Projected Impact of Pharmacogenomic Testing on Medications Beyond Antiplatelet
Therapy in Percutaneous Coronary Intervention Patients

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Abstract

CYP2C19 genotyping is used to guide antiplatelet therapy after percutaneous coronary intervention (PCI). This study evaluated the potential impact of *CYP2C19* and multigene pharmacogenomic (PGx) testing on medications beyond antiplatelet therapy in a real-world cohort of PCI patients that underwent *CYP2C19* testing. Multiple medications with actionable PGx recommendations, notably proton pump inhibitors, antidepressants and opioids, were commonly prescribed. Approximately 50% received a CYP2C19 metabolized medication beyond clopidogrel, and 7% met criteria for a *CYP2C19* genotype-guided intervention. A simulation analysis projected that 17.5 PGx-guided medication interventions per 100 PCI patients could have been made if multigene PGx results were available. This suggests that *CYP2C19* and multigene PGx results could be used to optimize medication prescribing beyond antiplatelet therapy in PCI patients.

Introduction

Selecting treatment strategies that account for individual genetic differences offers enormous potential to improve health outcomes and lower healthcare costs. While more than 170 medications have germline genetic information in the drug label approved by the U.S. Food and Drug Administration (FDA), pharmacogenomic (PGx) testing is not routinely used to guide prescribing in clinical settings.[1,3] PGx-guided prescribing offers the potential to optimize drug selection and dosing based on patient-specific genetic factors. However, in order for a gene-drug pair to be considered clinically actionable, there must be sufficient supporting evidence, an approved genetic test, and an alternative dose or drug for individuals with the 'at risk' genotype. Moreover, a structured approach to implement PGx-guided prescribing must be in place.[3]

The Clinical Pharmacogenomics Implementation Consortium (CPIC) publishes guidelines that systematically evaluate genotype and drug phenotype association data, and translates this information into evidence-based recommendations for clinicians.[4] To date, CPIC has identified over 80 medications impacted by approximately 20 genes with Level A or B evidence, whereby a prescribing action is recommended to avoid an adverse medication outcome and alternative therapies or dosing are highly likely to be effective and safe.[3–5] While approximately 7% of FDA approved medications have actionable PGx recommendations based on CPIC Level A or B evidence, these medications have been estimated to represent 18% of the outpatient medications prescribed in the U.S.[3] Furthermore, many of the at-risk genotypes that affect these medications are common, as 99% of individuals carry at least one actionable PGx genotype.[6,7]

Currently, when PGx testing is performed, genotyping typically occurs for putatively functional single nucleotide polymorphisms in a single gene and in a reactive manner after it has been determined that the patient will be prescribed a drug with actionable PGx recommendations. Notably, implementation of *CYP2C19* genotype testing to guide the selection of antiplatelet therapy in patients with coronary artery disease (CAD) undergoing percutaneous

coronary intervention (PCI) has become increasingly common.[8,9] It is now well-established

that patients with nonfunctional *CYP2C19* variant alleles are at increased risk of adverse

cardiovascular events after stent placement when treated with clopidogrel, which remains the

most commonly used $P2Y_{12}$ inhibitor after PCI.[10–12] Consequently, use of alternative therapy

(prasugrel or ticagrelor) is recommended in *CYP2C19* nonfunctional allele carriers, which

comprise approximately 30% of the U.S. population.[13]

Preemptive PGx testing, in which a patient is simultaneously tested for multiple PGx

actionable genes in advance of medication prescribing, likely offers advantages over single-

gene testing due to decreasing genotype costs secondary to technological advancements and

the potential benefits associated with PGx-guided prescribing.[14] However, the patient

populations in which multigene preemptive PGx testing offers the greatest impact to avoid

adverse drug outcomes have not been clearly defined, evaluated and validated. Due to the

benefit of *CYP2C19* genotype-guided antiplatelet therapy, and high prevalence of polypharmacy

among CAD patients due to advanced age and common comorbidities such as hyperlipidemia,

hypertension, atrial fibrillation and depression, the cardiac catheterization laboratory offers

potential to identify a high-risk population in which institutions can implement multigene PGx

testing.[15–18]

We hypothesize that PCI patients undergoing *CYP2C19* genetic testing to guide

antiplatelet therapy selection are also prescribed multiple medications, in addition to clopidogrel,

that have actionable PGx recommendations for at-risk genotypes in *CYP2C19* and other

established pharmacogenes. However, it is not known how frequently this patient population is

prescribed medications with actionable PGx recommendations and carry an at-risk genotype

that increases risk for therapeutic failure or adverse event that could be avoided by preemptive

PGx-based prescribing. Therefore, the objective of this study was to 1) describe the frequency

of genetically actionable medication use beyond antiplatelet therapy in a real-world cohort of

PCI patients that underwent *CYP2C19* genetic testing, 2) determine the proportion of PCI

patients at risk for an adverse medication outcome based on their known CYP2C19 metabolizer phenotype, and 3) evaluate the projected impact of multigene PGx testing on medication prescribing in CAD patients undergoing PCI.

Methods

Study Design and Population

This single center, retrospective observational cohort study included 646 consecutive patients 18 years of age or older who underwent PCI with coronary artery stent placement at an academic medical center between January 1, 2015 to December 31, 2015. Patients were eligible for clinical *CYP2C19* genetic testing at the interventional cardiologist's discretion, which was clinically implemented in 2012 to guide antiplatelet therapy prescribing in high-risk patients.[9,19] Patients who died before discharge from their PCI hospitalization were excluded from this analysis. The study was approved by the Institutional Review Board. Due to the retrospective nature of the study, informed consent was not required.

Data Abstraction

Demographic, clinical, medication, and *CYP2C19* genotype data were manually abstracted from encounters in the electronic health record (EHR). Physician-documented comorbid conditions were collected from the patient past medical history. CYP2C19 metabolizer phenotypes were assigned based on CPIC guidelines: ultrarapid (UM; **17/*17*), rapid (RM; **1/*17*), normal (NM; **1/*1*), intermediate (IM; **1/*2*, **1/*3*, **2/*17*, or **3/*17*), or poor (PM; **2/*2*, **2/*3*, or **3/*3*).[20] Medication use was reported for the total study population, as well as within the stratum of the cohort that underwent *CYP2C19* genotype testing.

Because antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) is indicated in all PCI patients, and *CYP2C19* genotype is already used clinically to guide antiplatelet therapy at our institution, the frequency of medication use beyond clopidogrel

was the focus of the current analysis. Prescribed medications with CPIC Level A or B evidence used to treat chronic medical conditions were collected at discharge from the index PCI hospitalization and at up to two follow-up encounters within one year of the index PCI (Supplemental Table 1).[4,5] Outpatient cardiology and primary care provider (PCP) follow-up visits with a full medication history over one year were prioritized for data abstraction. Since PCI patients are treated by cardiologists, 6 additional medications used to treat cardiovascular diseases (CVD) with genetic information in the FDA label and CPIC Level C-D evidence (propafenone, carvedilol, metoprolol, propranolol, rosuvastatin and hydralazine) were collected.[1,5] Medications used for the treatment of rare conditions and medications not commonly used in the U.S. were excluded due to the low likelihood of use one year after PCI. Medications used transiently, such as antibiotics, antifungals and anesthesiology drugs, were also excluded because documentation of use in hospital discharge and outpatient encounters would likely underrepresent their actual use. Based on these criteria, 5 CPIC Level A drugs and 31 Level B drugs were excluded from data collection, and 74 medications in total were included in data collection (Figure 1, Supplemental Table 1).

Data Analysis

Descriptive statistics were used to assess demographics, clinical characteristics, CYP2C19 phenotype, and PGx actionable medication use in the full study population as well as the stratum that underwent *CYP2C19* genetic testing. Data are reported as counts (%), mean ± standard deviation, or median [interquartile range] unless otherwise indicated. Analyses were performed using SAS-JMP Version 14.0 (Cary, NC).

The primary endpoint was the observed number of potential PGx directed medication interventions that could have been made to optimize prescribing beyond antiplatelet therapy in the stratum of patients with *CYP2C19* genotype results available (N=380). A potential intervention was defined as medication with a clinically actionable recommendation prescribed

to an individual that carried an at-risk CYP2C19 metabolizer phenotype (e.g., UM or PM). The

total number of potential interventions, as well as the total number of unique patients with a

potential intervention, were calculated to account for the possibility of multiple actionable

CYP2C19-guided interventions within the same patient. The proportion of use by drug class and

type of adverse outcome avoided (therapeutic failure or adverse event) were also calculated.

A secondary simulation analysis was conducted to evaluate the projected impact of a

multigene PGx testing strategy on medication prescribing in the overall PCI patient population

(N=646). The simulation was designed to determine the number of PGx-guided interventions

that could have been made based on genotype results in addition to *CYP2C19*. Actionable

gene-drug pairs for which the drug was used in at least 2% of the study population were

included. This resulted in inclusion of 6 genes in addition to *CYP2C19* (*CYP2C9*, *CYP2D6*,

G6PD, *HLA-B*, *SLCO1B1* and *VKORC1*) and 19 medications in the analysis (Supplemental

Table 2). At-risk genotype or phenotype frequencies, stratified by race, were abstracted from

CPIC guideline supplements for *CYP2C19* (UM, RM or PM), *CYP2D6* (UM, IM or PM),

SLCO1B1 (intermediate or low function), *G6PD* (deficient), and *HLA-B* (*58:01 carrier).[2,13,21–

25] For *VKORC1/CYP2C9* (highly sensitive or sensitive warfarin responders), the ENGAGE AF-

TIMI 48 trial was used in addition to the warfarin CPIC guideline to estimate phenotype

prevalence.[26,27] For genes without metabolizer phenotypes, in which only allele frequencies

were available, the Hardy-Weinberg equation was used to estimate the frequencies of the

actionable at-risk genotypes. Because panel-based genotype results were not available among

the patients in this cohort, the simulation analysis projected the population genotype/phenotype

frequency estimates for each gene onto the PCI study population, and assumed a population

comprised of 80% Caucasian and 20% African-American patients. A potentially PGx actionable

intervention was defined in the same manner as the primary outcome. The projected number of

PGx-guided medication interventions that could have been made, if genotype results were

available, was calculated by multiplying the observed frequency of medication use in the overall

study population by the estimated at-risk genotype/phenotype frequency for each medication. The sum of the total number of potential PGx directed interventions in the PCI study population (N=646), and the projected number of interventions per 100 PCI patients, were calculated for each gene and overall.

Results

Study population

The mean age of the PCI population was 63±12 years, 70% were male, and 20% were African-American (Table 1). Approximately half of the patients had an acute coronary syndrome indication for their current PCI, while 53% had a previous revascularization procedure. Common comorbid conditions included hypertension (88%), obesity (46%), diabetes (40%) and psychiatric disorders (18%), while active cancer and end stage renal disease were prevalent in less than 5% of the cohort.

Frequency of PGx actionable medication use in PCI patients

Overall, clopidogrel was prescribed in 68% of the cohort, with an alternative $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) prescribed in 32% of patients. The most commonly used PGx-actionable medications in the study population beyond antiplatelet therapy were omeprazole, oxycodone, pantoprazole, tramadol, glipizide, hydrocodone, esomeprazole, warfarin, citalopram, simvastatin, ondansetron, allopurinol, sertraline, paroxetine, escitalopram, venlafaxine, amitriptyline, mirtazapine and glimepiride (Figure 2A, Supplemental Table 2). In addition, there were 18 PGx-actionable medications with observed use in less than 2% of the population that were collectively prescribed to 50 (7.7%) patients. When evaluated by therapeutic area (Figure 2B), the proportion of PGx-actionable medications prescribed were most common for gastrointestinal indications (37%, proton pump inhibitors (PPI) and ondansetron), pain (26%, opioids), and mental health disorders (19%, selective serotonin reuptake inhibitors (SSRI) and

other antidepressants). Additional disease states with PGx-actionable medication use included CVD (9.4%, warfarin and simvastatin), diabetes (7.9%, sulfonylureas), and gout (3.6%, allopurinol). Of the CVD medications with FDA labeling information and CPIC Level C-D evidence, metoprolol (59%) and carvedilol (19%) were the most commonly used, followed by rosuvastatin (7.4%), hydralazine (3.7%) and propranolol (1.2%) (Supplemental Figure 1).

Observed number of potential *CYP2C19* genotype guided medication interventions

CYP2C19 genotype was available in 380 (59%) patients following the index PCI procedure, with 92 (24%) patients having undergone genotype testing at a prior PCI procedure. Among the 288 patients genotyped at the time of the index PCI, the median [IQR] genotype turnaround time was 1 [0-2] day and results were available for 199 (69%) patients by the day after the test was ordered. Overall, the distribution of CYP2C19 phenotypes was 5% UM, 28% RM, 39% NM, 27% IM, and 2% PM (Figure 3A).

Among the 380 PCI patients with a *CYP2C19* genotype result, 194 (51%) were prescribed one or more of nine distinct PGx-actionable medications, beyond antiplatelet therapy, affected by *CYP2C19* alleles (Figure 3B). As a result of 35 (9.2%) patients taking more than one PGx actionable medication, there were 229 total instances of a *CYP2C19*-affected medication being prescribed to a patient with a genotype result available in the EHR. As summarized in Table 2, we observed 30 instances in which a CYP2C19 UM, RM or PM was prescribed CYP2C19 metabolized medication (7.9 per 100 patients). As a result of 3 patients taking more than one medication, an actionable PGx intervention based on the genotype result could have been made in 27 (7.1%) of the 380 genotyped patients (13.9% of the 194 genotyped patients taking a medication affected by *CYP2C19*). The majority of the projected interventions would have served to avoid a potential therapeutic failure (87%) in a CYP2C19 UM or RM patient, with 13% preventing a potential adverse event in a PM (Table 2).

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Projected number of potential PGx guided interventions following multigene testing

A simulation analysis estimating the potential impact of multigene testing for *CYP2C19, CYP2D6*, *G6PD*, *VKORC1/CYP2C9*, *SLCO1B1*, and *HLA-B* in the overall study population (N=646) projected that 113 total interventions (17.5 per 100 patients) beyond antiplatelet therapy could have been made based on actionable PGx results (Figure 4). A detailed summary, by gene and drug, is provided in Supplemental Tables 3-8.

Among the 396 instances of CYP2C19 metabolized medication use, we estimated 55 projected PGx interventions beyond antiplatelet therapy (8.5 per 100 patients; Supplemental Table 3). The most common projected interventions involved prevention of a potential SSRI (27 interventions) and PPI (13 interventions) therapeutic failure in UMs or RMs, and avoidance of a potential PPI adverse effect in PMs (8 interventions). The number and distribution of projected interventions in the simulation analysis was consistent with our observed data in patients with available *CYP2C19* genotype results.

Among the 314 instances of CYP2D6 metabolized medication use, we estimated 29 projected PGx interventions (4.5 per 100 patients; Supplemental Table 4). The projected interventions involved antidepressants (amitriptyline, paroxetine, venlafaxine) in CYP2D6 UMs, IMs and PMs (7 interventions), opioids (tramadol, oxycodone, hydrocodone) in CYP2D6 UMs and PMs (21 interventions), and ondansetron in CYP2D6 UMs (1 intervention). Among the 44 and 41 patients taking warfarin and simvastatin, respectively, we projected 14 potential warfarin dose optimization interventions in *VKORC1/CYP2C9* sensitive or highly sensitive responders (2.2 per 100 patients; Supplemental Table 5) and 10 potential interventions in patients with a *SLC01B1* intermediate or low function phenotype that could be prescribed a lower dose or alternative statin (1.5 per 100 patients; Supplemental Table 6). We also projected 4 potential interventions in patients with *G6PD* deficiency taking glipizide or glimepiride (0.6 per 100 patients; Supplemental Table 7), and 1 potential intervention for a patient taking allopurinol (0.2 per 100 patients; Supplemental Table 8), which is contraindicated in *HLA-B**58:01 allele

carriers.[28]

Discussion

The projected impact of *CYP2C19* and multigene PGx testing on medications beyond

clopidogrel was evaluated in a real-world cohort of patients that underwent PCI and *CYP2C19*

testing. Our results demonstrate that medications with actionable PGx recommendations across

multiple drug classes, most notably PPIs, antidepressants and opioids, are commonly

prescribed in PCI patients. Among patients with an available *CYP2C19* genotype result in the

EHR, approximately 50% were prescribed a CYP2C19 metabolized medication beyond

clopidogrel and 7% met criteria for a *CYP2C19* genotype-guided medication intervention.

Further, our simulation analysis projected that approximately 17.5 medication interventions per

100 PCI patients could have been recommended if multigene PGx test results were available.

Taken together, these results suggest that multigene PGx testing could be used to optimize

prescribing for multiple medications beyond *CYP2C19* genotype-guided antiplatelet therapy in

PCI patients, and warrants further study.

Due to the benefit of *CYP2C19* genotype-guided antiplatelet therapy after PCI, use of

CYP2C19 testing in clinical practice to optimize antiplatelet therapy after PCI has become

increasingly common.[8,11,29] Our results demonstrate that an opportunity exists to optimize

use of medications beyond clopidogrel based on the results of a *CYP2C19* genotype test that

has already been performed. Approximately 50% of PCI patients in our cohort were prescribed

a CYP2C19 metabolized PPI or antidepressant at either discharge or an outpatient encounter

within one-year, with approximately 7% of patients qualifying for an evidence-based *CYP2C19*

genotype-guided medication intervention. In patients prescribed a PPI, interventions would

include increasing the PPI dose in CYP2C19 UM patients to prevent therapeutic failure, and

selecting an alternative PPI in CYP2C19 PM patients to avoid an adverse event.[30] In patients

prescribed a SSRI, interventions would include selecting an alternative agent in CYP2C19 UM

or RM patients to avoid therapeutic failure, and either a dose reduction or alternative agent in CYP2C19 PM patients to avoid a potential adverse event.[22]

Because it has been estimated that approximately 99% of the population carries at least one at-risk PGx genotype, identifying patient populations that are commonly prescribed PGx-actionable medications is an important prerequisite for efficient implementation of multigene PGx testing.[6,7] In addition to PPIs and antidepressants, opioids for chronic pain, warfarin for thromboembolic disease, and simvastatin for hyperlipidemia also were commonly prescribed in PCI patients. Our simulation analysis projected that multigene testing in our study PCI population could have yielded 17.5 PGx-guided medication interventions per 100 patients, of which approximately half were derived from *CYP2C19*. The primary genes in addition to *CYP2C19* yielding actionable results were *CYP2D6* for antidepressants and opioids, *VKORC1*/*CYP2C9* for warfarin, and *SLCO1B1* for simvastatin. These observations are consistent with two recent analyses that demonstrated multigene testing with *CYP2C19, SLCO1B1, VKORC1* and *CYP2C9*, and multigene testing with *CYP2C19* and *CYP2D6* was more cost effective than *CYP2C19* testing alone in patients undergoing PCI.[31,32] Taken together, our results suggest the cardiac catheterization laboratory is a logical "foot in the door" setting for institutions to efficiently implement preemptive multigene PGx testing, and can be used to inform the design of prospective studies that evaluate the feasibility and impact of this precision medicine strategy in PCI patients.

Results of our study demonstrating that approximately one of every six PCI patients met qualifications for a PGx-guided medication intervention beyond antiplatelet therapy may underestimate the value of preemptive genotyping since our analysis only considered prescribing during the 12 months after PCI. The number of interventions would be expected to increase over time as patients age and are prescribed additional medications. Furthermore, additional commonly prescribed medications with CPIC level C evidence, such as beta blockers, may be reclassified as clinically actionable as evidence supporting clinical use expands.

Considering additional medications with PGx actionable recommendations by the Dutch

Pharmacogenetics Working Group (DPWG) would also likely increase the number of potential

PGx-guided interventions in PCI patients. Our results also demonstrate that most PGx-guided

interventions would serve to prevent a potential therapeutic failure. While the clinical impact of

such medication optimization interventions might not be immediate, the longer-term effects

could be significant to patients, providers and payers.

Notably, SSRIs are the first line treatment for depression and anxiety, and treatment

failures can lead to significant health consequences for patients and increased healthcare costs

that are especially problematic in the elderly.[33] Moreover, suboptimal management of

depression is associated with adverse cardiovascular outcomes.[34] Given that over a third of

the U.S. population carries either a CYP2C19 or CYP2D6 UM or RM phenotype, PGx-guided

strategies that enable more precise initial selection and dosing of antidepressants offer

enormous potential to prevent or reduce the duration and impact of uncontrolled depressive

symptoms.[22] Furthermore, *CYP2D6* genotype-guided opioid prescribing has been shown to

improve pain control, with emerging data also showing benefit in CYP2D6 IMs and PMs.[35]

While the effect of *CYP2C19* genotype on PPI pharmacokinetics has been well documented,

the clinical significance on clinical outcomes remains less clear.[36] It has been suggested that

genotype-guided PPI prescribing has clinical benefit in the treatment of gastroesophageal reflux

disease (GERD) and *H. pylori* eradication, as well as the prevention of PPI-related adverse

events such as infection and acute kidney injury.[30] Given the high prevalence of PPI use in

PCI patients receiving antiplatelet therapy, studies evaluating the clinical effectiveness of

CYP2C19 genotype-guided PPI prescribing are still needed.

As multigene PGx testing becomes increasingly common in clinical practice, a more

comprehensive assessment of multiple medications (rather than a single medication) will be

necessary to effectively use each patient's genetic test results to optimize prescribing decisions

and minimize healthcare costs. Notably, our results showed that use of non-cardiac medications

in PCI patients is common. While this represents an opportunity for medication optimization to occur across a patient's entire medication list, many PGx actionable medications are used to treat psychiatric and pain conditions that are not typically managed by a cardiologist. Clinical pharmacists, clinical decision support tools, and multi-disciplinary collaboration are instrumental to improve the adoption and appropriate use of PGx based medication optimization strategies, and facilitate transitions of care in patients with a multitude of comorbidities and medications.[37,38] Innovative precision medicine services, such as a precision medicine pharmacist in cardiology or multi-clinic settings, will become especially important as the frequency of PGx testing increases and new evidence linking genetic variation to suboptimal medication outcomes continues to emerge.

There are several limitations to this study that should be acknowledged. The simulation analysis was limited by use of projected at-risk genotype frequencies and a probability-based estimation of potential PGx interventions in the overall population, rather than patient level data based on observed genotype results and medication use. However, the simulated *CYP2C19* analysis yielded very similar results to the observed analysis in patients with an available *CYP2C19* genotype, which increases confidence in our results. Furthermore, clinical outcomes were not evaluated. The direct impact of PGx-guided prescribing on adverse medication outcomes will require prospective investigation in subsequent studies. Due to the retrospective design, the observed medication use frequency may not reflect more contemporary prescribing patterns. Although medication use was evaluated at multiple encounters over time, misclassification bias cannot be excluded. Further, medications used transiently, such as antibiotics, antifungals and anesthesiology drugs, were not included since our data abstraction strategy would likely underestimate their actual use. Notably, the antifungal voriconazole has actionable prescribing recommendations based on *CYP2C19* genotype results.[39] Thus, exclusion of these medications from our analysis likely underestimated the projected impact of PGx testing in this population. Additionally, some patients likely receive some medications for

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non-cardiac disease states at other centers that may not be documented in the EHR, further

underestimating the number of actionable PGx recommendations. Lastly, although the study

population was derived from an academic, tertiary referral center with a population that is

approximately 20% African-American and representative of surrounding areas, medication use

frequency at this single-center may not be generalizable to other PCI populations. Prospective

studies in larger and more diverse multicenter populations, and over longer time-horizons after

PCI, are warranted. In addition, future studies evaluating the projected impact of multigene PGx

testing on medication optimization beyond PCI patients, and across multiple clinical settings, are

needed.

      In summary, the current study demonstrated that medications across multiple drug

classes with actionable PGx recommendations are commonly prescribed in PCI patients

receiving antiplatelet therapy. The projected impact of PGx testing on optimal medication

prescribing beyond clopidogrel in this real-world patient population suggests that multigene PGx

testing could be beneficial among PCI patients who are already indicated for *CYP2C19*

genotyping, and the cardiac catheterization laboratory could serve as a logical setting for

institutions to efficiently implement multigene PGx testing into routine clinical practice. Future

prospective studies evaluating the feasibility and effectiveness of multigene PGx testing in PCI

patients are needed.

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Figure Legends

Figure 1. Overview of the number of PGx actionable medications included in data collection. The number of medications included in and excluded from data collection are described. The 74 medications included in data collection, and the associated gene and CPIC level of evidence, are listed in Supplemental Table 1.

Figure 2. Frequency of PGx actionable medication use beyond antiplatelet therapy in PCI patients. **(A)** Use frequency of PGx actionable medications at discharge from the index PCI hospitalization (black) or initiation at an outpatient follow-up visit up to one-year post discharge (blue) in the overall study population (N=646). Medications used in ≥2% of patients, and the associated gene, are presented. *Other medications is a composite of 18 individual medications with <2% use frequency in the study population (listed in Supplemental Table 2). **(B)** The distribution of PGx actionable medication use by medication therapeutic area: gastrointestinal (GI), pain, mental health, cardiovascular (not including antiplatelet therapy and the CPIC Level C-D drugs described in Supplemental Figure 1), diabetes, gout, and other (immunosuppressants, antiviral, cancer, cystic fibrosis, and anticonvulsants).

Figure 3. Observed frequency of CYP2C19 phenotypes and actionable medication use beyond antiplatelet therapy in genotyped PCI patients. (A) CYP2C19 phenotype distribution in 380 genotyped patients: ultrarapid (UM: n=17; 4%), rapid (RM: n=106; 28%), normal (NM: n=148; 39%), intermediate (IM: n=102; 27%); poor (PM: n=7; 2%) metabolizers. The IM [*1/*2=73 (72%), *1/*3=0 (0%), *2/*17=29 (28%), *3/*17=0 (0%)] and PM [*2/*2=7 (100%), *2/*3=0 (0%), *3/*3=0 (0%)] phenotypes included multiple genotypes. **(B)** Use frequency of PGx actionable medications affected by CYP2C19 metabolism beyond antiplatelet therapy in *CYP2C19* genotyped patients, sorted by medication class. Rabeprazole and clomipramine use

20

was 0%, and thus not included in the graph.

Figure 4. Projected number of actionable PGx interventions beyond antiplatelet therapy by gene in PCI patients. Based on a simulation analysis including the 19 most frequently prescribed medications and corresponding 7 genes with actionable PGx recommendations, the projected number of potential PGx interventions were calculated (as summarized in detail in Supplemental Tables 3-8). Data are presented, by gene, as the projected number of actionable interventions per 100 patients.

Table 1: Study population baseline characteristics

Characteristic	N (%)*
N	646
Age, years (mean ± SD)	63.3±11.9
Male	453 (70.1%)
Race/Ethnicity	
Caucasian	461 (71.4%)
African American	128 (19.8%)
Asian	3 (0.5%)
Hispanic	22 (3.4%)
Native American	19 (2.9%)
Other/unknown	13 (2.0%)
Obese (body mass index >30 kg/m^2)	300 (46.4%)
Current smoker	150 (23.2%)
Hypertension	568 (87.9%)
Diabetes	261 (40.4%)
Depression or other psychiatric disorder	117 (18.1%)
End stage renal disease	20 (3.1%)
Active cancer	31 (4.8%)
History of myocardial infarction	195 (30.2%)
History of a prior revascularization procedure	345 (53.4%)
Acute coronary syndrome indication for PCI	315 (48.8%)
CYP2C19 genotype available	380 (58.8%)
Previously determined genotype[†]	92 (14.2%)
Genotype during current admission[^]	288 (44.6%)

*Data presented as N (%) unless otherwise stated.

† Genotype test performed at a prior PCI admission.

^ Genotype test performed during the index PCI admission.

Table 2: Summary of Potential *CYP2C19* Genotype-Guided Medication Interventions

Drug Class	Medication	Medication Use No.	At Risk CYP2C19 Phenotype Group	At Risk CYP2C19 Phenotype Frequency	No. Potential Actionable PGx Interventions*	Avoided Clinical Outcome
PPI	Esomeprazole Omeprazole Lansoprazole Pantoprazole Dexlansoprazole Rabeprazole	165	UM	4.5%	7	Therapeutic failure
			PM	1.8%	3	Adverse event
SSRI	Citalopram Escitalopram Sertraline	58	UM/RM	32.4%	18	Therapeutic failure
			PM	1.8%	1	Adverse event
TCA	Amitriptyline	6	UM/RM	32.4%	1	Therapeutic failure
			PM	1.8%	0	Adverse event
	Total	**229**			**30**	

PPI, proton pump inhibitor; PM, poor metabolizer, RM, rapid metabolizer; SSRI, selective serotonin reuptake inhibitor, TCA, tricyclic antidepressant; UM, ultrarapid metabolizer

*The number of potential actionable PGx interventions count the number of observed instances where a *CYP2C19* genotyped patient (n=380) was prescribed a CPIC Level A or B evidence medication and carried an actionable CYP2C19 phenotype

Figure 1: Overview of the number of PGx actionable medications included in data collection.

110 medications
(CPIC Level A or B evidence
+ 6 CVD medications with
PGx in the FDA label)

Exclude 29 medications
(transient use)

81 medications

Exclude 7 medications
(rare diseases or not
used in the U.S.)
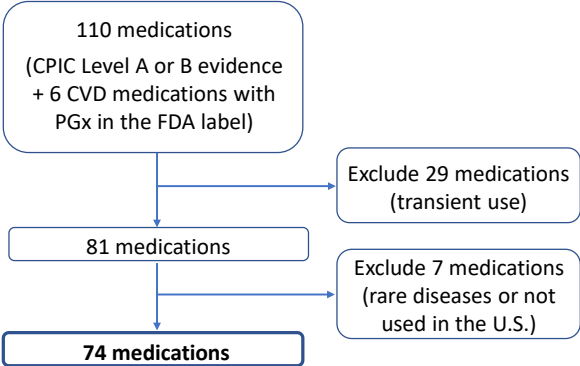
74 medications

Figure 2: Frequency of PGx actionable medication use beyond antiplatelet therapy in PCI patients.
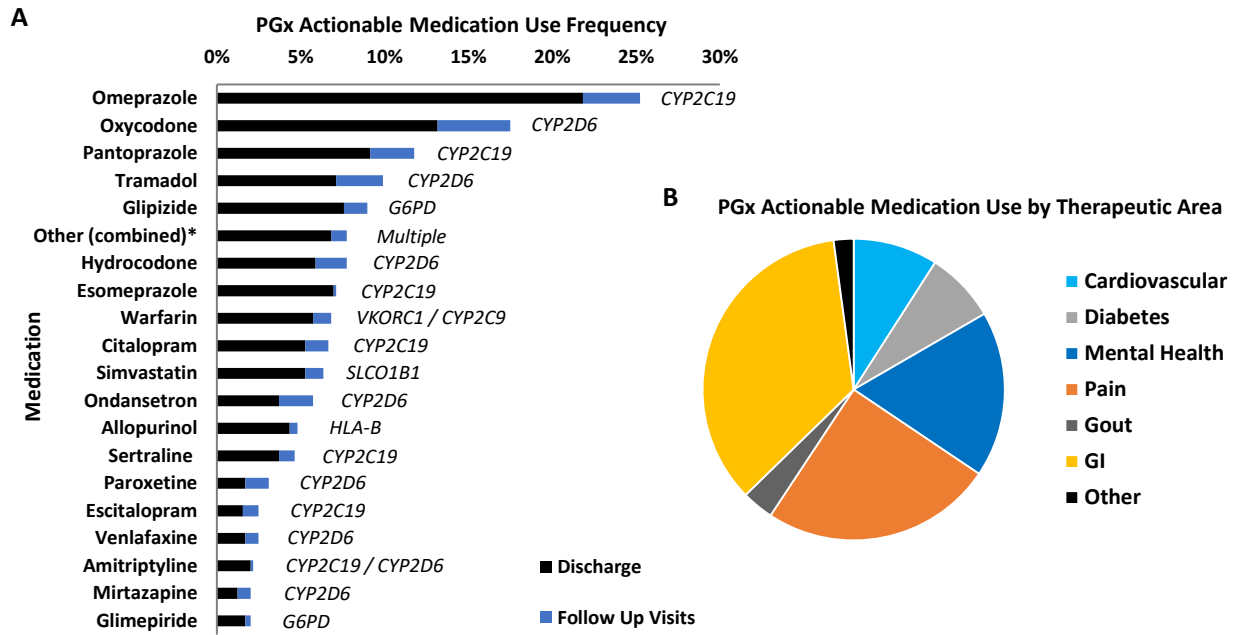
Figure 3: Observed frequency of CYP2C19 phenotypes and actionable medication use beyond antiplatelet therapy in genotyped PCI patients.
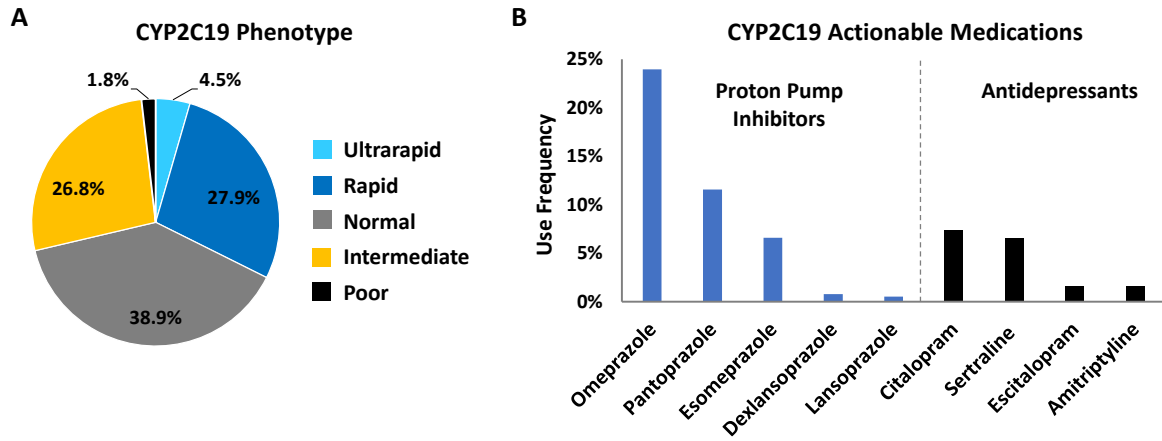
Figure 4: Projected number of actionable PGx interventions beyond antiplatelet therapy by gene in PCI patients.
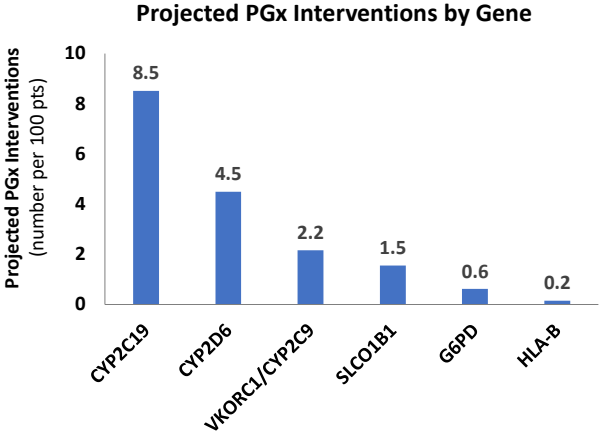
Projected PGx Interventions by Gene

Projected Impact of Pharmacogenomic Testing on Medications Beyond Antiplatelet

Therapy in Percutaneous Coronary Intervention Patients

Supplemental Figure 1.
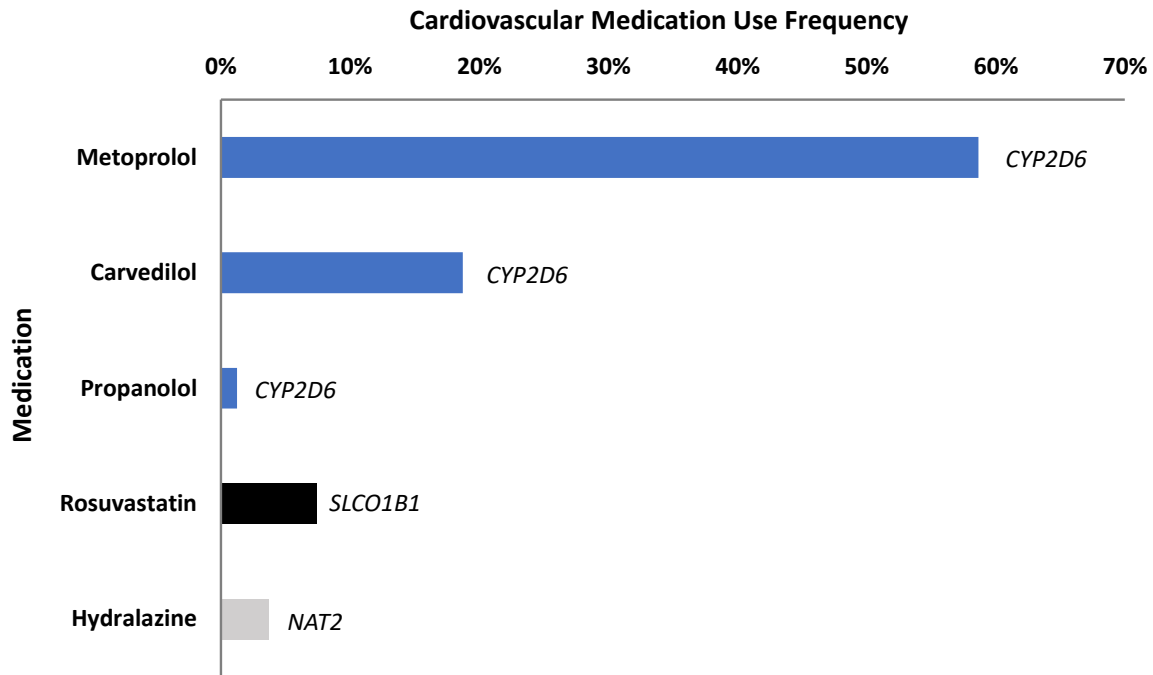
Supplemental Figure 1. Observed frequency of additional CVD medications with PGx information in the drug label. Use frequency of cardiovascular disease (CVD) medications with genetic information in the FDA label and CPIC Level C-D evidence at discharge from the index PCI hospitalization in the overall study population (N=646), sorted by medication class (beta-blockers: blue; statin: black; vasodilator: gray). Propafenone (anti-arrhythmic) use was 0%, and thus not included in the graph.

Supplemental Table 1: List of 74 medications collected in the study population (sorted by CPIC level of evidence).

Class	Gene	Medication	CPIC Level of Evidence
Anti-platelet	CYP2C19	Clopidogrel	A
Cholesterol	SLCO1B1	Simvastatin	A
Anticoagulant	VKORC1 / CYP2C9 (CYP4F2)	Warfarin	A
Antidepressant (TCA)	CYP2D6 / CYP2C19	Amitriptyline	A
	CYP2D6	Nortriptyline	A
Antidepressant (SSRI)	CYP2C19	Citalopram	A
		Escitalopram	A
	CYP2D6	Fluvoxamine	A
		Paroxetine	A
Analgesic (Opioid)	CYP2D6	Codeine	A
		Tramadol	A
		Oxycodone	A
		Hydrocodone	-*
Anti-seizure	HLA-B / HLA-A	Carbamazepine	A
	HLA-B / CYP2C9	Phenytoin	A
Immunosuppressive (thiopurine)	TPMT / NUDT15	Azathioprine	A
		Mercaptopurine	A
		Thioguanine	A
Immunosuppressive (calcineurin inhibitor)	CYP3A5	Tacrolimus	A
Anti-emetic	CYP2D6	Ondansetron	A
		Tropisetron	A
Gout (xanthane oxidase inhibitor)	HLA-B	Allopurinol	A
Gout (recombinant urate-oxidase)	G6PD	Rasburicase	A
Antiviral (HIV)	HLA-B	Abacavir	A
	UGT1A1	Atazanavir	A
Antiviral (Hep C)	IFNL3 (IL28B)	Peginterferon alfa-2a / 2b	A
		Ribavirin	A
Anti-cancer (chemotherapy)	DPYD	Capecitabine	A
		Fluorouracil	A
		Tegafur	A
	UGT1A1	Irinotecan	A
Anti-cancer (anti-estrogen)	CYP2D6	Tamoxifen	A
Cystic Fibrosis	CFTR	Ivacaftor	A

Class	Gene	Medication	CPIC Level of Evidence
Anti-arrhythmic (Ia)	CYP2D6	Quinidine	B
Antidepressant (TCA)	CYP2D6 / CYP2C19	Clomipramine	B
		Doxepin	B
		Imipramine	B
		Trimipramine	B
	CYP2D6	Desipramine	B
		Protriptyline	B
Antidepressant (SSRI)	CYP2C19	Sertraline	B
	CYP2D6	Vortioxetine	B
Antidepressant (SNRI)	CYP2D6	Venlafaxine	B
Antidepressant (multiple)	CYP2D6	Mirtazapine	B
Antidepressant / antipsychotic	CYP2D6	Aripiprazole	B
Antipsychotic	CYP2D6	Brexpiprazole	B
Antipsychotic / Tourette syndrome	CYP2D6	Pimozide	B
Antipsychotic	CYP2D6	Risperidone	B
ADHD (SNRI)	CYP2D6	Atomoxetine	B
Analgesic (NSAID)	CYP2C9	Celecoxib	B
Analgesic (Opioid)	CYP2B6	Methadone	B
Anti-seizure	HLA-B	Oxcarbazepine	B
Proton pump inhibitor	CYP2C19	Esomeprazole	B
		Omeprazole	B
		Lansoprazole	B
		Pantoprazole	B
		Dexlansoprazole	B
		Rabeprazole	B
Antiviral (HIV)	CYP2B6	Efavirenz	B
		Nevirapine	B
Gout	G6PD	Pegloticase	B
		Probenecid	B
Sulfonylurea	G6PD	Chlorpropamide	B
		Glibenclamide	B
		Glimepiride	B
		Glipizide	B
Anti-cancer (HDAC inhibitor)	UGT1A1	Belinostat	B
Anti-cancer	G6PD	Dabrafinib	B

Class	Gene	Medication	CPIC Level of Evidence
Anti-arrhythmic (Ic)	*CYP2D6*	Propafenone	C
Beta-blocker	*CYP2D6*	Carvedilol	C
		Metoprolol	C
		Propranolol	C
Cholesterol	*SLCO1B1*	Rosuvastatin	C
Vasodilator	*NAT2*	Hydralazine	D

* Although hydrocodone is metabolized by CYP2D6, and CPIC guidelines indicate it is not a good alternative to codeine in CYP2D6 ultrarapid or poor metabolizers (see Supplemental Table 4), hydrocodone does not have a CPIC Level of Evidence designation.

The 36 medications with CPIC Level A of B evidence excluded from the analysis (due to transient use, treatment of a rare disease, or primary use outside of the United States) are listed here: acenocoumarol, chloramphenicol, chloroquine, ciprofloxacin, dapsone, desflurane, dextromethorphan/quinidine, dimercaprol, eliglustat, erythromycin, hydroxychloroquine, isoflurane, levofloxacin, lidocaine, mafenide, mefloquine, mesalazine, methylene blue, moxifloxacin, nalidixic acid, nitrofurantoin, norfloxacin, phenazopyridine, phenprocoumon, primaquine, quinine, sevoflurane, sodium nitrite, succinylcholine, sulfacetamide, sulfadiazine, sulfamethoxazole/trimethoprim, sulfasalazine, sulfisoxazole, and voriconazole.

Supplemental Table 2: Summary of medication use for the PCI study population (N=646)

Medication Class	Medication	No.	% (of 646)	CPIC Level of Evidence	Gene
Proton pump inhibitor	omeprazole	163	25.2%	B	CYP2C19
Analgesic (Opioid)	oxycodone	113	17.5%	A	CYP2D6
Proton pump inhibitor	pantoprazole	76	11.8%	B	CYP2C19
Analgesic (Opioid)	tramadol	64	9.9%	A	CYP2D6
Sulfonylurea	glipizide	58	9.0%	B	G6PD
Analgesic (Opioid)	hydrocodone	50	7.7%	-	CYP2D6
Proton pump inhibitor	esomeprazole	46	7.1%	B	CYP2C19
Anticoagulant	warfarin	44	6.8%	A	VKORC1 / CYP2C9
Antidepressant (SSRI)	citalopram	43	6.7%	A	CYP2C19
Statin	simvastatin	41	6.3%	A	SLCO1B1
Anti-emetic	ondansetron	37	5.7%	A	CYP2D6
Anti-gout (xanthane oxidase inhibitor)	allopurinol	31	4.8%	A	HLA-B
Antidepressant (SSRI)	sertraline	30	4.6%	B	CYP2C19
Antidepressant (SSRI)	paroxetine	20	3.1%	A	CYP2D6
Antidepressant (SSRI)	escitalopram	16	2.5%	A	CYP2C19
Antidepressant (SNRI)	venlafaxine	16	2.5%	B	CYP2D6
Antidepressant (TCA)	amitriptyline	14	2.2%	A	CYP2D6 / CYP2C19
Antidepressant (mulitple)	mirtazapine	13	2.0%	B	CYP2D6
Sulfonylurea	glimepiride	13	2.0%	B	G6PD
Immunosuppressive (calcineurin inhibitor)	tacrolimus	11	1.7%	A	CYP3A5
Antidepressant (TCA)	nortriptyline	7	1.1%	A	CYP2D6
Antidepressant / antipsychotic	aripiprazole	5	0.8%	B	CYP2D6
Analgesic (Opioid)	codeine	4	0.6%	A	CYP2D6
Proton pump inhibitor	dexlansoprazole	4	0.6%	B	CYP2C19
Proton pump inhibitor	lansoprazole	4	0.6%	B	CYP2C19
Anti-cancer (anti-estrogen)	tamoxifen	2	0.3%	A	CYP2D6
Anti-seizure	carbamazepine	2	0.3%	A	HLA-B / HLA-A
Immunosuppressive (thiopurine)	azathioprine	2	0.3%	A	TPMT / NUDT15
ADHD (SNRI)	atomoxetine	1	0.2%	B	CYP2D6
Antidepressant (SSRI)	fluvoxamine	1	0.2%	A	CYP2D6
Antipsychotic	risperidone	1	0.2%	B	CYP2D6

Analgesic (Opioid)	methadone	1	0.2%	B	*CYP2B6*
Analgesic (NSAID)	celecoxcib	1	0.2%	B	*CYP2C9*
Anti-gout	pegloticase	1	0.2%	B	*G6PD*
Antiviral (HIV)	efavirenz	1	0.2%	B	*CYP2B6*
Antiviral (HIV)	abacavir	1	0.2%	A	*HLA-B*
Cystic Fibrosis	ivacaftor	1	0.2%	A	*CFTR*

Medication use reflects use at discharge from the index PCI hospitalization or initiation during a follow-up visit within one year after the index PCI.

The top 19 medications, with a use frequency of 2.0% or higher, were considered in the simulation analysis.

Supplemental Table 3. Summary of *CYP2C19* Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Phenotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
TCA	Amitriptyline	14	*CYP2C19*	Ultrarapid/rapid metabolizer	31.5%	27.3%	4	A	PMID: 23486447	Avoid tertiary amine use. Consider alternative drug not metabolized by CYP2C19. If tertiary amine use warranted, use TDM to guide dose adjustments.	Optional	Therapeutic failure
				Poor metabolizer	2.5%	4.3%	0			Avoid tertiary amine use. Consider alternative drug not metabolized by CYP2C19. If tertiary amine use warranted, consider a 50% reduction in starting dose and use TDM to guide dose adjustments.	Moderate	Side effects
SSRI	Citalopram Escitalopram Sertraline	89	*CYP2C19*	Ultrarapid/rapid metabolizer	31.5%	27.3%	27	A A	PMID: 25974703	Consider alternative drug not predominantly metabolized by CYP2C19	Moderate (cit/escitalopram); Optional (sertraline)	Therapeutic failure
				Poor metabolizer	2.5%	4.3%	3	B		Consider 50% reduction of starting dose or consider alternative drug not predominantly metabolized by CYP2C19	Moderate (cit/escitalopram); Optional (sertraline)	Side effects
PPI	Esomeprazole Omeprazole Lansoprazole Pantoprazole Dexlansoprazole	293	*CYP2C19*	Ultrarapid metabolizer	4.6%	3.8%	13	B	N/A	DPWG: consider dose increase by 50-100%	No recommendation	Therapeutic failure
				Poor metabolizer	2.5%	4.3%	8			FDA: use with caution; DPWG: No action required	No recommendation	Adverse events
		396					**55**			Projected number of medication interventions (in the PCI study population, n=646)		
							8.5			Projected number of medication interventions (per 100 PCI patients)		

CYP2C19 Phenotype Frequency source - PMID: 5974703 (SSRI CPIC guideline)

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American

* In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided

Supplemental Table 4. Summary of *CYP2D6* Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Phenotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
TCA	Amitriptyline	14	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	0	A	PMID: 23486447 27997040	Avoid TCA use. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose. Use TDM to guide dose adjustements.	Strong	Therapeutic failure
				Intermediate metabolizer	7.2%	13.2%	1			Consider a 25% reduction of recommended starting dose. Use TDM to guide dose adjustments.	Moderate	Adverse effects
				Poor metabolizer	6.1%	3.0%	1			Avoid TCA use. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose. Use TDM to guide dose adjustments.	Strong	Adverse effects
SSRI	Paroxetine	20	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	1	A	PMID: 25974703	Select alternative drug not predominantly metabolized by CYP2D6.	Strong	Therapeutic failure
				Poor metabolizer	6.1%	3.0%	1			Select alternative drug not predominantly metabolized by CYP2D6. If paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional	Adverse effects
SNRI	Venlafaxine	16	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	1	B	N/A	DPWG: increase dose to 150% of the normal dose or select an alternative to venlafaxine	No reccomendation	Therapeutic failure
				Intermediate/poor metabolizer	13.3%	16.3%	2			DPWG: select an alternative to venlafaxine or reduce the dose and monitor plasma metabolite levels.	No reccomendation	Adverse effects
Opioid	Tramadol	64	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	2	A	PMID: 22205192	Use with caution. Tramadol is not a good alternative to codeine because its metabolism is affected by CYP2D6. DPWG: use an alternative to tramadol, or use 40% of the standard dose and monitor for side effects.	No reccomendation	Adverse effects
				Poor metabolizer	6.1%	3.0%	4			Use with caution. Tramadol is not a good alternative to codeine because its metabolism is affected by CYP2D6, and should be avoided	No reccomendation	Therapeutic failure
Opioid	Oxycodone	113	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	4	A	PMID: 22205192	Use with caution. Oxycodone is not a good alternative to codeine because its metabolism is affected by CYP2D6.	No reccomendation	Adverse effects
				Poor metabolizer	6.1%	3.0%	6			Use with caution. Oxycodone is not a good alternative to codeine because its metabolism is affected by CYP2D6, and should be avoided.	No reccomendation	Therapeutic failure
Opioid	Hydrocodone	50	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	2	-	PMID: 22205192	Use with caution. Hydrocodone is not a good alternative to codeine because its metabolism is affected by CYP2D6.	No reccomendation	Adverse effects
				Poor metabolizer	6.1%	3.0%	3			Use with caution. Hydrocodone is not a good alternative to codeine because its metabolism is affected by CYP2D6, and should be avoided.	No reccomendation	Therapeutic failure
Anti-emetic	Ondansetron	37	*CYP2D6*	Ultrarapid metabolizer	3.3%	3.4%	1	A	PMID: 28002639	Select alternative drug not predominantly metabolized by CYP2D6.	Moderate	Therapeutic failure
		314					**29**			Projected number of medication interventions (in the PCI study population, n=646)		
							4.5			Projected number of medication interventions (per 100 PCI patients)		

CYP2D6 Phenotype Frequency source - PMID: 5974703 (SSRI CPIC guideline)

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American

* In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided

Hydrocodone does not have a CPIC Level of Evidence designation

Supplemental Table 5. Summary of *VKORC1/CYP2C9* (Warfarin) Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Phenotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)#	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
Anti-coagulant	Warfarin	44	VKORC1 CYP2C9	Sensitive responders	35.4%	8.9%	13	A	PMID: 28198005	Lower dose requirement. Calculate dose based on PGx algorithms.	Strong	Adverse effects
				Highly sensitive responders	2.9%	0.7%	1			Lower dose requirement. Calculate dose based on PGx algorithms.	Strong	Adverse effects
		44					14			Projected number of medication interventions (in the PCI study population, n=646)		
							2.2			Projected number of medication interventions (per 100 PCI patients)		

Warfarin Phenotype Frequency source - PMID: 28198005 (Wafarin CPIC guideline) and 25769357 (ENGAGE-TIMI 56 genetic substudy)

Based on the *VKORC1* and *CYP2C9* minor allele frequencies, we assumed the warfarin sensitivity phenotypes in African-Americans were one-fourth of the frequency in Caucasians

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American

Supplemental Table 6. Summary of *SLCO1B1* (Simvastatin) Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Phenotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
Statin	Simvastatin	41	*SLCO1B1*	Intermediate function	26.8%	2.0%	9	A	PMID: 22617227	Use lower dose or consider an alternative statin. Consider routine CK surveillance	Strong	Adverse effects
				Low function	2.5%	0.0%	1			Use lower dose or consider an alternative statin. Consider routine CK surveillance	Strong	Adverse effects

		41					10	Projected number of medication interventions (in the PCI study population, n=646)
							1.5	Projected number of medication interventions (per 100 PCI patients)

SLCO1B1 Phenotype Frequency source - PMID: 22617227 (Simvastatin CPIC guideline)

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American

Supplemental Table 7. Summary of *G6PD* Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Phenotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation*	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
Sulfonyl-urea	Glipizide	58	*G6PD*	G6PD deficient	3.9%	7.5%	3	B	N/A	FDA: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.	No recommendation	Adverse effect
	Glimepiride	13		G6PD deficient	3.9%	7.5%	1	B	N/A	FDA: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.	No recommendation	Adverse effect
		71					**4**			Projected number of medication interventions (in the PCI study population, n=646)		
							0.6			Projected number of medication interventions (per 100 PCI patients)		

G6PD Phenotype Frequency source - PMID: 4787449 (Rasburicase CPIC guideline)

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American

* In the absence of a specific recommendation by CPIC, the FDA and/or DPWG recommendation is provided

Supplemental Table 8. Summary of *HLA-B* (Allopurinol) Simulation Analysis

Medication Class	Medication	No. of Patients Prescribed in Study Population	Gene	At Risk Genotype Group	At Risk Phenotype Frequency (Caucasian)	At Risk Phenotype Frequency (AA)	Projected No. of PGx Interventions^	CPIC Level of Evidence	CPIC Guideline Citation	CPIC Recommendation	CPIC Strength of Recommendation	Avoided Clinical Outcome (type)
Anti-gout	Allopurinol	31	*HLA-B*	HLA-B*58:01 allele carriers	1.6%	7.6%	1	A	PMID: 23232549	Allopurinol use is contraindicated	Strong	Serious adverse event
		31					1			Projected number of medication interventions (in the PCI study population, n=646)		
							0.2			Projected number of medication interventions (per 100 PCI patients)		

G6PD Phenotype Frequency source - PMID: 26094938 (Allopurinol CPIC guideline update)

^ Calculation for each medication assumes that the study population is 80% Caucasion and 20% African-American