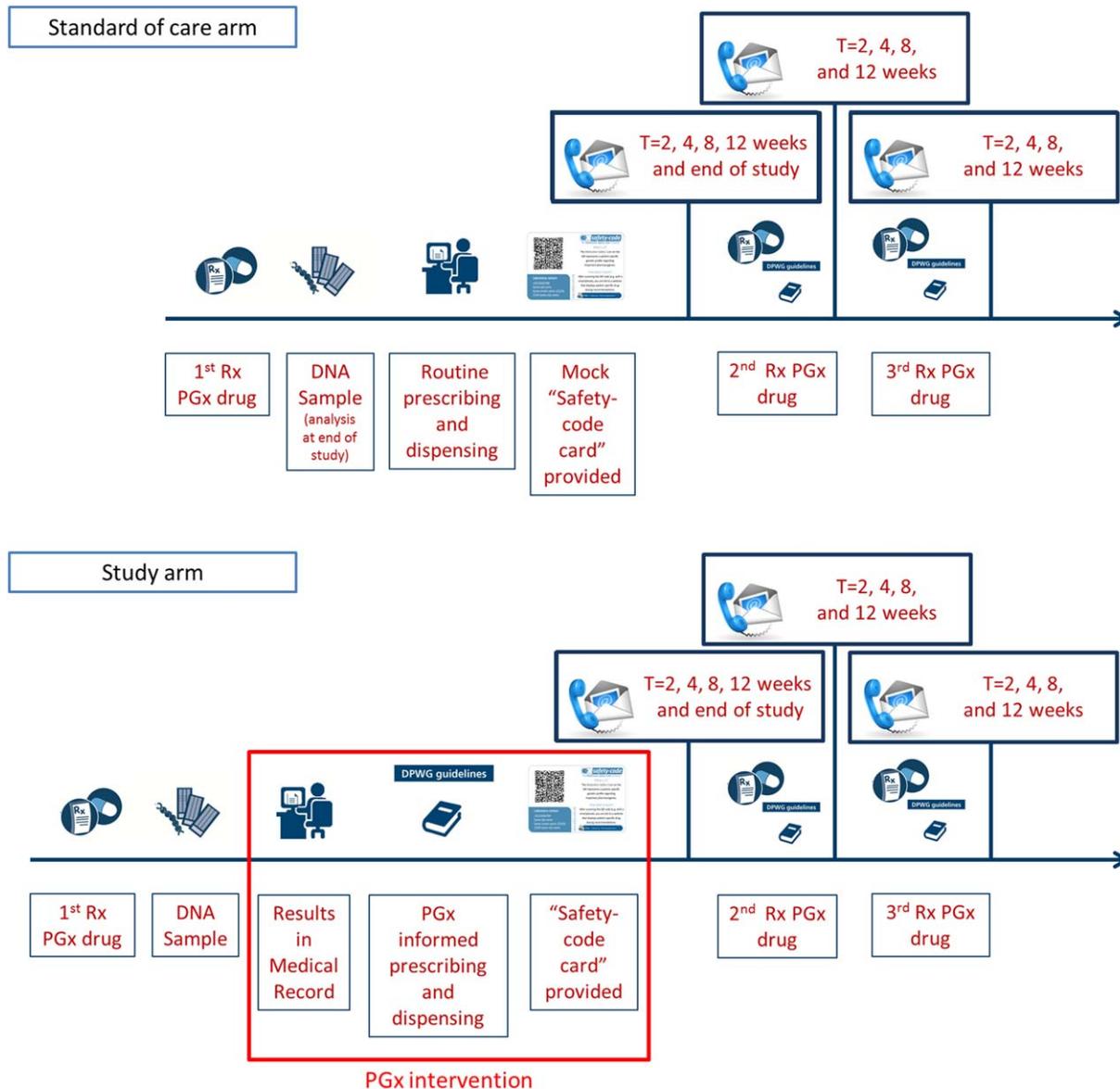
(from 4–2.8%). Pre-emptive PGx testing will be implemented in clinical sites across seven European countries (United Kingdom, The Netherlands, Austria, Greece, Slovenia, Italy, and Spain). The PREPARE protocol has been submitted for ethical approval, locally, in all seven countries. The study will be 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**.

**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 **Supplementary Table S3** online. The 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, among aberrant genotypes (in which ultra-rapid metabolizers are recommended a higher dose to ensure sufficient blood levels for an efficacious pharmacotherapy). Estrogen-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-up (see below “subsequent drugs”).

**The pharmacogenomics 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 3 working days.



**Figure 5** Study logistics in the PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (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 pharmacogenomics (PGx) results of patients in the intervention arm only will be used to guide drug and dose selection as per the Dutch Pharmacogenomics Working Group (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 Ubiquitous Pharmacogenomics Consortium 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 3 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 2 weeks and 8 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, comedication, and attitudes toward 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 estrogen-containing drugs) of interest during follow-up in addition to the index drug. This will trigger an identical 3-month follow-up.

**Follow-up**

Follow-up by the research team will assess incident adverse drug events, (index) drug modifications, drug adherence, quality of life, costs, comedication, and attitudes toward PGx. Assessment of ADRs will be performed by the research team and will involve

causality, severity, and genotype correlation assessments. Incident ADRs collected by the research team will contribute to the primary composite endpoint (see "primary composite endpoint"). The research team will contact patients at 4 weeks, 12 weeks, and at the end of the study arm by telephone (outpatients) or in

**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)	Clinically relevant genetic interaction	Actionable phenotypes/genotypes
Antiarrhythmic	Flecainide	<i>CYP2D6</i>	PM, IM, UM
	Propafenon	<i>CYP2D6</i>	PM, IM, UM
Analgesic	Codeine	<i>CYP2D6</i>	PM, IM, UM
	Oxycodone	<i>CYP2D6</i>	PM, IM, UM
	Tramadol	<i>CYP2D6</i>	PM, IM, UM
Anticancer	Capecitabine	<i>DPD</i>	Gene activity score 0, 0.5, 1.0, 1.5
	Fluorouracil	<i>DPD</i>	Gene activity score 0, 0.5, 1.0, 1.5
	Irinotecan	<i>UGT1A1</i>	PM, *28/*28
	Tamoxifen	<i>CYP2D6</i>	PM, IM
	Tegafur	<i>DPD</i>	Gene activity score 0, 0.5, 1.0, 1.5
Anticoagulation	Acenocoumarol	<i>VKORC1</i>	<i>VKORC1</i> TT
	Clopidogrel	<i>CYP2C19</i>	PM, IM
	Phenprocoumon	<i>VKORC1</i>	<i>VKORC1</i> TT
	Warfarin	<i>CYP2C9</i> <i>VKORC1</i>	*1/*3, *2/*2, *2/*3, *3/*3, IM, PM, TT
Antidepressant	Citalopram	<i>CYP2C19</i>	PM, IM
	Escitalopram	<i>CYP2C19</i>	PM, IM
	Paroxetine	<i>CYP2D6</i>	UM
	Sertraline	<i>CYP2C19</i>	PM, IM
	Venlafaxine	<i>CYP2D6</i>	PM, IM, UM
Antidepressant (TCA)	Amitriptyline	<i>CYP2D6</i>	PM, IM, UM
	Clomipramine	<i>CYP2D6</i>	PM, IM, UM
	Doxepin	<i>CYP2D6</i>	PM, IM, UM
	Imipramine	<i>CYP2D6</i> <i>CYP2C19</i>	PM, IM, UM PM
	Nortriptyline	<i>CYP2D6</i>	PM, IM, UM
Antiepileptic	Carbamazepine	<i>HLA B*5701</i>	–
	Phenytoin	<i>CYP2C9</i>	IM, PM, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3
Antihypertensive	Metoprolol	<i>CYP2D6</i>	PM, IM, UM
Anti-infective	Efavirenz	<i>CYP2B6</i>	PM, IM
	Flucloxacillin	<i>HLA B*5701</i>	–
	Voriconazole	<i>CYP2C19</i>	PM, IM
Antipsychotic	Aripiprazole	<i>CYP2D6</i>	PM
	Clozapine	<i>CYP1A2</i>	*1C heterozygote, *1C/*1C
	Haloperidol	<i>CYP2D6</i>	PM, UM
	Pimozide	<i>CYP2D6</i>	PM, IM
	Zuclopenthixol	<i>CYP2D6</i>	PM, IM, UM
Cholesterol-lowering	Atorvastatin	<i>SLC01B1</i>	521TC, 521CC
	Simvastatin	<i>SLC01B1</i>	521TC, 521CC

Table 2 Continued on next page

Table 2 Continued

Drug class	Drug (n = 43)	Clinically relevant genetic interaction	Actionable phenotypes/genotypes
Immunosuppressive	Azathioprine	TPMT	PM, IM
	Mercaptopurine	TPMT	PM, IM
	Tacrolimus	CYP3A5	Homozygote or heterozygote expressers
	Thioguanine	TPMT	PM, IM
Other	Atomoxetine	CYP2D6	PM, UM
	Estrogen containing drugs <sup>a</sup>	FVL	Homozygote expresser, Heterozygote expresser

CYP, cytochrome P450; DPD, dihydropyrimidinedehydrogenase; FVL, factor five Leiden HLA, human leucocyte antigen; SLCO, solute carrier organic anion transporter; TPMT, thiopurine S-methyltransferase; UGT, UDP-glucuronosyltransferase; VKORC, vitamin K oxide reductase complex.

<sup>a</sup>Only included for follow-up as a subsequent prescription, not for a drug of inclusion.

person (inpatients). 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.<sup>72</sup> This aspect of the study is important as patient-reported adverse events may differ from those collected by the research team.<sup>73</sup> 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.<sup>74</sup>

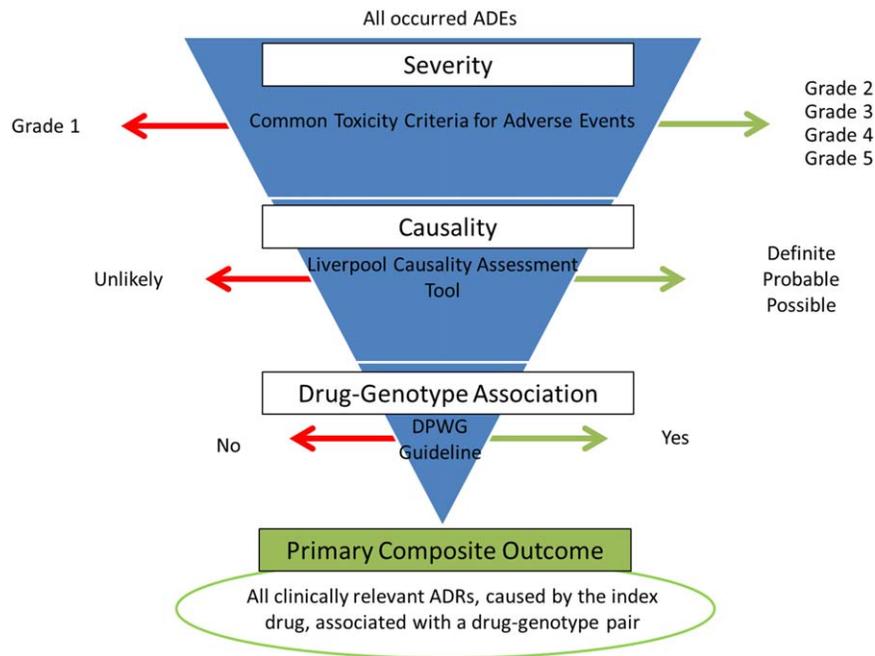
**Subsequent prescriptions of drugs of interest.** Patients are requested to notify the research team every time they receive a prescription for one of the 43 drugs of interest (as listed in Table 2) during follow-up. These drugs are referred to as “subsequent drugs.” This will trigger an identical 3-month follow-up as for the index drug (as illustrated in Figure 5). Patients are requested to provide their (mock) “Safety-Code card” to physicians who 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, in which a 3 workday lag-time is unavoidable. There is recognition for the fact that the research team is fully reliant on patient-reported subsequent prescriptions, in order to trigger follow-up for this subsequent prescription. This could introduce selection bias. Therefore, incident ADRs 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 and are classified according to causality, severity, and drug-genotype association. Causality will be classified using the Liverpool Causality Assessment Tool.<sup>75</sup> Severity will be classified using the National Cancer Institute Common Toxicity Criteria for Adverse Events scale. The

drug-genotype association will be assessed using the DPWG guidelines.<sup>31,32</sup> 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 that contribute to the primary endpoint, contribute equally, regardless of their severity.

**Primary analysis.** A gatekeeping analysis will be performed for the primary analysis only among 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. First, the frequency of drug discontinuation because of lack of efficacy will be compared in the standard of care arm to the intervention arm. Second, routine index drug levels of patients who received a dose alteration because 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, therefore, that efficacy must be similar. Data on costs associated with ADRs will be collected to perform a country-specific cost-effectiveness analysis. 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



**Figure 6** The primary endpoint is the frequency of clinically relevant adverse drug reactions within 3 months of initiating the index drug. All incident adverse drug events (ADEs) will be assessed regarding causality (using the Liverpool Causality Assessment Tool), severity (using the National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] scale), and association to genotype (using the Dutch Pharmacogenomics Working Group [DPWG] guidelines). Only ADEs defined as definitely, probably, or possibly adverse drug reactions (ADRs), according to the Liverpool causality assessment tool, classified as severe (defined as NCI-CTCAE grades 2, 3, 4, or 5), and associated with a drug-genotype pair contribute to the primary endpoint.

DPWG guideline adherence by both the healthcare professionals who recruit to the PREPARE study and the healthcare 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 healthcare professionals after they have received their patient's PGx results to ask whether they complied with the DPWG recommendation. When healthcare professionals do not comply with the recommendation, they are asked to report reasons for not doing so. Patient knowledge of and attitudes toward PGx will also be 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<sup>76-79</sup> 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 substudy; and (2) through a systems pharmacology approach, nongenetic determinants of drug response (such as gender, age, and drug-drug interaction) will be integrated

to create novel, powerful, and practice-oriented models of personalized medicine in pharmacokinetic substudies. Inclusion and exclusion criteria for the substudies are listed in **Supplementary Table S4** online.

**Extreme phenotype substudy.** Patients included in the PREPARE study who: (1) experience a serious ADR, which is not expected on the basis of the pre-emptive PGx testing results in the PGx intervention arm; (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. These 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., high performance liquid chromatography, liquid chromatography tandem

mass spectrometry) to perform additional phenotype (plasma level)-genotype correlation analysis.

**Pharmacokinetic substudy.** 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 **Supplementary Table S5** online) to quantify levels of the parent drug and respective metabolites. Through a systems pharmacology approach, nongenetic determinants of drug response (such as gender, age, disease-related factors, and 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 utilized. 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 preemptive PGx testing involving a panel of pharmacogenes into routine care to guide drug and dose selection for 43 drugs, through a multicenter, 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 modeling, 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. Because actionable PGx variants are ubiquitous and the results of PGx testing are life-long, we foresee a future in which 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.

Additional Supporting Information may be found in the online version of this article.

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## CONFLICT OF INTEREST

G.P.P. is Full Member and National Representative of the Committee for Human Medicinal Products (CHMP)-Pharmacogenomics Working Party of the European Medicines Agency (London, UK). M.S. and E.S. are contributors to a patent application related to a diagnostic test for detection of TPMT deficiency.

## AUTHOR CONTRIBUTIONS

C.H.v.d.W., A.C.-T., E.C., K.-C.C., C.L.D.-F., V.H.D., V.D., S.J., M.O.K., M.K., C.M., G.P.P., M.P., M.S., E.S., M.S., D.S., J.S., R.M.T., M.H.v.R., S.J.S., and H.-J.G. wrote the manuscript and designed the research. M.I.-S. and G.S.-P. reviewed the manuscript and designed the research

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