

**Warfarin**  
**Pharmacogenomic Implementation: Implications for Minorities and**  
**Opportunities for Education**

BY

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THESIS

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This thesis is dedicated to my husband, Lucas Bojarowski, without whom it would never have been accomplished.

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## TABLE OF CONTENTS

<u>CHAPTER</u>	<u>PAGE</u>
I. INTRODUCTION.....	1
II. METHODS .....	3
A. Study Population .....	3
B. Genotyping .....	4
C. Statistical Analysis.....	5
III. RESULTS.....	6
IV. DISCUSSION.....	9
CITED LITERATURE .....	22
VITA .....	25

## LIST OF TABLES

<u>TABLE</u>	<u>PAGE</u>
I. BASELINE DEMOGRAPHICS AND GENOTYPE FREQUENCIES.....	14
II. DOSING ERROR WITH PHARMACOGENOMIC ALGORITHMS BASED ON CYP2C9*5, *6, *8, OR *11 GENOTYPE.....	16
III. DOSING ERROR WITH PHARMACOGENOMIC ALGORITHMS BASED ON RS12777823 GENOTYPE.....	17

## LIST OF FIGURES

<u>FIGURE</u>	<u>PAGE</u>
1. Bland-Altman plots of the dose prediction error with the International Warfarin Pharmacogenetics Consortium (IWPC) and <a href="http://www.warfarindosing.org">www.warfarindosing.org</a> (WD) algorithms stratified by rs12777823 G>A genotype.....	18
2. Bland-Altman plots of the dose prediction error with the International Warfarin Pharmacogenetics Consortium (IWPC) and <a href="http://www.warfarindosing.org">www.warfarindosing.org</a> (WD) algorithms stratified by <i>CYP2C9</i> *5, *6, *8, or *11 carrier status.....	19
3. Observed and predicted doses with the International Warfarin Pharmacogenetics Consortium (IWPC), <a href="http://www.warfarindosing.org">www.warfarindosing.org</a> (WD) and WD-African American (WD-AA) algorithms in carriers of the <i>CYP2C9</i> *5, *6, *8, *11 or rs12777823A alleles carriers.....	20
4. Observed and predicted doses with the International Warfarin Pharmacogenetics Consortium (IWPC), <a href="http://www.warfarindosing.org">www.warfarindosing.org</a> (WD) and WD-African American (WD-AA) algorithms in non-carriers of the <i>CYP2C9</i> *5, *6, *8, *11 or rs12777823A alleles.....	21

## LIST OF ABBREVIATIONS

VKORC1	vitamin K epoxide reductase complex, subunit 1
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2
IWPC	International Warfarin Pharmacogenetics Consortium
WD	<a href="http://www.warfarindosig.org">www.warfarindosig.org</a>
CPIC	Clinical Pharmacogenetics Implementation Consortium
EU-PACT	The European Pharmacogenetics of Anticoagulation Therapy
COAG	The Clarification of Optimal Anticoagulation through Genetics
UI-Health	The University of Illinois Hospital & Health Sciences System

## SUMMARY

Recent clinical trial results cast doubt on the utility of genotype-guided warfarin dosing, specifically showing worse dosing with a pharmacogenetic versus clinical dosing algorithm in African Americans. However, trials did not include many genotypes important in African Americans. We aimed to determine if omission of the *CYP2C9*\*5, \*6, \*8, \*11 and rs12777823G>A genotypes affects performance of pharmacogenetic dosing algorithms in African Americans.

In a cohort of 274 warfarin-treated African Americans, we examined the association between *CYP2C9*\*5, \*6, \*8, \*11 and rs12777823G>A genotypes and warfarin dose prediction error with pharmacogenetic algorithms used in clinical trials. The warfarindosing.org algorithm over-estimated doses by a median (IQR) of 1.2 (0.02 to 2.6) mg/day in rs12777823 heterozygotes ( $p < 0.001$  for predicted versus observed doses), by 2.0 (0.6 to 2.8) mg/day with the rs12777823 A homozygotes ( $p = 0.004$ ), and by 2.2 (0.5 to 2.9) mg/day in carriers of a *CYP2C9* variant ( $p < 0.001$ ). The International Warfarin Pharmacogenetics Consortium (IWPC) algorithm under-dosed warfarin by 0.8 (-2.3 to 0.4) mg/day for patients with the rs12777823 GG genotype ( $p < 0.001$ ) and over-dosed warfarin by 0.7 (-0.4 to 1.9) mg/day in carriers of a variant *CYP2C9* allele ( $p = 0.04$ ). Modifying the warfarindosing.org algorithm to adjust for variants important in African Americans led to better dose prediction than either the original warfarindosing.org ( $p < 0.01$ ) or IWPC ( $p < 0.01$ ) algorithms.

These data suggest that, when providing genotype-guided warfarin dosing, it is important to account for variants prevalent in African Americans to avoid significant dosing error in this population.

## I. INTRODUCTION

Warfarin is one of the most commonly prescribed oral anticoagulants. However, its use is complicated by a narrow therapeutic index and wide inter-individual variability in dose requirements.(1) Numerous studies have consistently and unequivocally shown that genotype affects warfarin dose requirements.(2) Accordingly, guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommend dosing warfarin based on genotype when genetic information is available.(3) Guidelines further recommend using the International Warfarin Pharmacogenetics Consortium (IWPC) or [www.warfarindosing.org](http://www.warfarindosing.org) (WD) algorithm to assist with dosing.(4, 5)

Randomized, controlled trials evaluating the clinical utility of genotype-guided warfarin dosing were completed in late 2013, with varying results. The European Pharmacogenetics of Anticoagulation Therapy (EU-PACT) trial used a modified version of the IWPC algorithm to dose warfarin and showed that this approach was superior to conventional dosing in the homogenous European population. (6) The Clarification of Optimal Anticoagulation through Genetics (COAG) trial used the WD algorithm and found no benefit from dosing with a pharmacogenetic version of the algorithm compared to a clinical algorithm without genotypes in the ethnically diverse population where one-third of patients were African American.(7) In fact, African Americans were more likely to be overdosed with the pharmacogenetic approach.

Algorithms used in clinical trials were derived from mostly European populations, and genotyping was limited to the vitamin K epoxide reductase complex 1 (*VKORC1*) -1639

G>A (rs9923231), cytochrome P450 2C9 (*CYP2C9*) \*2 and *CYP2C9*\*3 polymorphisms.(4, 5, 8) While these are well recognized as the major genetic determinants of warfarin dose variability in Europeans,(9, 10)additional variants significantly contributed to dose requirements in African Americans.(11) Most notably, the *CYP2C9*\*5, \*6, \*8, and \*11 alleles, which occur almost exclusively in persons of African descent, significantly reduce warfarin clearance and dose requirements.(12-17)In a recent genome-wide association study (GWAS), the rs12777823 G>A variant emerged as an additional predictor of dose requirements in African Americans, with lower requirements in both minor allele heterozygotes and homozygotes.(18) Based on these data, we hypothesized that significant dosing error would occur from use of recommended warfarin pharmacogenetic dosing algorithms that include the *VKORC1* and *CYP2C9*\*2 and \*3 alleles only in persons of African descent who had the *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823 A allele. The objective of this study was to determine the effect of *CYP2C9*\*5, \*6, \*8, and \*11 alleles and the rs12777823G>A genotype on warfarin dose prediction with the IWPC and WD algorithms in African Americans.

## II. METHODS

### A. Study Population

Adult, warfarin-treated African Americans (by self-report) were enrolled from the University of Illinois Hospital & Health Sciences System (UI-Health), as previously described.<sup>(17)</sup> All patients were on a stable warfarin dose, defined as the dose that produced a therapeutic INR for  $\geq 2$  consecutive clinic visits  $\geq 14$  days apart. After obtaining written informed consent, a genetic sample (buccal cell or venous blood) was obtained and clinical data were collected from the electronic health record. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board.

## **B. Genotyping**

Genomic DNA was isolated from buccal cells or whole blood using a Puregene kit (Qiagen, Valencia, CA). The CYP2C9\*2 (p.R144C, rs1799853), \*3 (p.I359L, rs1057910), \*5 (p.D360E, rs28371686), \*6 (c.818delA, rs9332131), \*8 (p.R150H, rs7900194), \*11 (p.R335W, rs28371685), rs12777823 G>A, and VKORC1-1639 G>A genotypes were determined by PCR and pyrosequencing, as previously described.(17) The -1766 C>T (rs9332096) genotype was used to detect the CYP2C9\*8 allele because it is in strong linkage disequilibrium with R150H, and can be detected via pyrosequencing, whereas R150H cannot.(19) In addition, the -1766 C>T polymorphism decreases gene expression thereby contributing to the functional effects of the CYP2C9\*8 allele.(19) Individual genetic ancestry was determined in the majority of patients using 105 autosomal DNA ancestry informative markers, as previously described.(20)

### C. Statistical Analysis

The predicted warfarin maintenance dose was calculated for each patient using the IWPC and WD algorithms. Dose prediction error was defined as the predicted dose minus the observed (actual) dose. The correlation between dose prediction error and percent West African ancestry was assessed by Spearman correlation. Predicted doses and dose prediction error were compared between carriers and non-carriers of a *CYP2C9*\*5, \*6, \*8, and \*11 allele and between rs12777823 G>A genotype groups by the Kruskal-Wallis or Wilcoxon-Mann-Whitney *U* Test. Dose prediction error was also examined with *CYP2C9*\*8 alone, given how common it occurs in African Americans and with the rs12777823G>A genotype alone after excluding patients with a variant *CYP2C9*\*2, \*3, \*5, \*6, \*8, or \*11 allele. Additionally, Bland-Altman plots were created to visualize the amount of disagreement between predicted and actual doses. Finally, we tested whether adjusting doses predicted by the WD algorithm to account for the *CYP2C9*\*5, \*6, \*8, \*11, and rs12777823 variants would provide a more accurate means of dosing warfarin for African Americans. All statistical analyses were performed with the SAS software package, version 9.2 (SAS Institute, Cary, NC).

### III. RESULTS

A total of 274 African Americans on a stable warfarin dose were included. Patient characteristics and genotype frequencies are summarized in Table 1. Genotype frequencies were similar to those previously reported in persons of African descent.(16, 19) The mean observed warfarin maintenance dose was  $6.6 \pm 2.5$  mg/day in the study population. The IWPC algorithm predicted significantly lower doses ( $6.1 \pm 1.3$  mg/day;  $p < 0.0001$ ), and the WD algorithm predicted higher doses ( $7.2 \pm 1.8$  mg/day;  $p < 0.0001$ ) than that observed.

For 220 patients for whom individual genetic ancestry estimates were determined, the mean percent of West African ancestry was  $82 \pm 13\%$ . Percent West African ancestry was positively correlated with dose prediction error with the WD ( $r=0.148$ ,  $p=0.028$ ), but not IWPC ( $r=0.088$ ,  $p=0.194$ ) algorithm.

Observed and predicted doses, stratified by *CYP2C9* and rs12777823 genotypes, are shown in Tables 2 and 3. As previously reported, individuals with an *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823 A allele required significantly lower doses compared to those without a variant.(17, 18)The IWPC and WD algorithms predicted similar doses regardless of rs12777823 genotype. The IWPC algorithm also predicted similar doses regardless of *CYP2C9* genotype; however, the WD algorithm tended to predict higher doses in *CYP2C9* variant carriers versus non-carriers.

To examine the performance of the IWPC and WD algorithms by genotype, we compared observed and predicted doses within each genotype strata. There were

significant dose prediction errors by the *CYP2C9* (Table 2) and rs12777823 (Table 3) genotypes with both algorithms. The WD algorithm predicted higher doses than the IWPC algorithm across genotypes ( $p < 0.01$  for all *CYP2C9* and rs12777823 genotype groups). Both algorithms over-estimated doses for patients with a *CYP2C9*\*5, \*6, \*8, or \*11 variant. When limiting comparison to *CYP2C9*\*8 carriers and non-carriers, the WD algorithm over-estimated doses in \*8 carriers by a median (IQR) of 2.3 (0.4 to 3.0) mg/day ( $p < 0.001$ , for the predicted versus observed dose), while the IWPC algorithm had a dose prediction error of 1.0 (-1.3 to 1.9) mg/day ( $p = 0.13$ ).

For the rs12777823 genotype, the IWPC algorithm under-estimated doses for patients with the GG genotype by 0.8 mg/day, while the WD algorithm over-estimated doses by approximately 1 mg/day for heterozygotes and 2 mg/day for variant allele homozygotes. After excluding patients with a *CYP2C9* variant, the associations between the rs12777823 genotype and dose prediction error remained. Specifically, among 229 patients without a *CYP2C9*\*5, \*6, \*8, or \*11 allele, the IWPC algorithm under-dosed patients with the rs12777823 GG genotype ( $n = 147$ ) by 0.9 mg/day ( $p < 0.01$ ), and the WD algorithm over-dosed those with the rs12777823 GA or AA genotype ( $n = 82$ ) by 1.1 mg/day ( $p < 0.01$ ). Interestingly, when removing *CYP2C9* variant carriers, we noticed that disproportionately more patients with rs12777823A allele versus without an rs12777823A allele also had a *CYP2C9*\*5, \*6, \*8, or \*11 allele (78% versus 22%,  $p < 0.0001$ ), suggesting linkage disequilibrium among SNPs. We took into account when constructing the WD-African American model below.

Figures 1 and 2 show the level of disagreement between the IWPC and WD

predicted doses and observed doses, stratified by the *CYP2C9* and rs12777823 genotypes. The visual presentation of the individual data points further illustrates the extent to which the algorithms over- or under-estimated doses based on genotype. Specifically, the WD algorithm over-dosed warfarin by >1 mg/day in 64% of those with a *CYP2C9* variant and 70% of patients with the rs12777823 AA genotype. The IWPC over-dosed warfarin by >1 mg/day in 47% of *CYP2C9* variant allele carriers and under-estimated doses by >1 mg/day in 42% of those with the rs12777823 GG genotype.

Finally, we examined performance of the WD algorithm after adjusting for the *CYP2C9* and rs12777823 variants. The algorithm available through <http://www.warfarindosing.org> contains an option for inputting *CYP2C9*\*5 and \*6, which were added when present. The resultant dose was then reduced by 20% for the *CYP2C9*\*8 or \*11 allele, based on pharmacokinetic data,(14, 20) and by 7 mg/week for the rs12777823 AG genotype and 9 mg/week for the rs12777823 AA genotype, as suggested by Perera et al.(18) Since the rs12777823A and *CYP2C9*\*5, \*6, \*8, and \*11 allele tended to occur together, we only reduced doses for rs12777823G>A variant for patients without a *CYP2C9*\*5, \*6, \*8, or \*11 allele to avoid over-adjustment. The dose predicted by the new WD-African American (WD-AA) algorithm was  $6.6 \pm 1.8$  mg/day for the population overall, which was similar to the observed dose ( $p=0.97$ ), lower than the WD predicted dose ( $p=0.001$ ), and higher than the IWPC predicted dose ( $p=0.002$ ). The new algorithm performed better than the WD algorithm in *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823A allele carriers ( $p<0.0001$ ) and better than the IWPC algorithm in patients without a variant allele ( $p=0.0001$ ), as shown in Figures 3 and 4.

#### IV. DISCUSSION

We found that warfarin pharmacogenetic dosing algorithms used in recent clinical trials perform poorly in African Americans with the *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823 allele. Specifically, when including only the *VKORC1*, *CYP2C9*\*2, and *CYP2C9*\*3 genotypes in the WD algorithm, as done in the COAG trial, *CYP2C9*\*5, \*6, \*8,\*11, and rs12777823A allele carriers are significantly over-dosed, sometimes by 2 mg/day or more. The IWPC algorithm also over-dosed *CYP2C9*\*5, \*6, \*8,\*11 carriers, while it under-dosed rs12777823 G allele homozygotes.

The *VKORC1* -1639 G>A and *CYP2C9*\*2 and \*3 genotypes are widely believed to be the major genetic determinants of warfarin dose requirements across populations, as evident by dose recommendations based exclusively on these genotypes in the FDA-approved warfarin label and CPIC guidelines published in 2011.(3, 21)The CPIC guideline update is in progress and may address additional variants important in African Americans based on data that has emerged since the original guidelines were written. In particular, the novel association between the rs12777823 variant and dose requirements was discovered through a recent GWAS in African Americans. The rs12777823 polymorphism is located on chromosome 10 near the *CYP2C18* gene. The rs12777823A allele is associated with reduced *S*-warfarin clearance and lower dose requirements in African Americans.(18) Interestingly, while the allele is also common in Europeans and Asians, it is not associated with warfarin responses in these populations. As pointed out by authors of the GWAS, this is likely because the rs12777823 polymorphism is in linkage disequilibrium with one of more functional variants in African Americans, but not other groups. Our finding

that, compared to the rs12777823GG genotype, the rs12777823A allele occurred disproportionately more often with a *CYP2C9*\*5, \*6, \*8, or \*11 allele supports this. However, many African Americans have the rs12777823 variant in absence of a *CYP2C9*\*5, \*6, \*8, or \*11 allele, and they too require lower warfarin doses. In addition, we showed that the dosing error with the rs12777823 remains after controlling for *CYP2C9* variants. Therefore, the mechanism underlying associations with the rs12777823 genotype in African Americans is not solely due to linkage disequilibrium with *CYP2C9*\*5, \*6, \*8, and \*11, and remains to be further elucidated.

Additional data have also emerged with the *CYP2C9* variants since the original CPIC guidelines. Specifically, *in-vitro* and *in-vivo* studies have demonstrate lower S-warfarin clearance with the \*8 allele, which occurs in approximately 12% of African Americans.(14) Recent data also provide further evidence of reduced warfarin clearance and dose requirements with the \*5, \*6, and \*11 alleles.(20, 22)

While neither of the recent clinical trials genotyped for the *CYP2C9*\*5, \*6, \*8, \*11, or rs12777823 alleles, this was probably of no consequence in the EU-PACT trial, in which 99% of participants were European.(6) The EU-PACT trial demonstrated a significant improvement in time spent with the therapeutic INR range during the initial 12 weeks of warfarin therapy with genotype-guided versus conventional dosing. In contrast, the COAG trial, which was conducted in an ethnically diverse population, showed no difference in the time in range during the first 4 weeks of therapy with a pharmacogenetic versus clinical algorithm.(7) African Americans, who comprised approximately one-third of the COAG trial population, actually did worse when dosed with a pharmacogenetic algorithm, with a higher

likelihood of supra-therapeutic INR values with pharmacogenetic versus clinical algorithm-based dosing. Our data suggest that omission of the *CYP2C9*\*5, \*6, \*8, \*11 and rs12777823 genotypes was a major reason genotype-guided dosing performed poorly in African Americans. Specifically, the higher incidence of supratherapeutic anticoagulation with genotype-guided dosing in COAG is consistent with the over-estimation of doses we observed with the WD algorithm in *CYP2C9*\*5, \*6, \*8, \*11 and rs12777823 carriers, who likely comprised 50% of the African Americans COAG trial based on allele frequency data.

There are a couple of ways to account for the African-specific genotypes when dosing warfarin. One is to use an algorithm that contains these variants, such as that recently published by Hernandez et al.(23) Since most of the patients in the current study were included in the derivation cohort for Hernandez et al algorithm, it precluded non-biased evaluation of the algorithm in the current population. However, as described by Hernandez et al,(23) the therapeutic dose observed in an independent African American cohort was more highly correlated with the dose predicted with the novel algorithm ( $r=0.51$ ) than with the dose predicted by the IWPC pharmacogenetic algorithm ( $r=0.38$ ). Moreover, there was no significant difference between the mean predicted and observed doses with use of the novel algorithm in the validation cohort. In contrast, doses predicted with the IWPC algorithm varied significantly from actual, observed doses.

Another reasonable approach would be to calculate a dose with either the IWPC or WD algorithm, and then further modify the dose based on *CYP2C9* and rs12777823 genotypes. For example, Perera et al(18) suggest a further dose reduction of 7 mg/week with the rs12777823 GA genotype and 9 mg/week with the AA genotype. This approach

proved to provide a more accurate means of dosing warfarin in our patients, with no difference in observed and predicted doses with the WD-AA algorithm.

Evidence that the *CYP2C9*\*5, \*6, \*8, and \*11 and rs12777823 variants affect anticoagulation control, and particularly risk for over-anticoagulation and bleeding during warfarin initiation, would further support their consideration in warfarin dosing. Unfortunately, this could not be evaluated in the current study, as patients were past the warfarin initiation phase and had achieved stable and therapeutic dosing. However, there are previous data demonstrating an increased risk for over-anticoagulation and bleeding with *CYP2C9* polymorphisms.(24-26) Most relevant to this study, in a diverse population consisting of 50% African Americans, Limdi et al(25) reported a significantly higher risk for major hemorrhage with warfarin among carriers versus non-carriers of a *CYP2C9*\*2, \*3, \*5, \*6, or \*11 allele. Similar to these alleles, the rs12777823A and *CYP2C9*\*8 alleles are associated with reduced S-warfarin clearance, and thus, might be expected to have similar effects on bleeding risk.(14, 18, 20)

We focused on variants associated with lower warfarin dose requirements in the current study, partly to find an explanation for the higher risk for over-anticoagulation with use of recommended pharmacogenetic algorithms in African Americans.(7) However, it is important to point out that there are also variants that portend higher warfarin dose requirements in African Americans.(27, 28)Accounting for both low- and high-dose variants could further improve dosing.

In summary, our data indicate that, when dosing warfarin based on genotype, it is important to account for variants that are either common or specifically influence warfarin

response in African Americans and that not doing so can lead to significant over-dosing in a large portion of the African American population. Genotype-guided dosing has been shown to be of benefit in a European population for whom important variants are well defined.(6) The clinical utility of genotype-guided warfarin dosing in African Americans, when accounting for variants important in this population, remains to be determined.

**TABLE I**

**BASELINE DEMOGRAPHICS AND GENOTYPE FREQUENCIES**

Variable or genotype	n = 274
Age (years)	55 ± 16
Male sex	76 (28)
BSA (m <sup>2</sup> )	2.1 ± 0.3
Current smoker	47 (17)
Primary warfarin indication	
DVT or PE	150 (55)
Atrial fibrillation or flutter	38 (14)
Secondary stroke prevention	36 (13)
PVD	14 (5)
Heart valve replacement	17 (6)
Other*	19 (7)
Amiodarone use	7 (2.6)
CYP2C9 inducer <sup>†</sup> use	10 (3.7)
Genotype	
VKORC1-1639G>A	
GG	227 (82.9)
GA	45 (16.4)
AA	2 (0.7)
rs12777823 G>A	
GG	157 (57.3)
GA	97 (35.4)
AA	20 (7.3)
CYP2C9	
*1/*1	214 (78.1)
*1/*2	11 (4.0)
*1/*3	3 (1.1)
*2/*3	1 (0.4)
*2/*5	1 (0.4)
*2/*11	1 (0.4)
*1/*5	2 (0.7)
*1/*6	6 (2.2)
*1/*8	23 (8.4)
*1/*11	4 (1.5)
*5/*8	2 (0.7)
*8/*8	5 (1.8)
*8/*11	1 (0.4)
Mean ± SD or No. (%)	

\* left ventricular or right atrial thrombus, sinus thrombosis, cortical vein thrombosis

<sup>†</sup>phenytoin or carbamazepine

BSA, body surface area; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack; PVD, peripheral vascular disease

**TABLE II**

DOSING ERROR WITH PHARMACOGENOMIC ALGORITHMS BASED ON *CYP2C9*\*5, \*6, \*8, OR \*11 GENOTYPE

	<i>CYP2C9</i> *5, *6, *8, or *11		p value*
	Non-carrier (n=229)	Carrier (n=45)	
Dose (mg/day)			
Observed	6.4 (5.0 to 8.2)	5.0 (4.0 to 7.5)	0.0063
IWPC	6.0 (5.1 to 6.9) <sup>†</sup>	6.3 (5.4 to 6.9) <sup>§</sup>	0.2535
WD	7.0 (6.0 to 8.4) <sup>‡</sup>	7.7 (6.4 to 8.6) <sup>#</sup>	0.0559
Prediction error (mg/day)			
IWPC	-0.5 (-1.9 to 0.6)	0.7 (-0.4 to 1.9)	<0.0001
WD	0.5 (-0.9 to 1.6)	2.2 (0.5 to 2.9)	<0.0001
Median (IQR)			

\* Comparison between genotype groups

<sup>†</sup>p=0.005 for IWPC predicted versus observed dose in non-carriers

<sup>‡</sup>p=0.009 for WD predicted versus observed dose in non-carriers

<sup>§</sup>p=0.04 for IWPC predicted versus observed dose in carriers

<sup>#</sup>p<0.001 for WD predicted versus observed dose in carriers

**TABLE III****DOSING ERROR WITH PHARMACOGENOMIC ALGORITHMS BASED ON RS12777823 GENOTYPE**

	rs12777823 genotype			p value*
	GG (n=157)	GA (n=97)	AA (n=20)	
Dose (mg/day)				
Observed	6.8 (5.0 to 8.6)	5.7 (4.3 to 7.5)	5.2 (4.3 to 7.3)	0.0047
IWPC	6.0 (5.1 to 6.9) <sup>†</sup>	6.0 (5.3 to 7.0)	6.3 (4.9 to 6.8)	0.5803
WD	7.0 (5.9 to 8.3)	7.2 (6.3 to 8.6) <sup>‡</sup>	7.7 (6.2 to 8.5) <sup>§</sup>	0.1665
Prediction error (mg/day)				
IWPC	-0.8 (-2.3 to 0.4)	0.1 (-1.2 to 1.6)	0.7 (-0.4 to 1.5)	<0.0001
WD	0.3 (-1.4 to 1.4)	1.2 (0.02 to 2.6)	2.0 (0.6 to 2.8)	<0.0001
Median (IQR)				

\* Comparison between genotype groups

<sup>†</sup>p<0.001 for IWPC predicted versus observed dose with the GG genotype

<sup>‡</sup>p<0.001 for WD predicted versus observed dose with the GA genotype

<sup>§</sup>p=0.0036 for WD predicted versus observed dose with the AA genotype

Figure 1. Bland-Altman plots of the dose prediction error with the International Warfarin Pharmacogenetics Consortium (IWPC) and [www.warfarindosing.org](http://www.warfarindosing.org) (WD) algorithms stratified by rs12777823 G>A genotype

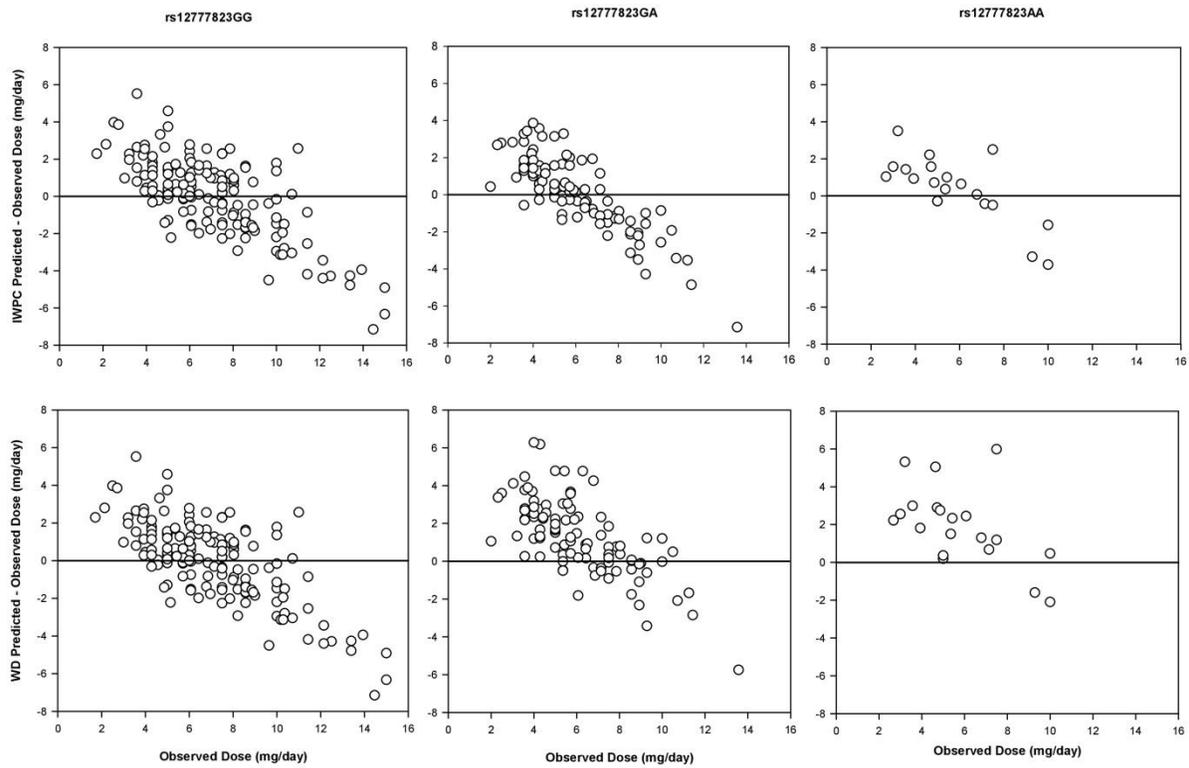


Figure 2. Bland-Altman plots of the dose prediction error with the International Warfarin Pharmacogenetics Consortium (IWPC) and [www.warfarindosing.org](http://www.warfarindosing.org) (WD) algorithms stratified by *CYP2C9*\*5, \*6, \*8, or \*11 carrier status

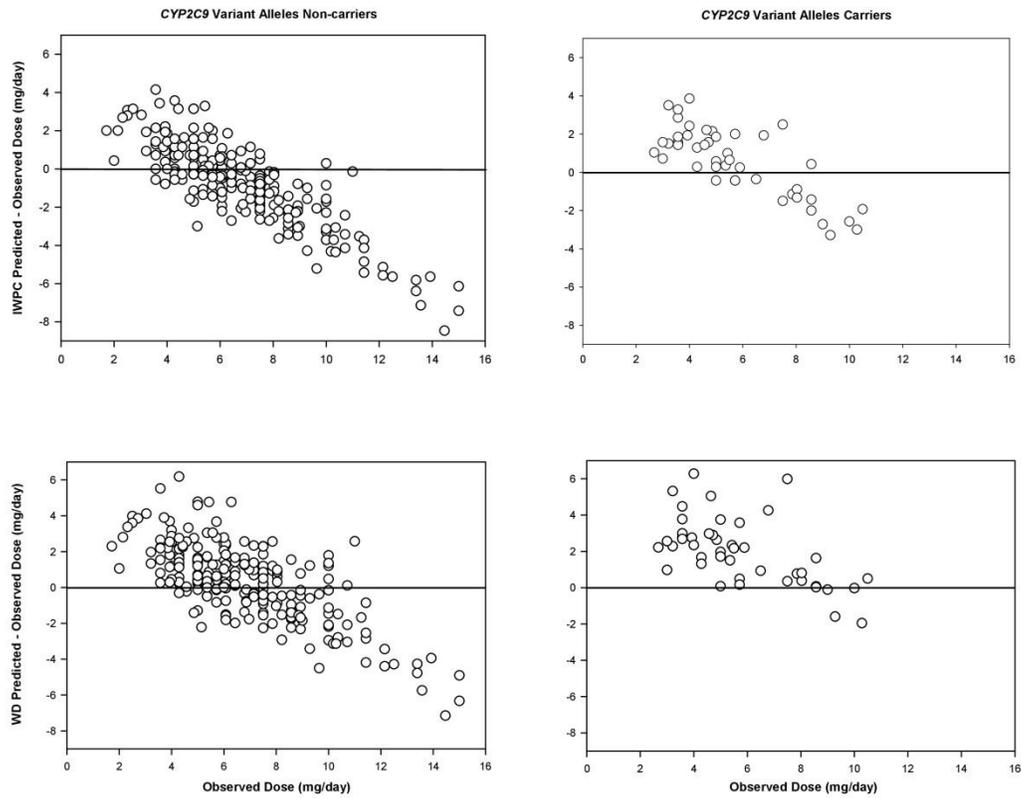


Figure 3. Observed and predicted doses with the International Warfarin Pharmacogenetics Consortium (IWPC), [www.warfarindosing.org](http://www.warfarindosing.org) (WD) and WD-African American (WD-AA) algorithms in carriers of the *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823A alleles carriers

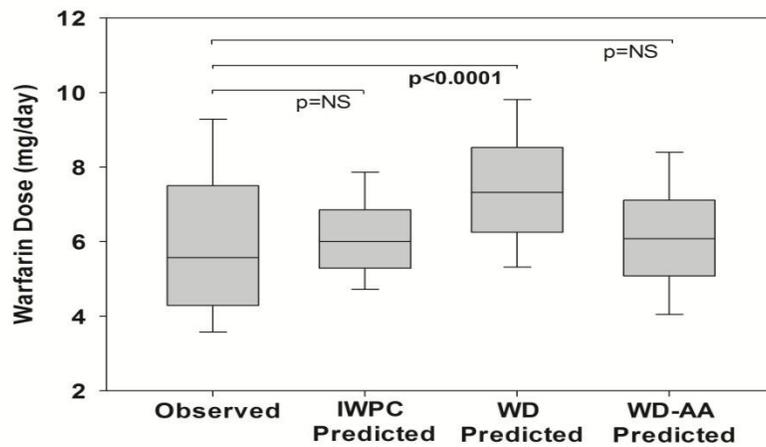
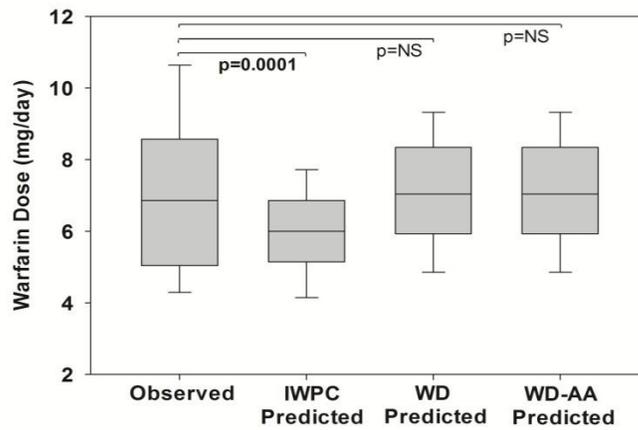


Figure 4. Observed and predicted doses with the International Warfarin Pharmacogenetics Consortium (IWPC), [www.warfarindosing.org](http://www.warfarindosing.org) (WD) and WD-African American (WD-AA) algorithms in non-carriers of the *CYP2C9*\*5, \*6, \*8, \*11 or rs12777823A alleles



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- (4) Klein, T.E. *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *The New England journal of medicine* **360**, 753-64 (2009).
- (5) Gage, B.F. *et al.* Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clinical pharmacology and therapeutics* **84**, 326-31 (2008).
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- (14) Liu, Y. *et al.* Decreased warfarin clearance associated with the CYP2C9 R150H (\*8) polymorphism. *Clinical pharmacology and therapeutics* **91**, 660-5 (2012).
- (15) Tai, G. *et al.* In-vitro and in-vivo effects of the CYP2C9\*11 polymorphism on warfarin metabolism and dose. *Pharmacogenetics and genomics* **15**, 475-81 (2005).
- (16) Limdi, N.A. *et al.* Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics* **9**, 511-26 (2008).
- (17) Cavallari, L.H. *et al.* Genetic and clinical predictors of warfarin dose requirements in African Americans. *Clinical pharmacology and therapeutics* **87**, 459-64 (2010).
- (18) Perera, M.A. *et al.* Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet* **382**, 790-6 (2013).
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- (20) Niinuma, Y. *et al.* Functional characterization of 32 CYP2C9 allelic variants. *The pharmacogenomics journal* **14**, 107-14 (2014).
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- (28) Voora, D. *et al.* A polymorphism in the VKORC1 regulator calumenin predicts higher warfarin dose requirements in African Americans. *Clinical pharmacology and therapeutics* **87**, 445-51 (2010).

## VITA

NAME KATARZYNA DROZDA

### EDUCATION

1996-2000 Medical Academy, Pharmacy Program  
Poznan, Poland

2001-2005 Pre-pharmacy  
Oakton Community College, Skokie IL

2006-2008 Pre-pharmacy  
William Rainey Harper College, Palatine IL

2008-2012 Doctor of Pharmacy,  
University of Illinois at Chicago, Chicago IL

2012-2014 Master of Science in Clinical and Translational Science, School  
of Public Health  
University of Illinois at Chicago, Chicago IL  
Thesis: "Poor Performance of Warfarin Pharmacogenomic  
Dosing Algorithms with Genotypes Important for African  
Americans"  
Advisors: Larisa Cavallari, Pharm.D. (Pharmacogenetics)  
Jack Zwanziger, Chair and Advisor  
Jeffrey R. Bishop, Pharmacogenetics  
Edith A. Nutescu, Pharmacy Systems, Outcomes  
and Policy  
Glen T. Schumock, Pharmacy Systems,  
Outcomes and Policy

### POST-DOCTORAL TRAINING

2012-2014 Cardiovascular and Psychiatric Pharmacogenomics Research  
Fellowship  
University of Illinois at Chicago, Chicago IL  
Advisor: Larisa H. Cavallari, Pharm.D., BCPS, FCCP  
Advisor: Jeffrey R. Bishop, Pharm.D., M.S., BCPP

## COURSES

05/27/2013 - 05/31/13 Montreal Spring School of Population Genomics and Genetic Epidemiology  
Montreal, Quebec, Canada

## LICENSURE AND CERTIFICATIONS

Licensure: Registered Pharmacist  
Illinois License No. 051.296068 (Issued 2012)

Certifications: APhA Pharmacy Based Immunization Delivery (2012-*present*)

## PROFESSIONAL APPOINTMENTS

1999 – 2000 Research Assistant  
Medical Academy, Poznan, Poland

2008 – 2009 Pharmacy Technician  
Del Lago Pharmacy, Wilmette IL

2010-2011 Research Assistant, Pharmacogenomics Laboratory  
University of Illinois at Chicago, Department of Pharmacy Practice, Chicago IL

2012-PRESENT Clinical Pharmacist, Warfarin Genetics Service  
University of Illinois Hospital & Health Sciences System, Chicago IL

## HONORS AND AWARDS

2008-2012 Dean's List of Outstanding Students,  
University of Illinois at Chicago, College of Pharmacy, Chicago

Spring 2012 W.E. van Doren Scholar,  
University of Illinois at Chicago, Department of Pharmacy Practice, Chicago IL

03/07/2014 Lundbeck Award for Excellence in Research,  
Scientific Poster Session Award Winner- 3rd Place in Post-doctoral Category

University of Illinois at Chicago, College of Pharmacy, Chicago IL

03/19/2014

The American Society for Clinical Pharmacology and Therapeutics (ASCPT),  
The 2014 Presidential Trainee Award

The American Society for Clinical Pharmacology and Therapeutics 2014 Annual Meeting, Atlanta GA

## PROFESSIONAL AFFILIATIONS

The Institute of Human Genetics, University of Illinois at Chicago, Chicago IL  
2011- present  
The American College of Clinical Pharmacy  
2011- present  
The American Society for Clinical Pharmacology and Therapeutics  
2013- present

## RESEARCH GRANTS

### Completed

Summer 2010

Source: University of Illinois at Chicago, College of Pharmacy  
Summer 2010

Title: David J. Riback 2010 Summer Research Fellowship

Project Title: Clinical and functional significance of the CYP2C9\*8 allele.

Time Period: May 2010 through August 2010

Amount: \$6,000 (\$5,000 student stipend plus \$1000 research costs)

Preceptor: Larisa H. Cavallari, PharmD., FCCP, BCPS

## PUBLICATIONS

1. Liu Y, Jeong HY, Takahashi H, **Drozda K**, Patel SR, Shapiro NL, Nutescu EA, Cavallari LH. Decreased warfarin clearance with the *CYP2C9* R150H (\*8) polymorphism. *Clin Pharmacol Ther.* 2012;91(4):660-5. Referenced in the Human Cytochrome P450 (CYP) Allele Nomenclature Database (www.cypalleles.ki.se.)
2. Cavallari LH, Vaynshteyn D, Freeman KM, Wang D, Perera MA, Takahashi H, **Drozda K**, Patel SR, Jeong H. *CYP2C9* promoter region single-nucleotide polymorphisms linked to the R150H polymorphism are functional suggesting their role in *CYP2C9*\*8-mediated effects. *Pharmacogenet Genomics.* 2013;23(4):228-31.
3. Daneshjou R, Tatonetti NP, Karczewski KJ, Sagreiya H, Bourgeois S, **Drozda K**, Burmester JK, Tsunoda T, Nakamura Y, Kubo M, Tector M, Limdi NA, Cavallari LH, Perera M, Johnson JA, Klein TE and Altman RB. Pathway analysis of genome-wide data improves warfarin dose prediction. *BMC Genomics.* 2013;14(3):1-12.
4. **Drozda K**, Labinov Y, Jiang R, Thomas MR, Wong SS, Patel S, Nutescu EA, Cavallari LH. A Pharmacogenetics service experience for pharmacy students, residents, and fellows. *Am J Pharm Educ.* 2013;77(8):1-10.
5. Nutescu EA, **Drozda K**, Bress AP, Galanter WL, Stevenson J, Stamos TD, Desai AA, Duarte JD, Gordeuk V, Peace D, Kadkol SS, Dodge C, Saraf S, Garofalo J, Krishnan JA, Garcia JGN, Cavallari LH. Feasibility of implementing a comprehensive warfarin pharmacogenetics service. *Pharmacotherapy.* 2013. doi: 10.1002/pharm.1329 [Epub ahead of print].
6. Daneshjou R, Cavallari LH, Karczewski KJ, **Drozda K**, Perera M, Johnson JA, Klein TE, Altman RB. Novel variant in protein S association with venous-thromboembolism in African Americans. *J Thromb Haemost.* 2013. [Submitted].
7. **Drozda K**, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy.* 2014. doi: 10.1002/phar.1398. Invited review.
8. **Drozda K**, Wong S, Patel S, Bress AP, Nutescu EA, Kittles RA, Cavallari LH. Poor Performance of Warfarin Pharmacogenomic Dosing Algorithms with Genotypes Important for African Americans. [Submitted].
9. Lee YM, Eggen J, Soni V, Patel S, **Drozda K**, Cavallari LH. Case report; Association of *CYP2C9* \*1/\*14 with lower warfarin dose requirement. [Submitted].

## ABSTRACTS AND SCIENTIFIC PRESENTATIONS

1. Cavallari L, **Drozda K**, Perera M, Patel S, Shapiro N, Nutescu E, Stamos T. Association between *CYP2C9* promoter region variants and warfarin dose requirements in African Americans. *Clin Pharmacol Ther* 2011;89 (Suppl 1):S77 (#PIII-33). Poster presentation at the 2011 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Dallas, TX. March 2011.
2. **Drozda K**, Takahashi H, Patel SR, Shapiro NL, Nutescu EA, Cavallari LH. Association between the *CYP2C9\*8* variant and warfarin clearance in African Americans. *Pharmacotherapy* 2011;31:436e (#459). Poster presentation at the 2011 Annual Meeting of the American College of Clinical Pharmacy. Pittsburgh, PA. October 17, 2011.
3. Perera MA, Daneshjou R, Gamazon ER, Hillenmeyer S, Karczewski K, Klein TE, Langae T, **Drozda K**, Patel S, Johnson JA, Cavallari LH, Altman RB. Folylpolylglutamate synthetase (*FPGS*) and warfarin: discovery of genes outside of *CYP2C9* and *VKORC1* through exome analysis. Platform presentation at the Pharmacogenomics Research Network Scientific Meeting, University of Chicago, Chicago IL. April 2013.
4. **Drozda K**, Nutescu EA, Bress AP, Galanter WL, Stevenson JM, Duarte JD, Cavallari LH. Description and feasibility of a comprehensive warfarin pharmacogenetics service. *Pharmacotherapy* 2013;33(10)e289. Poster presentation at the 2013 Annual Meeting of the American College of Clinical Pharmacy. Albuquerque, NM. October 14, 2013.
5. Duncan MK, Bress AP, Cavallari LH, Nutescu E, **Drozda K**, Galanter WL. Clinical decision support for initial dosing of warfarin and promotion of pharmacogenetic testing. Presented at the American Medical Informatics Association 2013 Annual Symposium. Washington, DC. November 16-22, 2013.
6. McDowell M, Patel R, Duarte J, Garofalo J, **Drozda K**, Galanter WL, Stamos T, Gordeuk V, Lee J, Krishnan J, Cavallari LH, Nutescu EA. The impact of a pharmacist guided pharmacogenetics service on prediction of warfarin stable dose. Presented at the 2013 Annual Meeting of the American Society of Health-System Pharmacists. Orlando, FL. December 8-12, 2013.
7. Lee YM, **Drozda K**, Stevenson J, Nutescu EA, Cavallari LH. Clinical factors affecting time to target INR in genotyped-guided warfarin dosing of inpatients. Presented at the 2013 Annual Meeting of the American Society of Health-System Pharmacists. Orlando, FL. December 8-12, 2013.

8. **Drozda K**, Wong S, Patel S, Nutescu EA, Cavallari LH. Effects of African-specific genetic variations on performance of warfarin pharmacogenetic dosing algorithms. To be presented at the 2014 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Atlanta, GA. March 18-22, 2014. **ASCPT 2014 Presidential Trainee Award.**
9. **Drozda K**, Patel R, Lee YM, Stamos T, Galanter WL, Nutescu EA, Cavallari LH. Influence of cytochrome P450 2C9 and vitamin K epoxide reductase variants on time to achieve first therapeutic international normalized ratio with warfarin. Presented at University of Illinois College of Pharmacy Research Day. Chicago, IL. March 7, 2014. **Scientific Poster Session Award Winner- 3<sup>rd</sup> Place in Post-doctoral Category.**
10. Relja L, **Drozda K**, Patel S, Sarapas C, Katz A, Shankman SA, Bishop JR. Effects of the *CACNA1C* variant on psychophysiological measures of emotion regulation. Presented at University of Illinois College of Pharmacy Research Day. Chicago, IL. March 7, 2014.
11. Rompelman G, Romadin K, **Drozda K**, Nutescu EA, Cavallari LH. Genetic effects on time to reestablish a post-procedural therapeutic anticoagulation with warfarin. Presented at University of Illinois College of Pharmacy Research Day. Chicago, IL. March 7, 2014.
12. Lee YM, **Drozda K**, Duarte J, Nutescu EA, Cavallari LH. Pharmacogenetic-guided warfarin dosing in patients with a *CYP2C9\*6* allele. Presented at University of Illinois College of Pharmacy Research Day. Chicago, IL. March 7, 2014.

## TEACHING

PMPR 355: Seminar in Pharmacy Research, 1 credit hour course (elective).

Role: Teaching Assistant,

Enrollment – 40 P1 to P2 students on the Chicago and Rockford campuses.

PMPR 355: Seminar in Pharmacy Research, 1 credit hour course (elective).

Role: Lecturer,

Provide one lecture hour on “Warfarin pharmacogenetics in African Americans”.

Provide one lecture hour on “Performance of warfarin pharmacogenomic dosing algorithms based on genotypes important for African Americans”.

PMPR 380/390: Undergraduate Research in Pharmacy Practice, 1 to 3 credit hours (elective).

Role: Instructor for practical experience in clinical and basic science research.

Enrollment – up to 5 P1 to P3 students per semester.

PMPR 388: Advanced Pharmacy Practice Specialty Experience, 4 credit hours (elective).  
Role: Co-preceptor for pharmacogenetics clerkship experience.  
Enrollment – 1 to 2 P4 students per 6 week rotation.

## SOFTWARE SKILLS

SAS 9.2, Plink, Stata, R