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

fVl	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; DPD: 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)