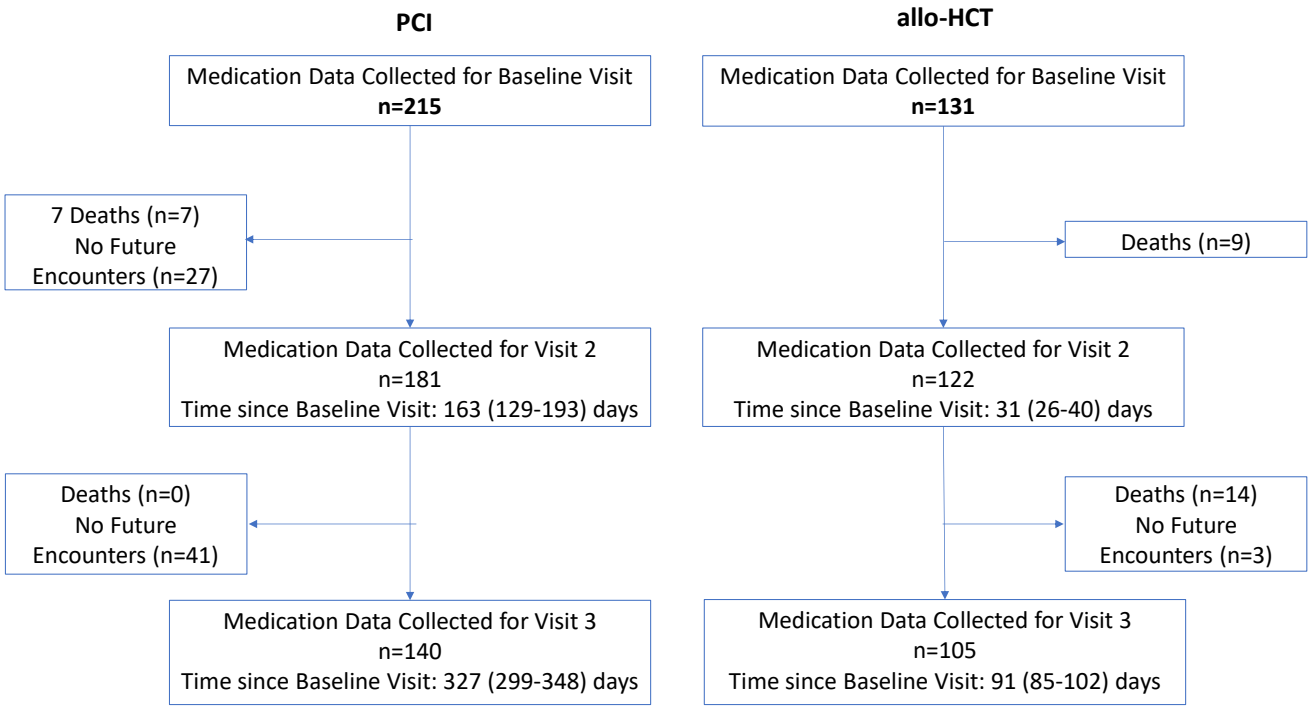
ONLINE SUPPLEMENTAL MATERIAL

Pharmacogenomic Prescribing Opportunities in Percutaneous Coronary Intervention and Bone Marrow Transplant Patients

Supplementary Figure 1.



Supplementary Figure 1. Flow diagram summarizing the number of patients with medication data available at each encounter across the two study populations. Medication data was collected from three distinct encounters in each population (baseline and two follow-up visits) based on the clinical opportunities for medication prescribing optimization. For the PCI population, the baseline encounter was defined as the index PCI hospitalization discharge summary. Visits 2 and 3 were a follow up cardiologist or primary care provider encounter within a year of the PCI procedure. For the allo-HCT population, the baseline encounter was defined as the pre-transplant visit with the clinical pharmacist. Visit 2 was the discharge summary from the allo-HCT hospitalization, and Visit 3 was a standardized follow-up outpatient clinical visit with the allo-HCT medical team conducted approximately 50 days after discharge from the allo-HCT procedure. The number of patients with medication data at each visit, the number of patients lost during follow-up, and the median (interquartile range) days between the baseline encounter and each follow-up visit are presented for the PCI and allo-HCT populations.

Supplemental Table 1. List of 65 medications collected in the PCI and allo-HCT populations with corresponding CPIC level of evidence and FDA evidence classification (sorted alphabetically).

Drug	Medication Class	Gene(s)	CPIC Level of Evidence Classification^	FDA Evidence Classification
Abacavir	Reverse transcriptase inhibitor	*HLA-B*	A	Data support therapeutic management recommendations
Allopurinol	Xanthine oxidase inhibitor	*HLA-B*	A	Potential impact on safety or response
Amitriptyline	Tricyclic Antidepressant	*CYP2C19* *CYP2D6*	A	*CYP2D6*: potential impact on pharmacokinetic properties only
Aripiprazole	Second Generation Antipsychotic	*CYP2D6*	B	Data support therapeutic management recommendations
Atazanavir	Protease Inhibitor	*UGT1A1*	A	*No recommendation provided*
Atomoxetine	Norepinephrine reuptake inhibitor	*CYP2D6*	A	Data support therapeutic management recommendations
Azathioprine	Immunosuppressant	*NUDT15* *TPMT*	A	Data support therapeutic management recommendations
Belinostat	Antineoplastic agent	*UGT1A1*	B	Data support therapeutic management recommendations
Brivaracetam	Anticonvulsant Agent	*CYP2C19*	B	Data support therapeutic management recommendations
Capecitabine	Antineoplastic agent	*DPYD*	A	Data support therapeutic management recommendations
Carbamazepine	Anticonvulsant Agent	*HLA-A* *HLA-B*	A	*HLA-B*: data support therapeutic management recommendations *HLA-A*: potential impact on safety or response
Celecoxib*	Non-Opioid Analgesic	*CYP2C9*	A	Data support therapeutic management recommendations
Chlorpropamide	Sulfonylurea	*G6PD*	B	*No recommendation provided*
Citalopram*	Selective Serotonin Reuptake Inhibitor	*CYP2C19*	A	Data support therapeutic management recommendations
Clomipramine	Tricyclic Antidepressant	*CYP2C19* *CYP2D6*	B	*CYP2D6*: potential impact on pharmacokinetic properties only.
Clopidogrel*	P2Y12 Inhibitor	*CYP2C19*	A	Data support therapeutic management recommendations
Codeine*	Opioid Analgesic	*CYP2D6*	A	Data support therapeutic management recommendations, Potential impact on safety or response
Desipramine	Tricyclic Antidepressant	*CYP2D6*	B	Potential impact on pharmacokinetic properties only
Dexlansoprazole*	Proton Pump Inhibitor	*CYP2C19*	B	Potential impact on pharmacokinetic properties only
Doxepin	Serotonin and Norepinephrine Reuptake Inhibitor	*CYP2C19* *CYP2D6*	B	Potential impact on pharmacokinetic properties only

Efavirenz	Reverse transcriptase inhibitor	*CYP2B6*	A	Potential impact on safety or response
Escitalopram*	Selective Serotonin Reuptake Inhibitor	*CYP2C19*	A	Potential impact on pharmacokinetic properties only
Fluorouracil	Antineoplastic agent	*DPYD*	A	Data support therapeutic management recommendations
Flurbiprofen	NSAID	*CYP2C9*	A	Data support therapeutic management recommendations
Fluvoxamine	Selective Serotonin Reuptake Inhibitor	*CYP2D6*	B	Potential impact on pharmacokinetic properties only
Glibenclamide	Sulfonylurea	*G6PD*	B	*No recommendation provided*
Glimepiride*	Sulfonylurea	*G6PD*	B	*No recommendation provided*
Glipizide*	Sulfonylurea	*G6PD*	B	*No recommendation provided*
Hydrocodone*	Opioid Analgesic	*CYP2D6*	B	*No recommendation provided*
Ibuprofen	NSAID	*CYP2C9*	A	*No recommendation provided*
Imipramine	Tricyclic Antidepressant	*CYP2C19* *CYP2D6*	B	*CYP2D6*: potential impact on pharmacokinetic properties only
Irinotecan	Antineoplastic agent	*UGT1A1*	A	Data support therapeutic management recommendations
Ivacaftor	Cystic Fibrosis	*CFTR*	A	*No recommendation provided*
Lansoprazole*	Proton Pump Inhibitor	*CYP2C19*	A	*No recommendation provided*
Meloxicam	NSAID	*CYP2C9*	A	*No recommendation provided*
Mercaptopurine	Antineoplastic agent	*NUDT15* *TPMT*	A	Data support therapeutic management recommendations
Methadone	Opioid Analgesic	*CYP2B6*	B	*No recommendation provided*
Nortriptyline	Tricyclic Antidepressant	*CYP2D6*	A	Potential impact on pharmacokinetic properties only
Omeprazole*	Proton Pump Inhibitor	*CYP2C19*	A	Potential impact on pharmacokinetic properties only
Ondansetron*	Antiemetic	*CYP2D6*	A	*No recommendation provided*
Oxcarbazepine	Anticonvulsant Agent	*HLA-B*	A	Potential impact on safety or response
Pantoprazole*	Proton Pump Inhibitor	*CYP2C19*	A	Data support therapeutic management recommendations
Paroxetine	Selective Serotonin Reuptake Inhibitor	*CYP2D6*	A	Potential impact on pharmacokinetic properties only
Peginterferon alfa-2a	Interferon	*IFNL3* *IFNL4*	A	*No recommendation provided*
Peginterferon alfa-2b	Interferon	*IFNL3* *IFNL4*	A	*No recommendation provided*
Pegloticase	Urate Oxidase Enzyme	*G6PD*	B	*No recommendation provided*
Phenytoin	Anticonvulsant Agent	*CYP2C9* *HLA-B*	A, A	*No recommendation provided*
Pimozide	First Generation Antipsychotic	*CYP2D6*	A/B	Data support therapeutic management recommendations
Piroxicam	NSAID	*CYP2C9*	A	Data support therapeutic management recommendations

Probenecid	Uricosuric Agent	*G6PD*	B	*No recommendation provided*
Quinine	Antimalarial Agent	*G6PD*	B	*No recommendation provided*
Rasburicase	Urate Oxidase Enzyme	*G6PD*	A	*No recommendation provided*
Risperidone	Second Generation Antipsychotic	*CYP2D6*	B	Potential impact on pharmacokinetic properties only
Sertraline*	Selective Serotonin Reuptake Inhibitor	*CYP2C19*	B	*No recommendation provided*
Simvastatin*	HMG-CoA Reductase Inhibitor	*SLCO1B1*	A	Potential impact on safety or response
Tacrolimus*	Immuno-suppressant	*CYP3A5*	A	Data support therapeutic management recommendations
Tamoxifen	Antineoplastic agent	*CYP2D6*	A	Potential impact on pharmacokinetic properties only
Thioguanine	Antineoplastic agent	*NUDT15 TPMT*	A	Data support therapeutic management recommendations
Tramadol*	Opioid Analgesic	*CYP2D6*	A	Data support therapeutic management recommendations
Trimipramine	Tricyclic Antidepressant	*CYP2C19 CYP2D6*	B	*CYP2D6*: Potential impact on pharmacokinetic properties only
Tropisetron	Antiemetic	*CYP2D6*	A	*No recommendation provided*
Venlafaxine*	Serotonin and Norepinephrine Reuptake Inhibitor	*CYP2D6*	A/B	Data support therapeutic management recommendations
Voriconazole*	Antifungal	*CYP2C19*	A	Potential impact on pharmacokinetic properties only
Vortioxetine	Selective Serotonin Reuptake Inhibitor	*CYP2D6*	A/B	Data support therapeutic management recommendations
Warfarin*	Anticoagulant	*CYP2C9 CYP4F2 VKORC1*	A	*CYP2C9, 4F2, VKORC1*: data support therapeutic management recommendations

* Medication used 1.5% in at least one of the populations and included in simulation analysis

^ Level A drugs have a large amount of evidence in favor of changing prescribing. Level A/B drugs have undergone a preliminary review which indicated the definitive CPIC level will be either A or B, but a full evidence review is needed before final designation is made. Level B drugs have evidence supporting use of genetic information to change prescribing as the alternative therapies or dosing are likely to be as effective and safe as non-genetically based dosing.

The following 50 medications with CPIC Level A, A/B, or B evidence were excluded from data collection (as summarized in Figure 1): Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine, amikacin, gentamicin, kanamycin, streptomycin, tobramycin, ciprofloxacin, chloramphenicol, dapsone, dimercaprol, mafenide, mesalamine, methylene blue, moxifloxacin, nalidixic acid, nitrofurantoin, norfloxacin, phenazopyridine, primaquine, sodium nitrite, sulfacetamide, sulfadiazine, sulfamethoxazole/ trimethoprim, sulfasalazine, sulfisoxazole, tafenoquine, fosphenytoin, divalproex sodium, valproic acid, mycophenolic acid, carglumic acid, velaglucerase alfa, eliglustat, siponimod, acenocoumarol, phenprocoumon, tetrabenazine, oliceridine, pitolisant, tenoxicam, lornoxicam, hydralazine, rosuvastatin, aspirin

Supplementary Table 2. Summary of *CYP2C19* Simulation Analysis

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
P2Y12i	Clopidogrel	A	N/A	N/A	0	0	Intermediate Metabolizers	27.70%	24.90%	N/A	0	PMID: 23698643	Use alternative agent	Moderate
							Poor Metabolizers	3.39%	2.20%	N/A	0			
PPI	Dexlansoprazole	B	15	72	18	80	Ultrarapid Metabolizers	4.29%	4.68%	4	5	PMID: 32770672	Increase dose by 100%	Omeprazole, Lansoprazole, Pantoprazole: Optional Dexlansoprazole: Optional
	Lansoprazole Omeprazole Pantoprazole	A					Intermediate Metabolizers	27.70%	24.90%	22	25		Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional
							Poor Metabolizers	3.39%	2.20%	2	2			Omeprazole, Lansoprazole, Pantoprazole: Moderate Dexlansoprazole: Optional
SSRI	Citalopram Escitalopram	A	8	24	2	16	Ultrarapid/Rapid Metabolizers	26.99%	31.68%	10	6	PMD: 25974703	Use a drug not metabolized by CYP219	Citalopram, Escitalopram: Moderate Sertraline: Optional
	Sertraline	B					Poor Metabolizers	3.39%	2.20%	1	0		Reduce dose by 50%	Citalopram, Escitalopram: Moderate Sertraline: Optional
Antifungal	Voriconazole	A	0	0	8	18	Ultrarapid Metabolizers	4.29%	4.68%	0	1	PMID: 27981572	Use alternative agent	Moderate
							Rapid Metabolizers	22.70%	27.00%	0	7			
							Poor Metabolizers	3.39%	2.20%	0	1			
CYP2C19 Phenotype Frequency Source: PMID: 32770672 (PPI CPIC Guideline)										39	47	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										18.1	35.9	Total Number of Interventions/100 patients		

Supplementary Table 3. Summary of *CYP2D6* Simulation Analysis

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
5-HT3RA	Ondansetron	A	1	14	9	73	Ultrarapid Metabolizers	4.67%	3.13%	0	3	PMID: 28002639	Use alternative agent not metabolized by CYP2D6	Moderate
Opioid	Hydrocodone	B	4	12	1	2	Intermediate Metabolizers	36.20%	38.95%	6	1	PMID: 33387367	Consider non-codeine or non-tramadol opioid	Optional
							Poor Metabolizers	2.33%	6.47%	1	0		Consider non-codeine or non-tramadol opioid	Optional
Opioid	Codeine Tramadol	A	1	20	1	19	Ultrarapid Metabolizers	4.67%	3.13%	1	1		Avoid Use	Strong
							Poor Metabolizers	2.33%	6.47%	1	1		Avoid Use	Strong
SSRI	Paroxetine	A	0	3	0	2	Ultrarapid Metabolizers	4.67%	3.13%	0	0	PMID: 25974703	Select alternative drug not predominantly metabolized by CYP2D6	Strong
							Poor Metabolizers	2.33%	6.47%	0	0		Select alternative drug not predominantly metabolized by CYP2D7	Optional
SNRI	Venlafaxine	A/B	0	6	0	1	Ultrarapid Metabolizers	4.67%	3.13%	0	0	N/A	DPWG: increase dose by 150%	N/A
							Intermediate/Poor Metabolizers	38.53%	45.42%	3	0		DPWG: Use alternative agent or monitor metabolite levels	N/A
CYP2D6 Phenotype Frequency Source: PMID: 33387367 (Opioid CPIC Guideline)										12	6	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										5.6	4.6	Total Number of Interventions/100 patients		

Supplementary Table 4. Summary of Simulation Analysis for additional genes

VKORC1/CYP2C9

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
Anticoagulant	Warfarin	A	1	6	0	2	Highly Sensitive Responders	0.7%	2.9%	0	0	PMID: 28198005	Lower dose requirement	Strong
							Sensitive Responders	8.9%	35.4%	2	1		Lower dose requirement	Strong
Warfarin Phenotype Frequency source - PMID: 28198005 (Wafarin CPIC guideline) and 25769357 (ENGAGE-TIMI 56 genetic substudy)										2	1	Total Number of Interventions		
^ Based on the *VKORC1* and *CYP2C9* minor allele frequencies, we assumed the warfarin sensitivity phenoytpes in African-Americans were one-fourth of the frequency in Caucasians										0.9	0.8	Total Number of Interventions/100 patients		

CYP3A5

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
Immuno-suppresant	Tacrolimus	A	1	4	N/A	N/A	Extensive Metabolizer	20.5%	0.6%	1	N/A	PMID: 25801146	Increase dose 1.5-2 times recommended starting dose	Strong
							Intermediate Metabolizer	49.6%	13.7%	1	N/A		Increase dose 1.5-2 times recommended starting dose	Strong
CYP3A5 Phenotype Frequency Source: PMID: 25801146 (Tacrolimus CPIC Guideline)										2	N/A	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										0.9	N/A	Total Number of Interventions/100 patients		

G6PD

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
Sulfonylurea	Glimepride Glipizide	B	5	22	1	5	G6PD Deficient	7.5%	3.9%	1	0	N/A	FDA: Avoid use	N/A
G6PD Phenotype Frequency Source: PMID: 24787449 (Rasburicase and G6PD CPIC Guideline)										1	0	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										0.5	0	Total Number of Interventions/100 patients		

Supplementary Table 4 (con't)**.** Summary of Simulation Analysis for additional genes

SLCO1B1

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
HMG-CoA Reductase Inhibitor	Simvastatin	A	0	4	1	1	Decreased Function	3.9%	31.5%	1	0	PMID: 24918167	Prescribe a lower dose, consider routine CK surveillance	Strong
							Poor Function	0.04%	3.83%	0	0		Prescribe a lower dose, consider routine CK surveillance	Strong
SLCO1B1 Phenotype Frequency Source: PMID: 24918167 (Simvastatin CPIC Guideline)										1	0	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										0.5	0	Total Number of Interventions/100 patients		

CYP2C9

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
NSAID	Celecoxib	A	0	6	2	1	Poor Metabolizer	0.52%	2.56%	0	0	PMID: 32189324	Initiate therapy at 25-50% of lowest recommended starting dose	Moderate
	Ibuprofen													
CYP2C9 Phenotype Frequency Source: PMID: 32189324 (NSAID CPIC Guideline)										0	0	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										0	0	Total Number of Interventions/100 patients		

HLA-B

Medication Class	Medication	CPIC Level of Evidence	# of Patients Prescribed PCI		# of Patients Prescribed allo-HCT		At Risk Genotype/Phenotype Group	At Risk Phenotype Frequency (AA)	At Risk Phenotype Frequency (European)	Projected No. of PGx Interventions PCI	Projected No. of PGx Interventions allo-HCT	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation
			AA	Non-AA	AA	Non-AA								
Antigout Agent	Allopurinol	A	1	8	1	2	HLA-B*58:01 allele positive	7.60%	1.60%	0	0	PMID: 26094938	Use is contraindicated	Strong
HLA-B Phenotype Frequency Source: PMID: 26094938 (Allopurinol CPIC Guideline)										0	0	Total Number of Interventions		
*In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided										0	0	Total Number of Interventions/100 patients		