Review Article

Precision Medicine in Everyday Practice: A Focus on Antithrombotic Therapy

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Precision medicine is an approach to patient care that utilizes genetic, environmental and lifestyle factors.[3-5] In recent years, genetic testing has become an important factor in better understanding a disease state and allowing for personalized drug therapy regimens. While the term precision medicine is newer to healthcare, the ideas behind it have been around for decades. For example, a laboratory identifies a patient's blood type before administering donated blood to ensure a proper match; likewise, a surgeon orders a crossmatching test before an organ transplant to prevent rejection. Precision medicine is becoming increasingly present in areas such as oncology and rare diseases, and it respects the fact that no two patients are alike, and no two patients are guaranteed to respond exactly the same to a treatment.

One area of this growing field of healthcare includes the study of genetic polymorphisms in drug metabolism enzymes such as cytochrome P450 (CYP) enzymes.[6,7] These enzymes are involved in the chemical modification of molecules so that the body can safely excrete substances such as drugs, toxins, and naturally-occurring bodily byproducts. Variations, or polymorphisms, of these enzymes naturally occur among the population due to genetic differences which, in turn, affect the functioning of the enzymes. As a result, patients may be classified as poor, intermediate, normal, rapid or ultrarapid metabolizers for a specific enzyme and substrate pair which can have profound effects on drug therapy. For example, a poor metabolizer may require a lower dose of a given drug, and if given a standard dose meant for an intermediate or extensive metabolizer, toxicities can potentially develop.[8] Conversely, if the drug is a prodrug which requires an activation step, a poor metabolizer may require a higher dose in order to produce enough of the active drug.[8] This phenomena is known as a drug-gene interaction and is one important facet of precision medicine.

The appeal and resources for precision medicine are quickly growing not just among healthcare professionals, but also among the government and businesses. In 2015, President Obama launched the Precision Medicine Initiative which resulted in the creation of the All of Us Research Program conducted by the National Institutes of Health (NIH).[1,2] Companies now offer direct-to-consumer genetic testing which provides individuals with information on genetic health risks and carrier status for genetic variants. There are also many public resources available that provide information on gene-drug associations. The Pharmacogenomics

Common Genetic Terms

- **Pharmacogenomics =** often used interchangeably with pharmacogenetics, the study of genetic effects on drug safety and efficacy
- **Polymorphism =** a DNA variation that normally occurs in >1% of the population
- **Allele =** any of the alternative or variant forms of a gene
- **Cytochrome P450 (CYP) =** a group of genes that produce various cytochrome P450 (CYP) enzymes which are involved in the metabolism of both endogenous and exogenous molecules
- **Drug-gene interaction =** an effect on drug safety or efficacy due to one or more specific genetic polymorphisms

Precision Medicine Initiatives

Precision Medicine Initiative[1]

- Launched by President Obama in 2015
- Created to better understand how environment, lifestyle and genetics affect disease prevention and treatment with a long-term goal of implementing precision medicine in all healthcare areas

All of Us[2]

- Research program conducted by the National Institutes of Health and funded by the Precision Medicine Initiative
- Intends to collect data from one million or more people in the United States regarding lifestyle, environment and biology
- Will allow researchers to access a database to gain insight into how variables affect disease prevention, progression and treatment

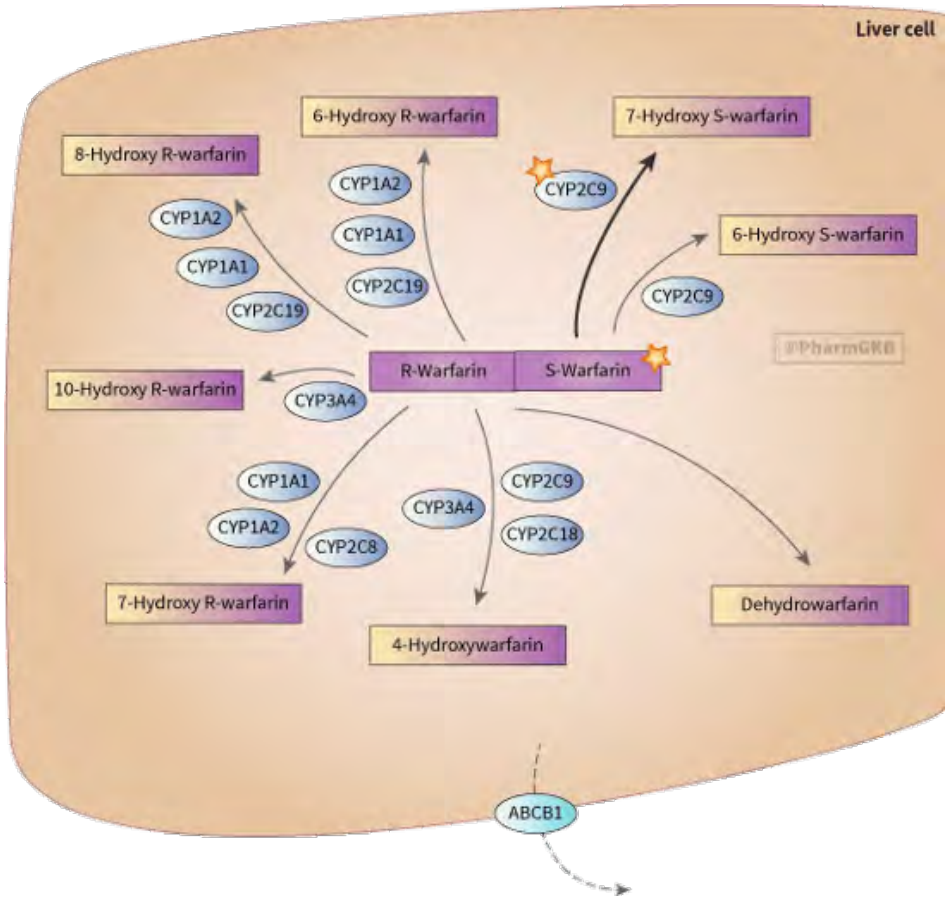
Knowledgebase (PharmGKB), which is managed by Stanford University and funded by the NIH, provides detailed scientific information for gene-drug associations.[9] Genetic Home Reference, created by the U.S. National Library of Medicine, aims to educate the public regarding genetics and disease.[10] Lastly, the Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international group of volunteers and staff and publishes peer-reviewed, evidence-based pharmacogenetic practice guidelines that are based on a totality of evidence approach. These guidelines are easily accessible to healthcare professionals via the CPIC website.[11]

As mentioned above, several companies have chosen to take advantage of the public's growing interest in genetics and precision medicine, and there are now several direct-to-consumer home-based genetic testing kits available. As an example, 23andMe provides an FDA approved pharmacogenetic report for 33 polymorphisms across 8 drug metabolizing genes, including genes involved in warfarin and clopidogrel metabolism.[12] This report can inform individuals of a potential risk for a drug-gene interaction. Since retail pharmacies such as CVS and Walgreens sell these kits, it is likely that direct-to-consumer genetic testing will only become more popular. No matter how pharmacogenetic test results are obtained, it is important that pharmacists are able to help patients interpret the results of these tests. Pharmacists also need to understand the validity and clinical utility of direct-to-consumer genetic testing. This is no easy task considering how rapidly this field is evolving, but PharmGKB and CPIC guidelines can be useful resources for pharmacists to interpret genetic results for drug metabolizing genes.

Precision medicine represents a growing opportunity for pharmacists, but there remain barriers to implementation.[13,14] At this time, there is a lack of guidance for clinical application of pharmacogenetic test results, and many clinicians have been slow to embrace the new concept. Some may even view genetic-based dosing as futile since various studies have shown patients to have similar clinical outcomes with and without it, while other studies have shown patients to have superior outcomes with specialized dosing. Although testing costs continue to decrease, there exists concern and confusion regarding reimbursement. While Wisconsin institutions such as Marshfield Clinic Research Institute and Medical College of Wisconsin have already implemented many CPIC guidelines, most others have not, and it is difficult to say how these organizations would be able to bill for such services.

Genetic testing can be completed for two common antithrombotic drugs, warfarin and clopidogrel. These medications can have severe clinical implications for patients (i.e. bleeding or clotting events) if they are not managed and monitored appropriately. In the next section, we will explore two case studies to better understand the advantages, drawbacks and practicality of precision medicine related to these medications.

FIGURE 1. Depiction of the Enzymes Involved in the Metabolism of Warfarin



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Warfarin

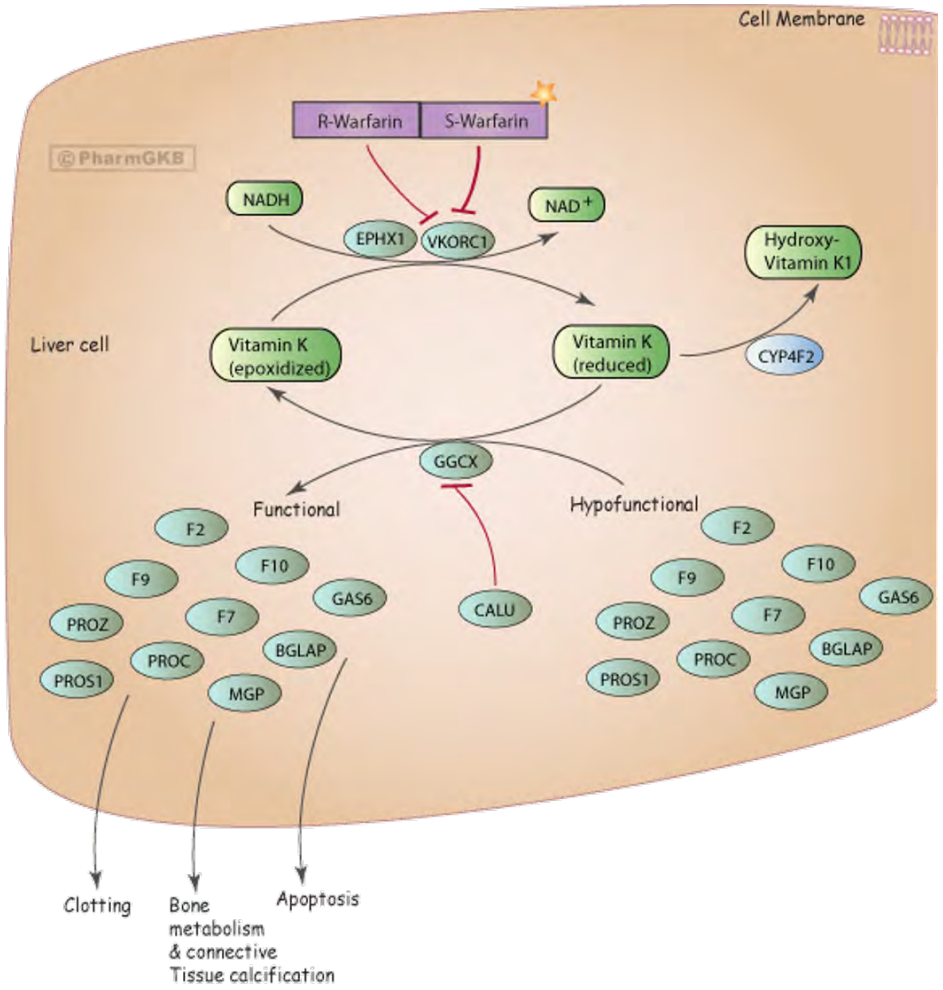
Case Report

A 74-year-old female with a history of atrial fibrillation, hypertension, and other comorbidities was started on 2 mg per day of warfarin due to a recurrence of atrial fibrillation.[15] The patient had reported a previous "hypersensitivity" to warfarin six years earlier. Three days after warfarin initiation, the patient's international normalized ratio (INR) was 1.4, and the dose was maintained. However, on day 9 the patient's INR was 9.1. Warfarin was stopped and vitamin K therapy was initiated. Over the course of several weeks, the patient experienced intermittent hemorrhages with several rounds of vitamin K therapy being necessary.

Metabolism

Warfarin, an anticoagulant used for prophylaxis and treatment of thromboembolic disorders and events arising from conditions such as atrial fibrillation, valvular replacement, or venous

FIGURE 2. Illustration of the Role of CYP4F2 in the Conversion of Vitamin K



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thromboembolism, is most commonly taken orally in an outpatient setting. The drug decreases the body's ability to clot by blocking vitamin K epoxide reductase (VKOR) which results in less active vitamin K1 and reduced clotting ability for factors II, VII, IX and X.[16] Warfarin is a racemic mixture of two enantiomers, S and R. The S-enantiomer is responsible for 60-70% of warfarin's anticoagulation effect and is mainly metabolized by CYP2C9 (Figure 1).[17] The R-enantiomer is comparatively less potent and is metabolized primarily by CYP1A2, CYP2C19 and CYP3A4.[17] Due to its diverse metabolism and nature of being a narrow therapeutic index drug, warfarin is prone to many drug-drug, drug-disease and drug-food interactions which may be augmented by inherent genetic differences. This can make initial dosing rather difficult even when using objective patient information such as age, weight and organ function.[18]

VKORC1

Vitamin K epoxide reductase complex subunit 1(VKORC1) is an enzyme not belonging to the CYP family that resides in the liver and converts forms of vitamin K in order to activate clotting factors.[19] VKORC1 is targeted by warfarin to reduce the amount of active vitamin K in the body, and may account for 30% of the variance in warfarin dosing due to polymorphisms.[20] One notable polymorphism, allele VKORC1 -1639G>A, is associated with lower dose requirements and tends to occur most frequently in Caucasian and Asian patients.[20]

CYP2C9

CYP2C9 is major metabolic pathway that metabolizes the S-warfarin enantiomer as mentioned above. CPIC recommends testing patients for CYP2C9 variant alleles (level A, prescribing based upon genetic information recommended) and provides appropriate initial doses.[21] The most common decreased function alleles include CYP2C9*2 and CYP2C9*3 and are most likely to be found in Caucasians of European ancestry.[21] These intermediate or poor metabolizers may require an increased amount of time (>2 to 4 weeks) to reach maximum INR effect and also a lower initial dose to decrease the risk of bleeding.[22,23]

CYP4F2

CYP4F2 is a lesser known and minor pathway which removes active vitamin K from warfarin's metabolic pathway (Figure 2).[24] One of the most common variant alleles of CYP4F2 is *3 which is associated with a higher warfarin dose requirement.[25] This allele is more likely to be found among Asians, Caucasians, Hispanics, and Ashkenazi Jews and least likely to be found in African Americans.[26]

Clinical Application

Studies comparing genotype-guided warfarin dosing to conventional warfarin dosing have provided mixed results for clinical and pharmacoeconomic benefit, and this topic remains controversial.[27] These mixed results could be due to differences in study design including differences in patient demographics, choice of genotypes for screening, dosing algorithms used, defining adverse events and type of health care system (e.g. United States vs United Kingdom or European Union).[27] However, most meta-analyses comparing genotype-guided warfarin dosing to conventional dosing suggest that genotype-guided dosing offers better results for many clinical outcomes.[28-30] Currently, the 2012 CHEST guidelines do not recommend routine pharmacogenetic testing for warfarin, although one could argue that these guidelines should likely be revisited given new data and changes in genetic test pricing since then. If pharmacogenomic test results are available, they should be considered for determining the initial warfarin dose (Figure 3).

FIGURE 3. Table 1 of the FDA-approved Package Insert for Warfarin Sodium[31]

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

Case Report

Conclusion

The patient agreed to genetic testing and was found to be CYP2C9*3/*3 and VKORC1 c.-1639 AA (rs9923231).[15] Given the genotype guided dosing table in Figure 3, it is debatable whether having this information would have made a difference when deciding on the initial starting dose. However, considering the severity of this particular genotype, a more cautious starting dose and titration may have been used. After a period of time, this patient restarted warfarin treatment at 0.5 mg twice a week and slowly titrated up to 0.5 mg daily over the next three months to achieve a therapeutic INR.[15]

Clopidogrel

Case Report

A 57-year-old, previously healthy male, presented to the hospital and was diagnosed with a myocardial infarction.[32] He was taken to the catheterization lab and a successful percutaneous coronary intervention (PCI) was completed with a drug-eluting stent (DES). Prior to the procedure, he was loaded with aspirin and clopidogrel 600mg which was followed by clopidogrel 75mg daily and aspirin. One week later, an elective PCI was performed to insert another DES in a different coronary artery. Three days later, the patient returned to the hospital with severe chest pain and in cardiogenic shock. Coronary angiography showed blockage in both stents that were placed, which were classified as in-stent thromboses.

Metabolism and Polymorphisms

Clopidogrel is an antiplatelet pro-drug used to reduce the risk of thrombotic events post-stent placement and myocardial infarction.[33] Although clopidogrel is generally very effective, recurrence of thrombotic events can occur. One reason could be due to inadequate platelet inhibition arising from polymorphisms and drug interactions.

CYP2C19

CYP2C19 is a major metabolic pathway for clopidogrel. Two allele variants, CYP2C19*2 and CYP2C19*3 result in loss of enzyme function and reduced enzyme function, respectively.[34] Since clopidogrel is a pro-drug, patients carrying these alleles produce less active drug, require higher doses to prevent clots, and are considered poor metabolizers.[34] These alleles accounted for 85% of the loss of function in Caucasians and 99% in Asians, putting these patients at risk of thromboembolic events.[35] Asian populations are the most likely group to be classified as poor metabolizers with about 14% fitting this category, as compared to 2% of Caucasians and 4% of African Americans.[35] Poor metabolizers are recommended by the 2013 CPIC guidelines to receive an alternative antiplatelet medication such as prasugrel or ticagrelor as these are not metabolized by CYP2C19.[34]

On the other hand, patients who smoke could have an increased effect from clopidogrel and risk for bleeding, commonly referred to as the "smoker's paradox."[36,37] Smoking induces CYP1A2 and CYP2B6 which are involved in the conversion of clopidogrel to the active metabolite.[37] This is a weaker interaction; thus, this pharmacogenomic interaction is not used frequently in clinical practice when using genetic testing results.

Clinical Application

A study conducted by the University of Florida analyzed the outcomes of 1,815 patients who received genetic testing for CYP2C19 variants at the time of a cardiac procedure.[38] Thirty percent of patients were found to have a polymorphism that resulted in a decreased efficacy of clopidogrel; consequently, these patients were prescribed a different, appropriate dose that reduced the percentage of death, heart attacks or strokes by nearly half.[38] Furthermore, a study in a community pharmacy setting found that when pharmacists recommended clopidogrel dose changes for patients with a variant allele of CYP2C19, prescribers were very receptive; however, reimbursement for this service proved to be a challenge.[39] In 2010, the FDA approved a boxed warning for patients with two loss of function alleles of CYP2C19, stating that the efficacy of clopidogrel depends upon the enzyme's ability to covert the drug to its active metabolite, and these patients should consider using a different P2Y12 inhibitor.[40] This FDA warning is aligned with current CPIC guidelines. However, the 2014 ACC/AHA guidelines do not recommend routine genetic testing for CYP2C19 alleles.[41]

Case Report

Conclusion

The patient agreed to genetic testing and was found to be CYP2C19*1/*2.[32]

Clopidogrel was discontinued, and the patient was started on prasugrel therapy as recommended in the CPIC guidelines.[34]

Role and Resources for Pharmacists

While it is apparent that many genetic differences exist among the population which can result in drug-gene interactions and different dosing requirements, it is not entirely clear how testing for these genetic differences will have an impact on patient outcomes. Implementing genetic testing in both inpatient and outpatient settings has already begun, and with direct to consumer genetic testing kits and the All of Us Research Program, the popularity is likely to increase. A common barrier to this is cost, but while genetic testing may seem expensive, so are adverse events from incorrect medication doses. It's important to note that genetic-based dosing would not be necessary for all drugs and patients, and the largest benefit would be seen in cases of drugs with narrow therapeutic indexes and those that carry possible serious implications for patients if not dosed appropriately.

PharmGenEd offers an evidence-based program including web-based and live presentations and written articles for healthcare professionals to learn more about pharmacogenomics and how to implement it into their practice.[42] Additionally, CPIC has curated an extensive list of pharmacogenomic guidance to help healthcare professionals understand precision medicine and interpret test results.[11]

Precision medicine can be useful in personalizing patient care. Challenges remain in assessing clinical utility and navigating reimbursement, but progress is being made in confronting these issues. While there may be downsides to genetic testing and practicality issues, precision medicine offers pharmacists an exciting and excellent opportunity to not only broaden their scope of practice, but also provide the best possible care.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

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References

1. NIH. What is the Precision Medicine Initiative? https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative. Published April 2015. Accessed October 29, 2019.
2. NIH. All of Us and Precision Medicine. https://allofus.nih.gov/about/all-us-research-program-overview. Published 2019. Accessed October 29, 2019.
3. Ashley EA. Towards precision medicine. *Nat Rev Genet.* 2016;17(9):507-522.
4. Ginsburg GS, Phillips KA. Precision medicine: from science to value. *Health Aff (Millwood)*. 2018;37(5):694-701.
5. Joyner MJ, Paneth N. Promises, promises, and precision medicine. *J Clin Invest*. 2019;129(3):946-948.
6. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. *PLoS One*. 2013;8(12):e82562.
7. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012;92(4):414-417.
8. NIH. Cytochrome P450. https://ghr.nlm.nih.gov/primer/genefamily/cytochromep450. Accessed October 29, 2019.
9. Barbarino JM, Whirl-Carrillo M, Altman RB, Klein TE. PharmGKB: a worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med*. 2018;10(4):e1417.
10. NIH. Genetics Home Reference. https://ghr.nlm.nih.gov/. Accessed October 29, 2019.
11. CPIC. Clinical Pharmacogenetics Implementation Consortium. https://cpicpgx.org/. Accessed October 29, 2019.
12. Bonner L. 23andMe releases pharmacogenomics test that doesn't require prescription. *Pharmacy Today.* 2019;25(1):1.
13. Borden BA, Galecki P, Wellmann R, et al. Assessment of provider-perceived barriers to clinical use of pharmacogenomics during participation in an institutional implementation study. *Pharmacogenet Genomics*. 2019;29(2):31-38.
14. Lam YW. Scientific challenges and implementation barriers to translation of pharmacogenomics in clinical practice. *ISRN Pharmacol*. 2013;2013:641089.
15. Johnson M, Richard C, Bogdan R, Kidd R. Warfarin dosing in a patient with CYP2C9(*)3(*)3 and VKORC1-1639 AA Genotypes. *Case Rep Genet*. 2014;2014:413743.
16. StatPearls. In:2019.
17. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. *Pharmacol Ther*. 1997;73(1):67-74.
18. Herman D, Locatelli I, Grabnar I, et al. Influence of CYP2C9 polymorphisms, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. *Pharmacogenomics J*. 2005;5(3):193-202.
19. NIH. Genetics Home Reference: VKORC1 gene. https://ghr.nlm.nih.gov/gene/VKORC1. Published 2019. Accessed November 20, 2019.
20. Fung E, Patsopoulos NA, Belknap SM, et al. Effect of genetic variants, especially CYP2C9 and VKORC1, on the pharmacology of warfarin. *Semin Thromb Hemost*. 2012;38(8):893-904.
21. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther*. 2017;102(3):397-404.
22. Higashi MK, Veenstra DL, Kondo LM, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA*. 2002;287(13):1690-1698.
23. Horne BD, Lenzini PA, Wadelius M, et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. *Thromb Haemost*. 2012;107(2):232-240.
24. NIH. Genetics Home Reference: CYP4F2 gene. https://ghr.nlm.nih.gov/gene/CYP4F2. Published 2019. Accessed November 20, 2019.
25. Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. *Blood.* 2008;111(8):4106-4112.
26. Scott SA, Khasawneh R, Peter I, Kornreich R, Desnick RJ. Combined CYP2C9, VKORC1 and CYP4F2 frequencies among racial and ethnic groups. *Pharmacogenomics.* 2010;11(6):781-791.
27. Pirmohamed M. Warfarin: the end or the end of one size fits all therapy? *J Pers Med*. 2018;8(3).
28. Kheiri B, Abdalla A, Haykal T, et al. Meta-analysis of genotype-guided versus standard dosing of vitamin K antagonists. *Am J Cardiol.* 2018;121(7):879-887.
29. Tse G, Gong M, Li G, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol*. 2018;84(9):1868-1882.
30. Shi C, Yan W, Wang G, Wang F, Li Q, Lin N. Pharmacogenetics-based versus conventional dosing of warfarin: a meta-analysis of randomized controlled trials. *PLoS One*. 2015;10(12):e0144511.
31. Warfarin sodium [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2017.
32. Rademakers LM, Dewilde W, van de Kerkhof D. Early double stent thrombosis

associated with clopidogrel hyporesponsivenesss. *Neth Heart J.* 2012;20(1):38-41.
33. NIH. Medline Plus: Clopidogrel. https://medlineplus.gov/druginfo/meds/a601040.html. Accessed October 29, 2019.
34. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013;94(3):317-323.
35. Martis S, Peter I, Hulot JS, Kornreich R, Desnick RJ, Scott SA. Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. *Pharmacogenomics J*. 2013;13(4):369-377.
36. Bliden KP, Dichiara J, Lawal L, et al. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. *J Am Coll Cardiol.* 2008;52(7):531-533.
37. Desai NR, Mega JL, Jiang S, Cannon CP, Sabatine MS. Interaction between cigarette smoking and clinical benefit of clopidogrel. *J Am Coll Cardiol.* 2009;53(15):1273-1278.
38. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2018;11(2):181-191.
39. Ferreri SP, Greco AJ, Michaels NM, et al. Implementation of a pharmacogenomics service in a community pharmacy. *J Am Pharm Assoc (2003)*. 2014;54(2):172-180.
40. Holmes DR, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation*. 2010;122(5):537-557.
41. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344-e426.
42. Lee KC, Ma JD, Hudmon KS, Kuo GM. A train-the-trainer approach to a shared pharmacogenomics curriculum for US colleges and schools of pharmacy. *Am J Pharm Educ*. 2012;76(10):193.