



Pharmacogenomics In Pharmacy Practice: Current Perspectives

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Abstract: Pharmacogenomics (i.e., the application of genetic information in predicting an individual's response to drug therapy) plays an increasingly important role in drug development and decision-making regarding precision medicine. This has been shown to reduce the risk of adverse events and improve patient health-care outcomes through targeted therapies and dosing. As the field of pharmacogenomics rapidly evolves, the role of pharmacists in the education, implementation, and research applications of pharmacogenomics is becoming increasingly recognized. This paper aims to provide an overview and current perspectives of pharmacogenomics in contemporary clinical pharmacy practice and to discuss the future directions on advancing pharmacogenomics education, application, and research in pharmacy practice.

Keywords: pharmacogenomics, pharmacy practice, precision medicine, pharmacist role

Introduction

Precision medicine refers to the use of genetic, environmental, lifestyle, and other unique patient or disease characteristics to guide drug selection and dosage. It is also highlighted as personalized medicine or precision health. Pharmacogenetics/pharmacogenomics (PGX) as a discipline is part of precision medicine and personalized healthcare. PGX uses genetic information to predict subject's response to a medication (i.e., responders vs nonresponders to a medication), and to determine patients likely to experience adverse events of the medication, and the optimal drug dose.¹

It was not until the completion of the human genome project that major advancements have been achieved in PGX and its role in improving the quality of health care.² Over the last two decades, PGX started to get integrated in drug development and clinical treatment decisions.³ Drug manufacturers and other pharmaceutical research laboratories have begun to screen different molecules to determine if they undergo metabolism through highly polymorphic pathways before proceeding to full-blown efficacy and safety evaluations.⁴ In addition, drug regulatory agencies have developed recommendations and guidelines to promote and regulate the clinical application of PGX.^{5,6} The US' Food and Drug Administration (FDA) currently endorses a broad list of approved drug labels carrying PGX-related information and recommendations.⁷

However, the integration and clinical application of PGX into clinical practice is not without challenges. For example, health-care practitioners' knowledge and experience in PGX application has been shown to remain lagging behind. In recent years, accreditation and educational councils as well as professional pharmacy organizations have begun advocating for PGX education in colleges' curricula.⁸ Another important

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challenge that is still facing the implementation and application of PGX in clinical practice is the limited availability of rapid genetic tests and the inability of health-care providers to use these tests.^{9,10} Other barriers include perceived lack of adequate evidence for the clinical utility of PGX test; lack of access to the test; data security and protection of personal information; cultural and religious belief; and limited resources.^{11–13} Examples of required resources may include financial resources, infrastructure, qualified staff to provide the PGX service, and proper platform to store and interpret the genetic data.

Pharmacist's role in patient care has evolved and become the cornerstone in different specialties such as pharmacokinetics, anticoagulation, antimicrobial stewardship, and medication therapy management (MTM).^{14–17} The knowledge and skills of clinical pharmacists in pharmacokinetics and pharmacodynamics of drugs give them an advantage to take the lead and provide clinical services in the evolving area of PGX. In a statement draft on the pharmacist's role in clinical PGX, the American Society of Health-System Pharmacists (ASHP) highlighted the ability of clinical pharmacist to lead interprofessional efforts to develop guidelines and protocols and to initiate PGX services.¹⁶ Different institutions have already initiated pharmacist-managed clinical PGX programs.^{16,18} Therefore, the potential role of pharmacist in the integration of PGXs into pharmacy practice is becoming increasingly important. The purpose of this paper is to provide an overview and current perspectives of PGX in contemporary clinical pharmacy practice. The paper also discusses the future directions on advancing PGX education, application, and research in pharmacy practice.

Pharmacist Role In Providing Pharmacogenomics Service

As PGX continues to evolve, the emerging discipline will play a significant role in drug development and treatment decision-making in clinical practice. Pharmacists currently lead PGX services that tailor patients' drug therapy using genetic information.^{19,20} In their work with pharmaceutical manufacturers, FDA, and other regulatory authorities, pharmacists play a major role to incorporate PGX data and apply this information into the drug development, drug labeling, and approval processes.²¹ With these advancements, new innovations and processes are needed to effectively integrate these PGX data into clinical practice.²²

In parallel, the role of pharmacist in collaborative care through MTM and other platforms has equally emerged in

the last few decades.^{16,23} The potential role of the pharmacists in integrating PGX data into clinical practice for the purpose of personalizing medicines and improving patient care outcomes is becoming increasingly important.^{16,23,24} This will require certain action plans, including, but not limited to, engagement with key stakeholders, establishing appropriate electronic health record (EHR) infrastructure, connectivity into the EHR, and demonstrating the evidence of benefit and value for pharmacist-involved PGX service.²⁵ In addition, understanding the potential barriers and system limitations to the implementation of PGX service and establishing effective infrastructure for the service will be necessary for successful implementation and for PGX to achieve its full potential.^{22,26}

Pharmacy profession has started defining its role and approaches to effectively integrate this evolving field into clinical pharmacy practice through professional pharmacy organizations. One strategy for implementation of PGX in pharmacy practice is through MTM, a service that is provided in diverse care settings and that is proven to optimize therapeutic outcomes for individual patients.²⁷ Therefore, MTM provides a unique opportunity for pharmacists to integrate PGX into clinical practice and to actively engage in collecting or ordering, interpreting, reporting, and utilizing PGX data to improve patient care outcomes including safety, quality, and effectiveness of medication therapy.²⁴

Although experts and researchers have proposed the integration of PGX testing into MTM to improve treatment outcomes and to reduce the risk of adverse events, little research has been done to demonstrate the benefit or value of this service integration.^{27–29} One pilot study aiming to assess the feasibility and satisfaction of patients with MTM plus PGX testing service in a cardiology outpatient clinic in the USA found that PGX testing incorporated into a pharmacist-delivered MTM service was feasible and that patients were very satisfied with the service.³⁰ Given the apparent lack of sufficient evidence of the effectiveness of PGX delivery models in MTM, this study has provided a preliminary evidence of benefit regarding the incorporation of PGX in MTM service. Haga et al have discussed the challenges to the integration and delivery of PGX testing in MTM services including, but not limited to, the timing of and access to PGX testing, extended MTM sessions, information technology and limited access to EHR, training/competence and workforce, and issues surrounding reimbursement of MTM services.³⁰

Pharmacists are uniquely positioned to guide optimal drug selection and dosing based on PGX testing.¹⁶ Therefore, pharmacists have an essential responsibility to make sure that testing is done when appropriate and that the results are utilized to optimize patients' medication therapy.²⁴ This implies that pharmacists share responsibility with other health-care providers such as physicians, laboratory scientists, and genetic counselors. The ASHP has published a position statement in 2015 highlighting the responsibilities and functions of pharmacists in PGX.³¹ According to the ASHP position statement, any clinical PGX service should include the following responsibilities: (1) promoting rational and routine use of PGX testing; (2) interpreting test results and communicating with patients and other health-care professionals; (3) optimization of medication therapy based on test results; (4) providing information on clinical application of PGX to health-care professionals, patients, and the public; and (5) contributing in PGXs research and other platforms concerned with the integration and application of PGX into clinical practice. The statement further provided recommendations for pharmacists' functions in PGX. The functions depend on the level of training, education, experience, and the practice setting. For example, it is recommended that all pharmacists should have a basic understanding of PGX, which should enable them to undertake some basic PGX functions, while pharmacists having specialized or advanced training, education, or experience in PGX should assume additional functions. For more information on pharmacists' responsibilities and functions for PGX, please refer to the ASHP position statement on the pharmacist's role in clinical PGX.³¹

Similarly, the American College of Clinical Pharmacy (ACCP) White Paper on integrating PGX into clinical pharmacy practice has articulated the real-world clinical applications of precision pharmacotherapy with a focus on the evolving field of clinical PGX.²⁵ This paper stresses that clinical pharmacists play an instrumental role in the implementation, education, and research applications of PGX. It further provides recommendations on how the ACCP can advance the implementation, education, and research application of clinical PGX.

Overall, pharmacists can play an invaluable role in leading the implementation of PGX in clinical practice and to lead the judicious use of PGX data for improving outcomes of care in health-care institutions.^{16,25,26} Academic pharmacy programs and professional pharmacy bodies such as ACCP and ASHP are well positioned to

implement curricula changes and to advance pharmacy students' and pharmacists' knowledge and skills in clinical PGX and precision pharmacotherapy.^{16,22,23,25,26,31}

Successful Examples Of Clinical Implementation Of Pharmacogenetic Testing In Pharmacy Practice

PGX has been widely studied in cardiovascular medicine. Clopidogrel and warfarin were among the most successful drugs that showed effect of genetic variants on clinical outcomes associated with these drugs.

Clopidogrel

Clopidogrel is the most widely used P2Y₁₂ inhibitor worldwide especially in the prevention of thrombotic events in patients with acute coronary syndrome (ACS) and/or stroke.^{32–34} Nevertheless, not all patients respond to clopidogrel therapy adequately. This interpatient variability may compromise both efficacy and safety.³⁵ Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits the purinergic P2Y₁₂ receptor and thus platelet aggregation for the platelet's life span. Fifteen percent of the prodrug gets activated while the remaining 85% are deactivated by esterases (Scott, Sangkuhl et al 2013). A wide variety of CYP enzymes contribute to the two-step bioactivation process of the clopidogrel; however, genetic studies showed that CYP2C19 mutations have the most pronounced effect on clopidogrel interindividual variability.³⁶ The wild-type CYP2C19*1 allele yields functional CYP2C19 enzyme with normal metabolism. Based on the genetic variants, most common mutations in CYP2C19 are classified into CYP2C19 no function allele *2 (c.681G>A; rs4244285); CYP2C19 no function allele *3 (c.636G>A; rs4986893); and CYP2C19*17 gain-of-function allele (c.-806C>T; rs12248560). While both CYP2C19*2 and *17 carriers are considered common among different ethnicities ranging from ~12–35% for *2 and ~3–21% for *17, CYP2C19*3 is very rare among all populations except Asians where it can reach 10%. Most of the PGX studies have found an association between CYP2C19 genetic variants and response to Clopidogrel.³⁷

The association between CYP2C19 genotype and cardiovascular outcomes in post-ACS and/or post-percutaneous coronary intervention (PCI) patients was studied in three main studies.^{38–40} In TRITON-TIMI 38 trial, carriers of CYP2C19 no function allele treated with clopidogrel were

at increased risk of major adverse cardiovascular events (MACE) (death from cardiovascular causes, myocardial infarction [MI], or stroke) when compared with noncarriers (HR 1.53, 95% CI 1.07–2.19, $P=0.01$) and the risk of stent thrombosis increased in the CYP2C19 no function allele carriers (HR 3.09, 95% CI 1.19–8.00, $P=0.02$).³⁹ In a subsequent study, a secondary analysis was performed to estimate the benefit of prasugrel compared to clopidogrel in subgroups defined by CYP2C19 genotype, using results from the published genetic sub-study and the overall TRITON-TIMI 38 trial.⁴¹ Carriers of the no function alleles had a reduction in the risk of the MACE outcome with prasugrel when compared to clopidogrel [RR 0.57, 95% CI 0.39–0.83]. However, there was no significant difference in the risk of MACE outcome when prasugrel and clopidogrel were compared in CYP2C19 extensive metabolizers (RR 0.98; 95% CI 0.80–1.20). Another study that was conducted by Collet and colleagues in young patients (<45 years) treated with clopidogrel for secondary prevention after MI found that CYP2C19*2 was the major predictor of MACE which included death, MI, and urgent coronary revascularization (HR 3.69, 95% CI 1.69–8.05, $P=0.0005$).³⁸ A third study that was conducted by FAST-MI Investigators suggested that the risk of MACE (death from any cause, nonfatal stroke, or MI) among clopidogrel-treated patients with two CYP2C19 no function alleles was higher than in those with the wild-type allele (HR 1.98, 95% CI 1.10–3.58).⁴⁰ In 2009, the first genome-wide association study with clopidogrel was published and it showed a significant association between CYP2C19*2 genotype and reduced platelet response.⁴² Additionally, during 1 year of follow-up, carriers of CYP2C19*2 variant were at higher risk of cardiovascular ischemic event or death (HR 2.42, 95% CI 1.18–4.99, $P=0.02$).

As a result of this accumulating evidence, Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for CYP2C19 Genotype and Clopidogrel Therapy. In this guideline, CYP2C19 genotype was grouped into four main phenotype categories and recommendations were made accordingly. The categories are ultrarapid (*1/*17, *17/*17); extensive (*1/*1); intermediate (*1/*2, *1/*3, *2/*17); and poor (*2/*2, *2/*3, *3/*3) metabolizers.⁶ Based on the reduced efficacy reported for both CYP2C19 intermediate and poor metabolizers, CPIC recommends using an alternative antiplatelet treatment (e.g., prasugrel or ticagrelor) for patients with these phenotypes.⁶ FDA, on the other hand, released a “boxed warning” regarding the CYP2C19 poor metabolizers and

the associated cardiovascular risk but mentioned that routine testing is not yet recommended.⁴³

One may argue that studying clopidogrel PGX is not that important, since we can use the more potent P2Y12 blockers (prasugrel and ticagrelor) that are also less likely to be associated with interpatient variability.^{44–46} However, studies have shown that clopidogrel is still the most commonly prescribed antiplatelet.⁴⁷ This may be due to its reasonable price which may enhance patient adherence. Additionally, clopidogrel is associated with lower bleeding risk compared to prasugrel and ticagrelor.^{48,49}

To date, the PHARMCLO trial is the largest trial that evaluated the bedside genotyping in selecting the appropriate antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) and the associated outcomes in patients with ACS (majority of which underwent PCI).⁵⁰ Only 888 participants were enrolled; then, the study was stopped prematurely because of “lack of in vitro diagnosis certification” for the genotyping instrument (ST Q3). Data from this study showed a lower risk of the primary outcome (composite of cardiovascular death and nonfatal MI, nonfatal stroke, and major bleeding) in the genotype-guided arm versus the standard care. However, the early termination of the study left it underpowered. IGNITE is another multicenter observational study that assessed MACE outcome (death, MI, or stroke) after the implementation of CYP2C19 genotype-guided approach in selecting the appropriate antiplatelet therapy after PCI. The study found that carriers of CYP2C19 no function alleles who were prescribed clopidogrel versus alternative therapy were at increased risk of cardiovascular outcomes (HR 2.26, 95% CI 1.18–4.32, $P=0.013$).¹⁹

In addition to clinical studies, several studies assessed the cost-effectiveness of applying genotype-guided antiplatelet therapy compared to the universal use of antiplatelet therapy in patients with MI. Majority of these pharmacoeconomic evaluations have shown that implementing genotype-guided antiplatelet therapy, followed by a targeted administration of the expensive ticagrelor or prasugrel in CYP2C19 no function allele carriers and clopidogrel in noncarriers is the most cost-effective approach compared to the universal use of antiplatelets.^{51–54}

However, powered randomized clinical trials are still needed to determine the effectiveness of routine CYP2C19 genetic testing for clopidogrel therapy in ACS patients. Currently, there are two ongoing clinical trials to address this need which are TAILOR-PCI and the POPular Genetics study.^{55,56}

Warfarin

For more than half a century, warfarin has been the cornerstone oral anticoagulant medication used in the treatment and prevention of various thromboembolic conditions.⁵⁷ Warfarin is a vitamin K antagonist that inhibits the vitamin K cycle by binding to the oxidized vitamin K epoxide reductase (VKOR) and prevents the reduction of vitamin K.^{58,59} Reduced vitamin K is essential for the activation of the coagulation factors (II, VII, IX, and X), in addition to proteins C and S. Consequently, coagulation factors with impaired activity are produced in the liver which leads to a state of anticoagulation. Warfarin is administered as a racemic mixture of two enantiomers (*R* and *S*) in almost equal proportions. The *S* isomer is mainly metabolized by the cytochrome P450 family 2 subfamily C polypeptide 9 (CYP2C9) and it is five times more potent than the *R* isomer but has faster clearance.⁶⁰ Among the most important drawbacks of warfarin is its narrow therapeutic index which can mediate serious bleeding adverse events that can even lead to hospitalization and death.^{61,62} Another disadvantage is the inter- and intra-patient variability in the dose required to achieve the optimal anticoagulation response. Dose requirements can vary from 0.5 mg to 20 mg per day.⁶³ Various studies showed that genetic and nongenetic factors contribute to warfarin dose variability.⁶⁴⁻⁶⁶ The most important genes affecting warfarin dose among different populations are the *CYP2C9* – a gene that codes for CYP2C9 enzyme which metabolizes and eliminates the more potent *S* enantiomer of warfarin, and *VKORC1* – a gene that codes for the VKOR which is the enzyme inhibited by warfarin.^{64,65} CYP4F2, an enzyme that metabolizes vitamin K, has also mutations in the gene coding for its enzyme that may play a role in warfarin dose variability but to a limited extent and not consistent among all populations.^{67,68} As such, the FDA updated the drug label for warfarin with PGX information in 2007.⁶⁹

In 2009, the International Warfarin Pharmacogenetics Consortium reported that the PGX algorithm they developed from clinical characteristics (warfarin indication, target international normalized ratio [INR], height, and weight), demographic characteristics (gender, age, and concurrent medications), and genetic information of over 4000 patients has helped to create a dosing algorithm for estimating the appropriate initial dose of warfarin. In this algorithm, the presence of the following led to reduction in the maintenance warfarin dose: VKORC1 polymorphism (1639/3673 G>A by 28% per allele, CYP2C9*3 by 33% per allele, CYP2C9*2 by

19% per allele), the age by 7% per decade, amiodarone use by 22%, and race by 9% for African American race. On the other hand, the presence of the following increased the required maintenance dose: body surface area by +11% per 0.25 m², target INR by 11% per 0.5 unit increase, smoker status by 10%, and current thrombosis by 7%. This study concluded that algorithms incorporating genetic variants (*CYP2C9* and *VKORC1*) can improve dose prediction compared with algorithms based solely on clinical and demographic factors.⁷⁰

The Clarification of Optimal Anticoagulation through Genetics (COAG) and the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) are two landmark trials that aimed to evaluate the utility of warfarin genotype-guided dosing.^{71,72} Results from both trials were not consistent with each other. COAG trial showed no benefit of genetic-guided dosing, compared to clinical dosing while EUPACT did. Furthermore, COAG found that the percent time in therapeutic range (PTTR) was significantly lower in blacks in the genetic-guided arm compared to the clinical dosing arm.⁷¹ This is possibly due to the fact that blacks may have other less common variants affecting warfarin dose that were not well represented in the genetic algorithm used in the COAG trial.⁷³ The EU-PACT study, on the other hand, compared PGX-based dosing versus fixed-dose strategy and was performed in a predominantly white population from Europe.⁷² Recently, a third landmark trial – Genetics-InFormatics Trial (GIFT) – also tested the utility of warfarin pharmacogenetic-guided dosing.⁷⁴ The PGX dosing algorithm used included genotypes for CYP2C9*2 and *3, CYP4F2*3, and VKORC1-1639. The primary endpoint was a composite of major bleeding, INR \geq 4, venous thromboembolism, or death. GIFT indicated that genotype-guided dosing could improve the composite outcome of efficacy and safety. Of the participants, 10.8% had at least one composite endpoint in the genotype-guided arm, compared to 14.7% in the clinical arm, resulting in an absolute risk difference of 3.9% (95% CI, 0.7–7.2; P=0.02). There was also an improvement in the mean PTTR (54.7% vs 51.3%, P=0.003) in the genotype-guided group compared to the clinical group.

While the performance of genetic testing prior to warfarin initiation is not recommended in evidence-based practice guidelines, it may be worth considering to use genetic data if available prior to warfarin initiation.⁶³ Guidance on the exact algorithm to use and race-specific recommendations are provided through different PGX

working groups.^{75,76} Another important aspect is the increasing use of direct oral anticoagulants (DOACs) as a replacement for warfarin. However, due to cost, contraindications (major renal impairment), and harm, when used for certain indications (valvular replacement, anti-phospholipid antibody syndrome), warfarin is still considered a very important option when choosing an oral anticoagulant. As such, genetics may be used as a guide to choose warfarin versus DOACs in addition to its use to tailor warfarin dosing. Patients with high-risk genotypes (carriers of variants associated with very low or very high warfarin dose) may benefit from DOACs in a cost-effective way. This, however, remains to be tested.

Future And Challenges Of Pharmacogenomics

It is well documented in the literature that the application of pharmacogenomics in clinical practice has resulted in improving the efficacy and minimizing the untoward effects of several drugs. A recent paper has provided an overview of the evolution of pharmacogenomics in clinical pharmacy practice and the advancement of its implementation, education, and research (Hicks, Aquilante, Dunnenberger et al 2019).²⁵ The authors believe that future implementation models of pharmacogenomics and precision pharmacotherapy will include the integration of the “omics” (epigenomics, transcriptomics, proteomics, and metabolomics) information. Undoubtedly, these advances will require health information technology (i.e., health informatics) solutions and effective EHR systems.²⁷ With the revolution in whole-genome sequencing and tremendous drop in its cost, genetic data are expected to be present at the tip of our fingers. Data storage, quality checking, mapping and integration with EHRs remain the biggest challenges. In addition, ethical, legal, and social concerns should be taken very seriously to avoid any discrimination against individuals based on their DNA. With increasing recognition of the value of precision pharmacotherapy and its implementation in many practice settings, more outcome-based studies are needed in order to quantify the impact on health outcomes. Furthermore, advanced pharmacist functions in applying pharmacogenomics in clinical practice may require specialized education, training, and relevant experiences.^{77,78} More pharmacogenomic courses and content are likely to be seen in the curricula of colleges of pharmacy and certification programs globally.^{77,78} Given the need for infrastructure, resources, and capacity building, the application and implementation

of PGX in clinical practice may be slow in resource-constrained environments.

Conclusion

Pharmacists can and should play an integral role in applying PGX into clinical practice to improve both the quality and safety of health care.

Disclosure

The authors report no conflicts of interest in this work.

References

- Shi MM, Bleavins MR, de la Iglesia FA. Pharmacogenetic application in drug development and clinical trials. *Drug Metab Dispos.* 2001;29(4 Pt 2):591–595.
- Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature.* 2001;409(6822):860–921.
- Feero WG, Guttmacher AE, Collins FS. Genomic medicine—an updated primer. *N Engl J Med.* 2010;362(21):2001–2011. doi:10.1056/NEJMr0907175
- Kleyn PW, Vesell ES. Genetic variation as a guide to drug development. *Science.* 1998;281(5384):1820–1821. doi:10.1126/science.281.5384.1820
- Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther.* 2011;90(4):625–629. doi:10.1038/clpt.2011.185
- 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. doi:10.1038/clpt.2013.105
- FDA. Table of pharmacogenomic biomarkers in drug labeling. FDA. Available from: <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>. Published 2015. Accessed January 23, 2015.
- Streetman DS. Emergence and evolution of pharmacogenetics and pharmacogenomics in clinical pharmacy over the past 40 years. *Ann Pharmacother.* 2007;41(12):2038–2041. doi:10.1345/aph.1K273
- Gurwitz D, Zika E, Hopkins MM, Gaisser S, Ibarreta D. Pharmacogenetics in Europe: barriers and opportunities. *Public Health Genomics.* 2009;12(3):134–141. doi:10.1159/000189625
- Lee JW, Aminkeng F, Bhavsar AP, et al. The emerging era of pharmacogenomics: current successes, future potential, and challenges. *Clin Genet.* 2014;86(1):21–28. doi:10.1111/cge.2014.86.issue-1
- Stanek EJ, Sanders CL, Taber KA, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther.* 2012;91(3):450–458. doi:10.1038/clpt.2011.306
- Tamaoki M, Gushima H, Tsutani K. Awareness survey of parties involved in pharmacogenomics in Japan. *Pharmacogenomics.* 2007;8(3):275–286. doi:10.2217/14622416.8.3.275
- McMahon T, Tucci J. The perceptions of pharmacists in Victoria, Australia on pharmacogenetics and its implications. *Pharm Pract (Granada).* 2011;9(3):141–147.
- Ratanajamit C, Kaewpibal P, Sethhawacharavanich S, Faroongsarn D. Effect of pharmacist participation in the health care team on therapeutic drug monitoring utilization for antiepileptic drugs. *J Med Assoc Thai.* 2009;92(11):1500–1507.
- Elewa HF, DeRemer CE, Keller K, Gujral J, Joshua TV. Patients satisfaction with warfarin and willingness to switch to dabigatran: a patient survey. *J Thromb Thrombolysis.* 2014;38(1):115–120. doi:10.1007/s11239-013-0976-y

16. Owusu-Obeng A, Weitzel KW, Hatton RC, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. *Pharmacotherapy*. 2014;34(10):1102–1112. doi:10.1002/phar.2014.34.issue-10
17. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159–177. doi:10.1086/510393
18. Nutescu EA, Drozda K, Bress AP, et al. Feasibility of implementing a comprehensive warfarin pharmacogenetics service. *Pharmacotherapy*. 2013;33(11):1156–1164. doi:10.1002/phar.2013.33.issue-11
19. Cavallari LH, Lee CR, Beitelshes 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. doi:10.1016/j.jcin.2017.07.022
20. Shuldiner AR, Palmer K, Pakyz RE, et al. Implementation of pharmacogenetics: the University of Maryland personalized anti-platelet pharmacogenetics program. *Am J Med Genet C Semin Med Genet*. 2014;166(1):76–84. doi:10.1002/ajmg.c.v166.1
21. Drozda K, Pacanowski MA, Grimstein C, Zineh I. Pharmacogenetic labeling of FDA-approved drugs: a regulatory retrospective. *JACC Basic Transl Sci*. 2018;3(4):545–549. doi:10.1016/j.jacbs.2018.06.001
22. Johnson JA. Pharmacogenetics in clinical practice: how far have we come and where are we going? *Pharmacogenomics*. 2013;14(7):835–843. doi:10.2217/pgs.13.52
23. Gregory Feero W, Kuo GM, Jenkins JF, Rackover MA. Pharmacist education in the era of genomic medicine. *J Am Pharm Assoc*. 2012;52(5):e113–e121. doi:10.1331/JAPhA.2012.12149
24. Swen J, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte— an update of guidelines. *Clin Pharm Therapeut*. 2011;89(5):662–673. doi:10.1038/clpt.2011.34
25. Hicks JK, Aquilante CL, Dunnenberger HM, et al. Precision pharmacotherapy: integrating pharmacogenomics into clinical pharmacy practice. *JACCP*. 2019;2(3):303–313.
26. Zakinova A, Long-Boyle JR, French D, et al. A practical first step using needs assessment and a survey approach to implementing a clinical pharmacogenomics consult service. *JACCP*. 2019;2(3):214–221.
27. Owen JA. Integrating pharmacogenomics into pharmacy practice via medication therapy management: American Pharmacists Association. *J Am Pharm Assoc*. 2011;51(6):e64–e74. doi:10.1331/JAPhA.2011.11543
28. Gervasini G, Benítez J, Carrillo JA. Pharmacogenetic testing and therapeutic drug monitoring are complementary tools for optimal individualization of drug therapy. *Eur J Clin Pharmacol*. 2010;66(8):755–774. doi:10.1007/s00228-010-0857-7
29. Relling M, Klein T. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. *Clin Pharm Therapeut*. 2011;89(3):464–467. doi:10.1038/clpt.2010.279
30. Haga SB, Moaddab J, Mills R, Patel M, Kraus W, Allen LaPointe NM. Incorporation of pharmacogenetic testing into medication therapy management. *Pharmacogenomics*. 2015;16(17):1931–1941. doi:10.2217/pgs.15.124
31. American Society of Health System Pharmacists. ASHP statement on the pharmacist's role in clinical pharmacogenomics. *Am J Health Syst Pharm*. 2015;72(7):579–581. doi:10.2146/sp150003
32. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. *Cleve Clin J Med*. 2011;78(4):243–257. doi:10.3949/ccjm.78a.10145
33. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008;39(5):1647–1652. doi:10.1161/STROKEAHA.107.189063
34. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411–2420. doi:10.1001/jama.288.19.2411
35. Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease—implications for personalized medicine. *Pharmacol Rev*. 2013;65(3):987–1009. doi:10.1124/pr.112.007252
36. Sangkuhl K, Klein TE, Altman RB. Clopidogrel pathway. *Pharmacogenet Genomics*. 2010;20(7):463–465. doi:10.1097/FPC.0b013e3283385420
37. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos*. 2010;38(1):92–99. doi:10.1124/dmd.109.029132
38. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373(9660):309–317. doi:10.1016/S0140-6736(08)61845-0
39. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354–362. doi:10.1056/NEJMoa0809171
40. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360(4):363–375. doi:10.1056/NEJMoa0808227
41. Soricich MJ, Vitry A, Ward MB, Horowitz JD, McKinnon RA. Prasugrel vs. clopidogrel for cytochrome P450 2C19-genotyped subgroups: integration of the TRITON-TIMI 38 trial data. *J Thromb Haemost*. 2010;8(8):1678–1684. doi:10.1111/j.1538-7836.2010.03923.x
42. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302(8):849–857. doi:10.1001/jama.2009.1232
43. FDA drug safety communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. U. S. Food and Drug Administration. Published 2010. Accessed 2016.
44. Paravattil B, Elewa H. Strategies to optimize dual antiplatelet therapy after coronary artery stenting in acute coronary syndrome. *J Cardiovasc Pharmacol Ther*. 2017;22(4):347–355. doi:10.1177/1074248416683048
45. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol*. 2015;12(1):30–47. doi:10.1038/nrcardio.2014.156
46. Giorgi MA, Cohen Arazi H, Gonzalez CD, Di Girolamo G. Beyond efficacy: pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. *Expert Opin Pharmacother*. 2011;12(8):1285–1295. doi:10.1517/14656566.2011.550573
47. Esteve-Pastor MA, Ruiz-Nodar JM, Orenes-Pinero E, et al. Temporal trends in the use of antiplatelet therapy in patients with acute coronary syndromes. *J Cardiovasc Pharmacol Ther*. 2017;1074248417724869.
48. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–2015. doi:10.1056/NEJMoa0706482
49. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057. doi:10.1056/NEJMoa0904327
50. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO trial. *J Am Coll Cardiol*. 2018;71(17):1869–1877. doi:10.1016/j.jacc.2018.02.029
51. Jiang M, You JH. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. *Pharmacogenomics*. 2016;17(7):701–713. doi:10.2217/pgs-2016-0008
52. Kazi DS, Garber AM, Shah RU, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. *Ann Intern Med*. 2014;160(4):221–232. doi:10.7326/M13-1999

53. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. *Pharmacoeconomics*. 2016;34(8):771–793. doi:10.1007/s40273-016-0397-9
54. Wang Y, Yan B, Liew D, Lee V. Cost-effectiveness of cytochrome P450 2C19* 2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. *Pharmacogenomics J*. 2018;18(1):113. doi:10.1038/tj.2016.94
55. Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI). ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/ct2/show/NCT01742117>. Published 2012. Updated October 30, 2018. Accessed 2019.
56. Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPular Genetics). ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/ct2/show/NCT01761786>. Published 2013. Updated April 17, 2018. Accessed 2019.
57. Elewa H, Ahmed D, Barnes GD. Triple oral antithrombotic therapy in atrial fibrillation and coronary artery stenting: searching for the best combination. *Semin Thromb Hemost*. 2016 Sep;42(6):662–670.
58. Gong X, Gutala R, Jaiswal AK. Quinone oxidoreductases and vitamin K metabolism. *Vitam Horm*. 2008;78:85–101.
59. Oldenburg J, Marinova M, Muller-Reible C, Watzka M. The vitamin K cycle. *Vitam Horm*. 2008;78:35–62.
60. Militaru FC, Vesa SC, Pop TR, Buzoianu AD. Pharmacogenetics aspects of oral anticoagulants therapy. *J Med Life*. 2015;8(2):171–175.
61. Offermanns S, Rosenthal W, editors. *Encyclopedia of Molecular Pharmacology*. Berlin, Heidelberg: Springer; 2008:109–111.
62. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med*. 1993;95(3):315–328. doi:10.1016/0002-9343(93)90285-W
63. Nunnelee JD. Review of an article: the International Warfarin Pharmacogenetics Consortium (2009). Estimation of the warfarin dose with clinical and pharmacogenetic data. *NEJM* 360 (8): 753–64. *J Vasc Nurs*. 2009;27(4):109. doi:10.1016/j.jvn.2009.09.001
64. Kamali F, Khan TI, King BP, et al. Contribution of age, body size, and CYP2C9 genotype to anticoagulant response to warfarin. *Clin Pharmacol Ther*. 2004;75(3):204–212. doi:10.1016/j.clpt.2003.10.001
65. Wadelius M, Chen LY, Eriksson N, et al. Association of warfarin dose with genes involved in its action and metabolism. *Hum Genet*. 2007;121(1):23–34. doi:10.1007/s00439-006-0260-8
66. Yuan HY, Chen JJ, Lee MT, et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet*. 2005;14(13):1745–1751. doi:10.1093/hmg/ddi180
67. Shahin MH, Khalifa SI, Gong Y, et al. Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. *Pharmacogenet Genomics*. 2011;21(3):130–135. doi:10.1097/FPC.0b013e3283436b86
68. Takeuchi F, McGinnis R, Bourgeois S, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet*. 2009;5(3): e1000433. doi:10.1371/journal.pgen.1000433
69. Gage BF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *J Thromb Thrombolysis*. 2008;25(1):45–51. doi:10.1007/s11239-007-0104-y
70. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010;115(18):3827–3834. doi:10.1182/blood-2009-12-255992
71. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283–2293. doi:10.1056/NEJMoa1310669
72. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369(24):2294–2303. doi:10.1056/NEJMoa1311386
73. Johnson JA, Cavallari LH. Warfarin pharmacogenetics. *Trends Cardiovasc Med*. 2015;25(1):33–41. doi:10.1016/j.tcm.2014.09.001
74. Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA*. 2017;318(12):1115–1124. doi:10.1001/jama.2017.11469
75. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharm Therapeut*. 2017;102(3):397–404. doi:10.1002/cpt.668
76. Bank P, Caudle K, Swen J, et al. Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the Dutch Pharmacogenetics Working Group. *Clin Pharm Therapeut*. 2018;103(4):599–618. doi:10.1002/cpt.v103.4
77. ASHP. ASHP statement on the pharmacist's role in clinical pharmacogenomics. ASHP statement Web site. Available from: <http://www.ashp.org/DocLibrary/Policy/HOD/StPharmacogenomicsPrepress.aspx>. Published 2014. Accessed January 17, 2015.
78. Caudle KE, Gammal RS, Karnes JH, et al. PRN OPINION PAPER: application of precision medicine across pharmacy specialty areas. *J Am Coll Clin Pharm*. 2019;2(3):288–302. doi:10.1002/jac5.2019.2.issue-3

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