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Permalink

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Journal

Pharmacogenomics, 19(9)

ISSN

1462-2416

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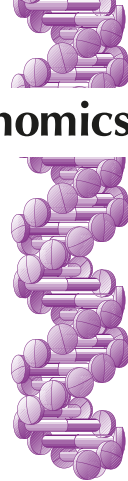
Publication Date

2018-06-01

DOI

10.2217/pgs-2018-0049

Peer reviewed



Projected impact of a multigene pharmacogenetic test to optimize medication prescribing in cardiovascular patients

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Aim: To determine the projected impact of a multigene pharmacogenetic (PGx) test on medication prescribing. **Materials & methods:** A retrospective analysis was conducted with 122 cardiac catheterization laboratory patients undergoing angiography for eligibility of potential PGx-guided interventions that could have occurred if multigene PGx information was pre-emptively available at the time of the procedure. Medication data and presence of actionable at-risk genotypes were used to determine eligibility of a PGx intervention. **Results:** 20% of the study population (n = 24) would have qualified for at least one PGx-based medication intervention per US FDA or Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines within 6 months of their cardiac catheterization procedure. Commonly encountered gene–drug pairs for these interventions included: *CYP2C19* for clopidogrel and antidepressants, *CYP2D6* for antidepressants and codeine, *SLCO1B1* for simvastatin, and *VKORC1/CYP2C9* for warfarin. **Conclusion:** Pre-emptive use of a multigene PGx test in the cardiac catheterization laboratory offers potential to reduce adverse medication outcomes.

First draft submitted: 6 April 2018; Accepted for publication: 10 May 2018; Published online: 25 May 2018

Keywords: cardiovascular pharmacogenetics • multigene testing • pharmacogenetics • pharmacogenomics • pre-emptive genotyping

Currently, over 160 unique drugs spanning various therapeutic areas contain US FDA or actionable Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance for germline mutations in over 30 genes. Although pharmacogenetic (PGx)-guided prescribing offers promise to prevent adverse medication outcomes, clinical implementation of PGx information remains a challenge as only 7% of US hospitals offer PGx testing [1]. Implementation of reactive PGx testing has recently increased at certain centers [2,3]. This strategy provides genetic information relevant for the immediate prescribed PGx-guided drug; however, there are associated implementation challenges that contribute to its low clinical adoption, such as inefficient and costly medical care due to the relatively high cost and delay of obtaining results from an individual PGx test [4,5]. The turnaround time of 0.3–16 days [3] required to obtain results can discourage use because results are not immediately available for clinicians. Given these limitations of reactionary PGx testing, a potentially more effective method of ensuring genetic information is available when drugs are prescribed using a comprehensive PGx test given pre-emptively to help increase clinical adoption of PGx testing. PGx tests that include a comprehensive gene panel offers the potential to avoid inefficiencies associated with individual gene tests, reduce costs and ultimately prevent adverse medication outcomes in patients because the

information is immediately available for use [4,6]. To ensure potential benefits of pre-emptive testing are achieved in clinical practice, the patient population and timing of testing must be considered.

CYP2C19 testing to guide antiplatelet therapy selection in cardiac catheterization laboratory patients undergoing a coronary angiography to detect coronary artery disease (CAD) is one instance where reactionary, single gene–drug PGx testing has been implemented at multiple centers [7]. However, the benefits of providing a comprehensive, multigene PGx test pre-emptively in this setting has not been well characterized. We hypothesize that cardiac catheterization laboratory patients undergoing a coronary angiography to detect CAD will likely benefit from a pre-emptive multigene PGx test given their high likelihood of requiring one or more PGx-guided medications for the management of multiple chronic medical conditions [8,9].

To this end, the objective of this study was to retrospectively assess patients undergoing a coronary angiogram for eligibility of PGx-guided interventions that could have occurred if multigene PGx information was pre-emptively available at the time of the procedure. This retrospective analysis investigated the projected impact of using a newly developed multigene PGx test, DNA2Rx™ [10], which contains genetic markers for 16 germline PGx genes which have CPIC or FDA guidance for over 120 drugs on medication prescribing in cardiac catheterization patients.

Materials & methods

Patient population

This was a single-center, retrospective cohort analysis of previously assembled population of patients 18–80 years of age referred to the UNC cardiac catheterization laboratory for nonemergent coronary angiography to detect CAD from September 2012 to February 2014 who enrolled in a biorepository study. Key exclusion criteria included the presence of the following conditions: current ST-elevation myocardial infarction, prior heart transplantation, severe concurrent illness (e.g., active pneumonia or acute decompensated heart failure, history of systemic inflammatory disease and/or current use of a systemic immunosuppressive medication, current treatment for active cancer, current end-stage renal disease on dialysis, current end-stage liver disease, hematological disorder affecting platelet function, hematocrit <30% and pregnancy. Comprehensive exclusion criteria and study procedures have been previously published [8]. The UNC Biomedical Institutional Review Board approved the study protocol. Patients provided consent for participation in a DNA biorepository and access to electronic medical records (EMR) for review.

Data collection

Patient demographics, clinical information and medication use were retrospectively abstracted from the EMR. Patients were required to have at least one follow-up visit within 6 months of the catheterization procedure to be included in the analysis. The focus of this analysis is on a 6 month time frame to assess the short-term use of PGx-guided medications. The biorepository contained 138 patients with follow-up data in the EMR for medication information abstraction. Out of these 138 patients, 16 were excluded for missing medication data ($n = 2$) or having a follow-up visit >180 days ($n = 14$). The study population, meeting an inclusion criteria of having an encounter and medication history in the UNC Health Care system within 180 days of the angiography procedure included 122 patients, which served as the primary study population for analysis.

Active medication prescription information was collected at two time points: one at the discharge from the cardiac catheterization procedure and other at the first follow-up visit that occurred within 6 months of the procedure. Medications with actionable PGx guidance from the FDA (i.e., genotype specific dosing) or high levels of evidence (A or B) for CPIC guidance and prescribed for a chronic condition were collected. Oncology (e.g., tamoxifen), immunomodulatory (e.g., tacrolimus) and specialty drugs (e.g., ivacaftor) were not collected due to the biorepository exclusion criteria, and antibiotics and antifungal drugs (e.g., voriconazole) were not collected since they are not chronically administered. The FDA and CPIC guidelines were last accessed in November 2015 and 26 medications met these criteria and were included in the analysis (Supplementary Table 1). Descriptive statistics was used to determine drug prevalence at discharge and first follow-up. The medication prevalence observed in the study population was used to simulate the medication prevalence in a theoretical annual population of catheterization laboratory of 2000 patients.

Genetic analysis

Genetic information relevant in drug prescribing was obtained for the study population who participated in the biorepository using the DNA2Rx™ assay, which provides information for 120 drugs [10]. DNA was extracted from patient samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA2Rx™ con-

Table 1. DNA2Rx™: Genetic markers included on the assay with CPIC or FDA guidance.

Gene	Default haplotype [†]	Haplotype or single nucleotide polymorphism tested
1. <i>BCHE</i>	wildtype	rs28933390, rs28933389, rs1799807
2. <i>CYP2B6</i>	*1	*2, *4, *5, *6, *6A, *7, *11A, *16, *18, *19, *20, *22, *26, *27, *28, *33, *34, *35, *36
3. <i>CYP2C9</i>	*1	*2, *3, *4, *5, *6, *8, *9, *10, *11, *12, *13, *14, *15, *24, *25, *27, *31, *33, *35
4. <i>CYP2C19</i>	*1	*2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *11, *14, *15, *16, *17, *18, *19, *22, *24, *25, *26, *27, *29, *33, *34, *35
5. <i>CYP2D6</i>	*1A	*1D, *1xN, *2A, *2D, *2G, *2xN, *3A, *3xN, *4A, *4B, *4J, *4K, *4M, *4xN, *6A, *6C, *6xN, *7, *8, *9, *9xN, *10A, *10xN, *11, *12, *14A, *14B, *15, *17, *17xN, *18, *19, *20, *21A, *29, *29xN, *30, *34, *38, *39, *40, *41, *41xN, *42, *44, *45A, *45xN, *47, *49, *50, *51, *53, *56A, *56B, *58, *60, *64, *65, *69, *70, *72, *81, *82, *83, *91, *96, *100, *107, *109
6. <i>CYP3A5</i>	*1	*2, *3, *4, *5, *6, *7, *8, *9
7. <i>CYP4F2</i>	*1	*3
8. <i>DPYD</i>	*1	*2, *3, *7, *9A, *9B, *12, *13
9. <i>G6PD</i>	B	A, A- 202A.376G, A- 968C.376G, Mediterranean Haplotype, Asahi, Hechi, Sierra Leone, Ananindeua, Miaoli, Viangchan, Jammu, Kalyan-Kerala, Jamnaga, Rohini, Mira d'Aire, Bangkok Noi, Cosenza, Kaiping, Anant, Dhon, Sapporo-like, Wosera
10. <i>IL28B</i>	N/A	rs12979860
11. <i>NAT2</i>	*4	*5, *5A, *5B, *5C, *5E, *5G, *5J, *5K, *5P, *5Q, *5R, *5S, *5T, *5V, *6, *6A, *6C, *6E, *6F, *6I, *6N, *6P, *6R, *6S, *6T, *7, *7B, *7C, *7D, *7E, *7F, *10, *11, *12, *12B, *12C, *12G, *12H, *12M, *13, *14, *14B, *14C, *14D, *14E, *14F, *14G, *14I, *17, *18, *19, *20, *21, *22, *24
12. <i>NUDT15</i>	*1	*3
13. <i>SLCO1B1</i>	*1A	*1B, *2, *3, *4, *5, *6, *9, *10, *12, *14, *15, *17, *19, *20, *21, *23, *31
14. <i>TPMT</i>	*1	*2, *3A, *3B, *3C, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *20, *21, *22, *23, *24, *25, *26, *29, *31
15. <i>UGT1A1</i>	*1	*6, *27, *28, *36, *37, *80
16. <i>VKORC1</i>	H1	H2, H3, H4, H6, H7, H9

[†] Designated haplotype when all other tested haplotypes are absent.

tains genetic markers for 20 genes, but only 16 genes, which are associated with actionable FDA or CPIC guidelines will be reported since these are most clinically relevant (Table 1). These include: *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *IL28B*, *NAT2*, *NUDT15*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*. Excluded genes include: *ABCB1*, *CYP3A4*, *RYR1*, and *TYMS*. DNA2Rx™ uses a custom-capture method using molecular inversion probes designed using the MIPgen program [11] to generate library fragments for next-generation sequencing. Preparation of the library fragments followed standard protocol that has been previously published [12]. These fragments subsequently undergo sequencing using the Illumina HiSeq 2500 Rapid Run platform (Illumina, CA, USA). *CYP2D6* copy number variant (CNV) was determined using the TaqMan copy number assay ID Hs04502391_cn with the RNase P reference assay (Life Technologies, CA, USA). CNV was calculated using the $2^{\Delta\Delta Cq}$ equation with known reference DNA samples; quantification cycle was determined using FPK-PCR [13]. Burrows–Wheeler aligner [14] and FreeBayes [15] were used for DNA sequence analysis. A minimum sequencing depth of 20× was used for genotype and haplotype calling except for a single nucleotide polymorphism (rs3892097) in *CYP2D6* where a 10x sequencing depth was used for 15 patients.

DNA2Rx™ provides genetic results for five of the six actionable PGx genes (i.e., *CYP2C9*, *CYP2C19*, *CYP2D6*, *SLCO1B1* and *VKORC1*) that are relevant in the drug prescribing of the 26 PGx-guided medications included in the analysis. In the case of *HLA-B*, which was not reported from the assay, projected frequencies for Caucasian-dominated populations were used for the study population to estimate the actionable at-risk genotype frequencies from CPIC supplements [16]. The Hardy–Weinberg equation was used to calculate the actionable at-risk genotype frequencies for *HLA-B*1502* allele carriers where only allele frequencies were available [16].

Genetic information for the simulated population of 2000 patients undergoing coronary angiography annually in the UNC cardiac catheterization laboratory was estimated based on published population data. Published data for Caucasian-dominated populations from CPIC supplements were used for *CYP2C19*, *CYP2C9*, *CYP2D6*, *HLA-B*, *SLCO1B1* and in the case of *VKORC1/CYP2C9*, the ENGAGE AF-TIMI 48 study was used to project the expected actionable at-risk genotypes in patients [16–21]. For *HLA-B*1502* allele carriers and *SLCO1B1* genotypes, where only allele frequencies were available, the Hardy–Weinberg equation was used to calculate the actionable at-risk genotype frequencies. Published allele frequency data were used instead of results from the current study

sample (n = 122) in order to obtain a distribution of genetic variation, especially, rarer alleles that would be more representative of the population.

Determining the outcome measures

The primary outcome of interest for the analysis is the number of cases where PGx information could have been utilized to optimize drug dosing or selection for patients undergoing coronary angiography at either discharge from the catheterization laboratory or at the first follow-up visit within 6 months of the procedure in the study population (n = 122). Cases where PGx information could optimize medication prescribing are defined as having the combination of a medication prescription that can be optimized using PGx information and the presence of an actionable at-risk genotype associated with medication dosing different from standard of care per FDA or CPIC guidelines (A or B evidence level). As this is a retrospective analysis, these medication changes have not been clinically implemented and are potential instances where PGx information could have optimized medication prescribing if it were available to the prescriber. The secondary outcome of interest is delineating which PGx gene–drug pairs were encountered in this patient population.

CPIC and FDA guidelines were used to translate genetic information into established actionable at-risk genotypes that are often characterized into phenotype groups (e.g., metabolizer status). For *NAT2*, where the actionable at-risk genotype is associated with the slow acetylator phenotype, the NAT2PRED algorithm was used to predict the *NAT2* acetylator phenotype because of the difficulty in *NAT2* haplotype inference [22]. Supplementary Table 2 summarizes phenotype subgroups for each gene that are associated with actionable at-risk genotypes.

Patients were deemed to qualify for a PGx-guided intervention if they had an active prescription for a PGx-guided medication and carried an actionable at-risk genotype that carries a recommendation for altered selection or dosing of the associated PGx-guided medication. Where published genotype data is used to project PGx interventions, each drug was calculated by multiplying the observed drug frequency, actionable genotype frequencies and number of patients in the study population. The number of interventions for each actionable at-risk subgroup was rounded before summing. For instance, to project the annual number of *CYP2C19*-based dosing changes for clopidogrel in the simulated population of patients that undergo coronary angiography at the UNC cardiac catheterization laboratory annually (n = 2000), PGx interventions for the actionable at-risk groups are summed. The drug prevalence at discharge or first follow-up in the study population of 122 patients (48.36%) is multiplied by the intermediate metabolizer actionable at-risk genotype frequency (26.4%) and then by the simulated patient population (n = 2000), which results in 255 projected-PGx interventions. The same drug prevalence at discharge and first follow up (48.36%) is then multiplied by the poor metabolizer actionable at-risk genotype frequency (2.50%) and then by the simulated patient population (n = 2000), resulting in 24 projected-PGx interventions. Summing the interventions for the two actionable at-risk genotype groups yields 279 interventions projected for *CYP2C19* and clopidogrel dosing.

Results

Patient demographics

This analysis was carried out using a previously published study of patients treated at the cardiac catheterization laboratory at University of North Carolina at Chapel Hill (NC, USA) who enrolled in a DNA biorepository [8]. The study population for analysis included 122 patients and was on average 63 year olds, 57% male, predominantly Caucasian (73%), and approximately 38% of patients underwent a percutaneous coronary intervention. Comorbidities included hypertension (77.9%), hyperlipidemia (63.9%), heart failure (17.2%) and history of depression (13.9%). Table 2 summarizes additional key characteristics of the patient population.

Genotype frequencies

For the study population, DNA was successfully extracted from all blood samples (average concentration 192.9 ng/ul; range: 57.1–704.5 ng/ul). Genotype and haplotype calling was 100% successful for the 16 clinically relevant PGx genes except for *CYP2D6* (96.7%), *VKORC1* (95.1%) and *NAT2* (89%).

The percentages of actionable at-risk genotypes among subjects in decreasing prevalence were: *IL28B* (54.9%), *NAT2* (53.3%), *CYP2C19* (52.5%), *CYP4F2* (40.2%), *VKORC1/CYP2C9* (35.2%), *CYP2C9* (33.6%), *CYP3A5* (24.6%), *SLCO1B1* (20.5%), *CYP2D6* (14.8%), *UGT1A1* (10.7%), *G6PD* (9.0%), *CYP2B6* (6.6%), *TPMT* (6.6%), *DPYD* (2.5%), *HLA-B* (0.8%), *NUDT15* (0.8%) and *BCHE* (0%). The median number of actionable at-risk genotypes a person carried in this cohort was four (range: 0–7) with one subject (0.8%) carrying none, six

Table 2. Characteristics of the study patients (n = 122).

Demographics	n (%), unless specified
Age (mean ± SD)	62.8 ± 10.4
Male	69 (56.6%)
Race:	
– Caucasian	89 (73.0%)
– African–American	26 (21.3%)
– Native–American	2 (1.6%)
– Asian	0 (0%)
– Hawaiian/other Pacific islander	0 (0%)
– Other	5 (4.1%)
Ethnicity:	
– Non Hispanic	117 (95.9%)
– Hispanic	2 (1.6%)
– Declined/unavailable/unknown	3 (2.5%)
Comorbidities	
Hypertension	95 (77.9%)
Hyperlipidemia	78 (63.9%)
Obese (BMI ≥30)	62 (50.8%)
Diabetes	41 (33.6%)
Heart failure	21 (17.2%)
Depression	17 (13.9%)
Chronic kidney disease	9 (7.4%)
CAD history	
PCI during index visit	46 (37.7%)
PCI	37 (30.3%)
Previous MI	22 (18.0%)
Days to follow-up visit (median[(IQR)])	24 (34)

BMI: Body mass index; CAD: Coronary artery disease; IQR: Interquartile range; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

Table 3. Actionable drugs and associated actionable at-risk genotype frequencies in the study population (n = 122).

Gene	Referenced subgroup	Genotype frequencies based on actual genotypes, n (%)	Genotype frequencies based on published literature, n (%)	Actionable drug(s)
<i>CYP2C19</i>	Ultrarapid metabolizer	36 (29.5%)	37 (30%)	Antidepressants
	Intermediate metabolizer	24 (19.7%)	32 (26.4%)	Clopidogrel
	Poor metabolizer	4 (3.3%)	3 (2.5%)	Clopidogrel, antidepressants
<i>CYP2C9</i>	Intermediate metabolizer	36 (29.5%)	36 (29.3%)	Phenytoin
	Poor metabolizer	5 (4.1%)	5 (4.1%)	Phenytoin
<i>SLCO1B1</i>	Intermediate function	25 (20.5%)	26 (21.6%)	Simvastatin
	Low function	0 (0%)	2 (2%)	Simvastatin
<i>VKORC1/CYP2C9</i>	Sensitive responders	37 (30.3%)	43 (35.4%)	Warfarin
	Highly sensitive responders	6 (4.9%)	4 (2.9%)	Warfarin
<i>HLA-B</i>	<i>HLA-B*5801</i> allele carriers	N/A	1 (0.8%)	Allopurinol
	<i>HLA-B*1502</i> allele carriers	N/A	0 (0.01%)	Carbamazepine, phenytoin
<i>CYP2D6</i>	Ultrarapid metabolizer	4 (3.3%)	2 (1.5%)	Antidepressants, codeine
	Intermediate metabolizer	5 (4.1%)	8 (6.5%)	Antidepressants, codeine
	Poor metabolizer	9 (7.4%)	9 (7.5%)	Antidepressants, codeine

subjects (4.9%) carrying one, 23 subjects (18.9%) carrying two, 25 subjects (20.5%) carrying three, 35 subjects (28.7%) carrying four, 20 subjects (16.4%) carrying five, seven subjects (5.7%) carrying six, and five subjects (4.1%) carrying seven actionable at-risk genotypes. Supplementary Table 3 summarizes the genetic results for 16 of the genes included on DNA2Rx™ with FDA or CPIC guidance and where available from CPIC guidelines, expected frequencies reported across various ethnic groups. Supplementary Table 2 provides the actionable at-risk genotypes present in the study population. Table 3 summarizes the frequencies of each actionable at-risk phenotype

Table 4. Prevalence of medication use at either discharge or first follow-up (n = 122) and the associated gene(s) with FDA or CPIC pharmacogenetic guidance.

Drug	Gene(s)	Pharmacogenetic guidance	Prevalence (n)
Cardiovascular disease			
Clopidogrel	<i>CYP2C19</i>	FDA, CPIC	48.4% (59)
Simvastatin	<i>SLCO1B1</i>	CPIC	13.9% (17)
Warfarin	<i>CYP2C9, VKORC1</i>	FDA, CPIC	9.0% (11)
Chronic pain/analgesia			
Celecoxib	<i>CYP2C9</i>	FDA	0% (0)
Codeine	<i>CYP2D6</i>	FDA, CPIC	1.6% (2)
Depression			
Amitriptyline	<i>CYP2C19, CYP2D6</i>	FDA, CPIC	3.3% (4)
Citalopram	<i>CYP2C19</i>	FDA, CPIC	6.6% (8)
Clomipramine	<i>CYP2C19, CYP2D6</i>	FDA, CPIC	0% (0)
Desipramine	<i>CYP2D6</i>	FDA, CPIC	0.8% (1)
Doxepin	<i>CYP2C19, CYP2D6</i>	FDA, CPIC	0% (0)
Escitalopram	<i>CYP2C19</i>	FDA, CPIC	1.6% (2)
Fluvoxamine	<i>CYP2D6</i>	FDA, CPIC	0% (0)
Imipramine	<i>CYP2C19, CYP2D6</i>	FDA, CPIC	0.8% (1)
Nortriptyline	<i>CYP2D6</i>	FDA, CPIC	0% (0)
Paroxetine	<i>CYP2D6</i>	FDA, CPIC	2.5% (3)
Sertraline	<i>CYP2C19</i>	CPIC	4.9% (6)
Trimipramine	<i>CYP2C19, CYP2D6</i>	FDA, CPIC	0% (0)
Vortioxetine	<i>CYP2D6</i>	FDA	0% (0)
			Total antidepressants: 20.0% (25)
Gout			
Allopurinol	<i>HLA-B</i>	CPIC	2.5% (3)
Psychiatric disease			
Aripiprazole	<i>CYP2D6</i>	FDA	0% (0)
Clozapine	<i>CYP2D6</i>	FDA	0% (0)
Iloperidone	<i>CYP2D6</i>	FDA	0% (0)
Pimozide	<i>CYP2D6</i>	FDA	0% (0)
Seizure disorder			
Carbamazepine	<i>HLA-B</i>	FDA, CPIC	0% (0)
Clobazam	<i>CYP2C19</i>	FDA	0% (0)
Phenytoin	<i>CYP2C9, HLA-B</i>	FDA, CPIC	1.6% (2)

for genes with an active prescription among subjects in the study population and the projected annual population seen in the cardiac catheterization laboratory.

Prevalence of genetically actionable drugs

Table 4 summarizes the 26 PGx-guided medications established *a priori* to guide medication abstraction from patient records, the relevant gene(s) with actionable PGx guidance and the prevalence of medication use with actionable PGx guidance among patients in the cohort. Out of the 16 genes tested on the DNA2Rx™ assay, six of these genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-B*, *SLCO1B1* and *VKORC1*) guide dosing for these 26 drugs. In the cohort, 35 subjects (28.7%) were on no PGx-guided medications, 59 subjects (48.4%) were on one PGx-guided medication, 25 subjects (20.5%) on two PGx-guided medications, two subjects (1.6%) on three PGx-guided medications, and one subject (0.8%) on four PGx-guided medications. There were a total of 119 prescriptions for PGx-guided medications in this cohort; of these, 93 prescriptions (78.2%) were for medications that have both actionable FDA and CPIC guidance, 26 prescriptions (21.8%) were for medications with guidance only from CPIC and no prescriptions had guidance only from the FDA.

Primary outcome

Cases where PGx information could be used to optimize drug dosing were determined for the study population and the simulated population. For the six genes that are involved in the dosing of the 26 PGx-guided medications, 87.8% (n = 107) of the study population carried one or more actionable at-risk genotype (median 1.5; range: 0–5). Of the 107 who carried an at-risk genotype, there were 26 instances where the patient was also prescribed the associated PGx-guided medication at either discharge or a follow-up visit within six months of a cardiac catheterization laboratory visit, and thus would have qualified for a PGx-guided intervention. Two of the 26 instances occurred in the same patient and the remaining 24 instances occurred in unique patients (20% of the study population). Using medication prevalence data in the cohort to extrapolate potential PGx interventions to the annual UNC cardiac catheterization laboratory population, there were 571 projected cases where a genotype-guided action could have been recommended within 6 months of the cardiac catheterization laboratory visit. Assuming each intervention occurred in a unique individual, approximately 28.6% (571/2000) of these patients would have qualified for a PGx-guided intervention.

Secondary outcome

Results from the primary outcome were used to delineate PGx gene–drug pairs commonly encountered in the two patient populations (Figure 1). For the 26 instances in the study population (n = 122) where a PGx intervention could have occurred, ten cases (38.5%) involved *CYP2C19* (clopidogrel), five cases (19.2%) involved *CYP2C19* (non-clopidogrel), five cases (19.2%) involved *SLCO1B1*, four cases (15.4%) involved *CYP2D6*, and two cases (7.7%) involved *VKORC1/CYP2C9*. For the 571 cases projected for the annual cardiac catheterization laboratory population, a total of 279 cases (48.9%) involved *CYP2C19* (clopidogrel), 118 cases (20.7%) involved *CYP2C19* (non-clopidogrel), 69 cases (12.1%) involved *VKORC1/CYP2C9*, 66 cases (11.6%) *SLCO1B1*, 27 cases (4.7%) involved *CYP2D6* and 12 cases (2.1%) involved *CYP2C9*.

Discussion

This retrospective analysis indicated that 20% (24/122) of the study population would have qualified for a PGx intervention or opportunities to optimize drug prescribing as per FDA or CPIC guidelines using PGx information within 6 months of their cardiac catheterization procedure if, multigene PGx results were pre-emptively available. When extrapolating to the number of patients typically seen annually in the cardiac catheterization laboratory for angiography at UNC, approximately 29% (571/2000) of patients would have qualified for the PGx intervention.

Our results suggest that PGx testing beyond *CYP2C19* to guide antiplatelet therapy selection could be beneficial in cardiac catheterization laboratory patients. For the study population (n = 122), 61.5% of potential PGx interventions (16/26) were for nonclopidogrel medications that could be guided with PGx information and 42% (11/26) of the potential PGx interventions were for non-*CYP2C19* genes. Commonly encountered gene–drug pairs in the study population included: *CYP2C19* and *CYP2D6* for antidepressants, *SLCO1B1* for simvastatin and *VKORC1/CYP2C9* for warfarin. For the simulated population expected annually in the cardiac catheterization laboratory for angiography (n = 2000), 51.1% (292/571) were for non-clopidogrel medications that could be guided with PGx information and 30.5% (174/571) of potential PGx interventions were for non-*CYP2C19* genes. The most commonly prescribed drugs outside the cardiovascular area were antidepressants prescribed in approximately 20% of patients.

Almost all subjects (99.2%) in the study population carried ≥ 1 actionable at-risk genotype when considering all 16 genes tested on DNA2Rx™; when limited to *CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-B*, *SLCO1B1* and *VKORC1*, which provides guidance for the 26 medications that were included in this analysis, the majority (87.8%) carried ≥ 1 actionable at-risk genotype. This high prevalence of actionable at-risk genotypes is expected and is confirmed by previous studies [4,23,24]. A high proportion of patients are at risk for adverse medication outcomes given the high prevalence of carrying these actionable at-risk genotypes across multiple genes and the potential for being prescribed PGx-guided medications. Therefore, PGx testing to optimize drug prescribing offers enormous potential to prevent adverse medication outcomes in a substantial number of these patients. Studies have been conducted to confirm the health outcome benefit and feasibility of using *CYP2C19* testing to guide antiplatelet therapy selection at our institution and others [7,25,26] but studies investigating the benefits of providing additional gene–drug information as part of a multigene PGx test for this population are missing. Future studies are needed to prospectively assess the benefits of providing patients seen in the cardiac catheterization laboratory for angiography with pre-emptive multigene PGx testing.

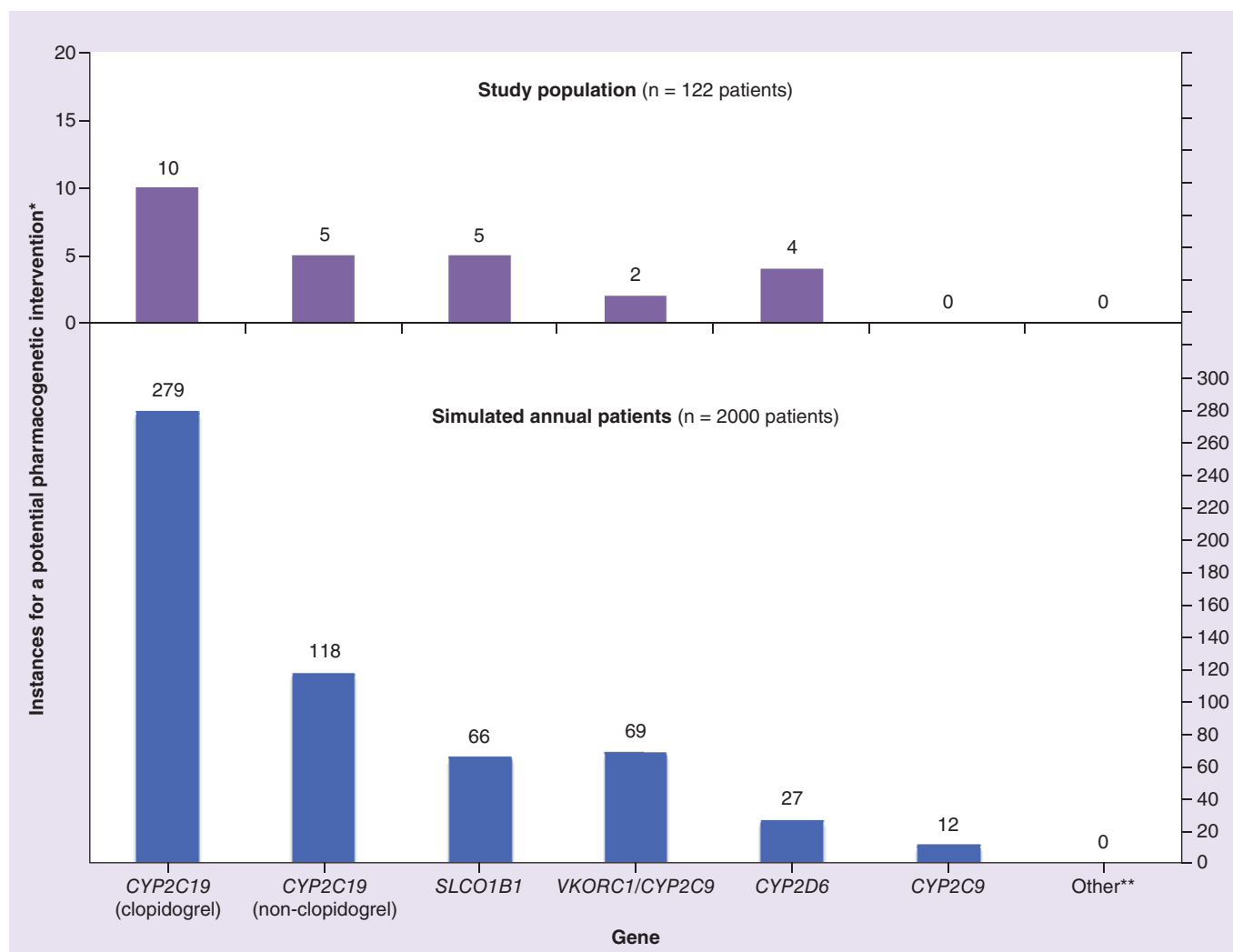


Figure 1. Number of instances where pharmacogenetic information could have optimized drug prescribing as an intervention in cardiac catheterization laboratory patients undergoing angiography. Patients were required to carry an actionable at-risk genotype and be prescribed a medication with actionable PGx guidance to qualify for an intervention.

*A potential pharmacogenetic intervention is based on a gene–drug pair. The actionable at-risk genotypes are listed in Table 3 and the corresponding drug(s) for each gene is listed in Table 4.

Other = *BCHE, CYP2B6, CYP3A5, CYP4F2, DPYD, G6PD, HLA-B*, IL28B, NAT2, NUDT15, TPMT, UGT1A1*.

***Based on published frequencies for the study population.

Identifying patient populations that would derive short-term benefit from comprehensive PGx information is important for successful implementation of PGx testing. Cardiac catheterization laboratory patients often carry a burden of disease that is managed with numerous medications and may be good candidates for comprehensive PGx testing. Approximately 38% of these patients underwent a percutaneous coronary intervention at the index visit to the cardiac catheterization laboratory, which involves using *CYP2C19* genetic information to optimize the required antiplatelet therapy that is initiated [27–29]. Implementing a multigene PGx test in patients undergoing a coronary angiogram to detect CAD has the potential to provide genetic information relevant for drug dosing beyond *CYP2C19* to manage additional comorbidities, which was confirmed in this analysis. For instance, hypercholesterolemia is a risk factor for CAD and CPIC guidelines, is available for simvastatin and a commonly prescribed statin therapy [18]. Another common comorbidity is major depression, which has been reported to affect 17–27% of these patients, and *CYP2D6* and *CYP2C19* advisories for antidepressants from the FDA and CPIC have been established [30]. Being prescribed multiple PGx-guided medications have been reported in a previous study, which investigated pre-emptive genotyping for five PGx-guided drugs (clopidogrel, simvastatin, warfarin, thiopurines and

tacrolimus) in 10,000 cardiac catheterization laboratory patients. The study found that most patients were exposed to at least one of these PGx-guided medications and those who were prescribed one PGx-guided medication were likely to be prescribed a second PGx-guided drug [4]. The benefits of having more comprehensive genetic information available for drug prescribing among this population have not been well investigated and the current analysis provides preliminary insight into this area.

Key limitations of the current study are important to highlight. First, the samples that were available for genotyping were obtained from an existing biorepository [8]. This study excluded patients with specific conditions (including current ST-elevation myocardial infarction, active cancer, prior heart transplant, systemic inflammatory conditions and severe concurrent illness), which may limit generalizability of the results to a cardiac catheterization laboratory by underestimating the prevalence of certain medications with actionable PGx information. For instance, since the biorepository excluded individuals with active cancer, PGx-guided medications such as tamoxifen, which have CPIC and FDA guidelines were not captured in this analysis. Second, the biorepository was assembled during a specific 2-year period (2012–2014), and these results may differ from more contemporary prescribing patterns of PGx-guided medications. Collecting more contemporary medication use over longer time periods is an important next step and would enable a more extensive evaluation of the projected impact of comprehensive PGx information in this population. Third, the projected benefits of PGx testing may be underestimated since a short 6 month time frame was used to collect medication use in this population. These limitations also apply to the simulation analysis, which extrapolate medication prevalence data observed in the study sample to the annual population patients seen at the UNC cardiac catheterization laboratory. The projected PGx interventions for the simulated annual population of cardiac catheterization laboratory patients were also based on genotype frequencies for Caucasians-dominated populations, which may not be reflective of different ethnic populations. Despite these limitations, this analysis provides new insight into the number of PGx-guided interventions that could occur in the cardiac catheterization laboratory if multigene PGx information was available at the time of prescribing and highlights the need for future prospective studies in larger, more diverse cohorts over a longer time period to help strengthen the generalizability of these results. Future studies are also needed to determine whether PGx-guided interventions that encompass multiple genes and drugs and follow CPIC of FDA guidelines can be implemented clinically in the cardiac catheterization laboratory and ultimately result in better patient outcomes and lower healthcare costs.

This analysis also provides important insight into the challenges that could be encountered if comprehensive PGx testing is implemented in a specialty clinical setting, like the cardiac catheterization laboratory, to inform drug prescribing. Since the PGx field likely needs to move away from single gene–drug testing and toward more comprehensive genetic testing to maximize impact [31], infrastructure for information to follow patients is critical. In this patient population, 20–25% of patients were referred to UNC for their initial cardiac catheterization laboratory visit but were followed up outside of the UNC healthcare system. It is common for patients to be seen at different clinics and future clinicians caring for the same patient will need to access genetic results to avoid repeat testing. Additionally, comprehensive PGx tests provide information for various therapeutic areas and a mechanism alerting clinicians in disparate fields to the availability of this information is key. Issues regarding how best to incorporate these data into the EMR and provide clinical decision support systems have not been well developed in most health systems and require further study.

Conclusion

In summary, this retrospective analysis suggests that multigene PGx testing could be beneficial for patients with CAD undergoing a coronary angiogram and relevant gene–drug pairs to manage comorbidities in these patients were identified. Future studies are warranted to further investigate benefits of providing PGx testing in these patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:

<https://www.futuremedicine.com/doi/suppl/10.2217/pgs-2018-0049>

Acknowledgements

The authors would like to thank the cardiac catheterization laboratory at University of North Carolina at Chapel Hill for participation in this study.

Summary points

Methods

- Successful implementation of comprehensive pre-emptive pharmacogenetic (PGx) testing in the clinical setting requires defining a well-characterized population that would derive short-term and long-term benefit from this PGx-guided prescribing.
- The objective of this retrospective analysis was to determine the projected impact of providing a multigene PGx test on medication prescribing based on medication prescriptions and actionable at-risk genotypes in 122 cardiac catheterization laboratory patients undergoing angiography.

Results

- Results indicated 20% of the patients (n = 24) would have qualified for at least one PGx-based medication intervention as per US FDA or CPIC guidelines within 6 months of their cardiac catheterization procedure.
- Commonly encountered gene–drug pairs for these interventions included: *CYP2C19* for clopidogrel and antidepressants, *CYP2D6* for antidepressants and codeine, *SLCO1B1* for simvastatin, and *VKORC1/CYP2C9* for warfarin.

Discussion

- These results indicate that pre-emptive use of a multigene PGx test in the cardiac catheterization laboratory offers potential to reduce adverse medication outcomes in this patient population.

Author's contributions

OM Dong wrote manuscript, designed research, performed research, and analyzed data. A Li designed research, performed research, analyzed data. O Suzuki designed research, and analyzed data. A Oni-Orison performed research, designed research, analyzed data. R Gonzalez analyzed data. GA Stouffer designed research. CR Lee designed research, performed research, and analyzed data. T Wiltshire designed research. All authors approved of the final manuscript.

Financial & competing interests disclosure

The project described was supported by American Heart Association grant 16GRNT29300003 to C Lee, 13PRE16470017 to A Oni-Orison, and 18PRE33960079 to O Dong. In addition, this project was supported by the UNC Eshelman Institute for Innovation grant R1020 RX03612214 to T Wiltshire. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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