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Implementation of inpatient models of pharmacogenetics programs

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Abstract

Purpose—The operational elements essential for establishing an inpatient pharmacogenetic service are reviewed, and the role of the pharmacist in the provision of genotype-guided drug therapy in pharmacogenetics programs at three institutions is highlighted.

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Summary—Pharmacists are well positioned to assume important roles in facilitating the clinical use of genetic information to optimize drug therapy given their expertise in clinical pharmacology and therapeutics. Pharmacists have assumed important roles in implementing inpatient pharmacogenetics programs. This includes programs designed to incorporate genetic test results to optimize antiplatelet drug selection after percutaneous coronary intervention and personalize warfarin dosing. Pharmacist involvement occurs on many levels, including championing and leading pharmacogenetics implementation efforts, establishing clinical processes to support genotype-guided therapy, assisting the clinical staff with interpreting genetic test results and applying them to prescribing decisions, and educating other healthcare providers and patients on genomic medicine. The three inpatient pharmacogenetics programs described use reactive versus preemptive genotyping, the most feasible approach under the current third-party payment structure. All three sites also follow Clinical Pharmacogenetics Implementation Consortium guidelines for drug therapy recommendations based on genetic test results.

Conclusion—With the clinical emergence of pharmacogenetics into the inpatient setting, it is important that pharmacists caring for hospitalized patients are well prepared to serve as experts in interpreting and applying genetic test results to guide drug therapy decisions. Since genetic test results may not be available until after patient discharge, pharmacists practicing in the ambulatory care setting should also be prepared to assist with genotype-guided drug therapy as part of transitions in care.

Keywords

clopidogrel; genotype; inpatient; pharmacists; pharmacogenetics; warfarin

Drug complications are the most common type of adverse event in hospitalized patients and are associated with significant morbidity, mortality, and healthcare costs.^{1–3} Anticoagulant and cardiovascular medications are among the top causes of drug-related adverse events during hospitalization.¹ Pharmacogenetics has the potential to improve the safety and effectiveness of medications prescribed during hospitalization, potentially improving patient outcomes and reducing healthcare costs. Pharmacists have long been at the forefront of scientific discovery in the field of pharmacogenetics, generating evidence to support its clinical implementation. Now that pharmacogenetics is entering clinical practice for some drugs, pharmacists are well positioned to serve integral roles in translating genetic discoveries to drug therapy decisions, given their extensive education and training in pharmacology and therapeutics. According to ASHP, every pharmacist should be knowledgeable about genetic contributions to drug response and serve as a key resource for interpreting genetic test results and applying genetic information to drug therapy decisions.⁴ Specially trained pharmacists may serve in leadership roles in multidisciplinary efforts to establish genotype-guided drug therapy as part of clinical care, and postgraduate residencies and fellowships have emerged to provide such specialty training at institutions currently implementing pharmacogenetics.

Pharmacists also have leading roles in the development of guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC), which are designed to assist clinicians with interpreting genetic test results and applying these results to therapeutic decisions.⁵ As of late 2015, CPIC guidelines were available for 17 drugs or drug classes,

including a number of drugs commonly initiated in the inpatient setting (e.g., thiopurines, clopidogrel, warfarin, codeine, carbamazepine). This review focuses on pharmacogenetics implementation for cardiovascular drugs in the inpatient setting, specifically summarizing the data supporting implementation of genotype-guided antiplatelet and warfarin therapies and describing the operational elements of pharmacogenetics programs for these drugs, including unique aspects with implementation in the inpatient setting. Specific examples of pharmacogenetics programs to optimize antiplatelet drug selection and improve warfarin dosing in the inpatient setting are also described.

Data supporting pharmacogenetics implementation and implementation guidelines

Clopidogrel

Clopidogrel is a prodrug that requires hepatic biotransformation to its pharmacologically active thiol metabolite, which inhibits the platelet P2Y₁₂ receptor to prevent platelet activation and subsequent aggregation. Cytochrome P-450 (CYP) isozyme 2C19 is involved in both steps of the biotransformation pathway. Genetic variation leading to deficiency of CYP2C19 function results in reduced production of the active thiol metabolite and decreased inhibition of platelet aggregation with clopidogrel.⁶

The *CYP2C19**1/*1 genotype is associated with “normal” enzyme activity and confers the extensive metabolizer (EM) phenotype. The most commonly described *CYP2C19* loss-of-function variants are the *CYP2C19**2 and *CYP2C19**3 alleles, which result from a splicing defect and stop codon, respectively. Additional loss-of-function alleles include the *CYP2C19**4, *CYP2C19**5, and *CYP2C19**6 alleles. Individuals with a single loss-of-function allele (e.g., *CYP2C19**1/*2 genotype) have the intermediate metabolizer (IM) phenotype, while those with two loss-of-function alleles (e.g., *CYP2C19**2/*2 or *CYP2C19**2/*3 genotype) have the poor metabolizer (PM) phenotype. Approximately 30% of whites, 35% of blacks, and 65% of Asians have the PM or IM phenotype.⁷ Two additional phenotypes—rapid metabolizer (RM) and ultrarapid metabolizer (UM)—occur in the presence of one or two gain-of-function *CYP2C19**17 alleles, respectively. However, the clinical implications of the *CYP2C19**17 allele remain unclear, and guidelines provide similar recommendations for antiplatelet therapy selection in RMs, UMs, and EMs.⁸

Numerous studies have documented an increased risk of adverse cardiovascular events after acute coronary syndrome and percutaneous coronary intervention (PCI) in clopidogrel-treated patients with the PM or IM phenotype, compared with similarly treated patients with the EM, RM, or UM phenotype.^{9,10} The Food and Drug Administration (FDA) approved a boxed warning on the clopidogrel labeling in 2010 regarding reduced effectiveness in PMs and recommending alternative therapy in such patients.¹¹ Neither prasugrel nor ticagrelor is affected by the *CYP2C19* genotype.^{12,13} Thus, CPIC guidelines recommend alternative therapy with prasugrel or ticagrelor (in the absence of contraindications) in patients with a loss-of-function allele after acute coronary syndrome and PCI.⁸

Warfarin

There is substantial variability in the warfarin dose needed for therapeutic anticoagulation, with dose requirements varying over 20-fold among patients.¹⁴ Studies have consistently shown that the *CYP2C9* and vitamin K epoxide reductase complex 1 (*VKORC1*) genotypes contribute to the variability in warfarin dose requirements.¹⁵ The *CYP2C9* gene encodes for the enzyme that metabolizes the more potent *S*-warfarin enantiomer, while *VKORC1* encodes for the target protein of warfarin. The most common *CYP2C9* variants in whites are the *CYP2C9*2* and *CYP2C9*3* alleles, each resulting from a single nucleotide polymorphism in the gene coding region.¹⁵ The *CYP2C9*2* and *CYP2C9*3* alleles reduce enzyme activity and confer lower warfarin dose requirements.¹⁶ Additional variants, namely the *CYP2C9*5*, *CYP2C9*6*, *CYP2C9*8*, and *CYP2C9*11* alleles, occur almost exclusively in blacks and also reduce enzyme activity and dose requirements.^{17–19} A single variant, -1639G>A, occurs in the *VKORC1* gene regulatory region and influences gene expression, with reduced expression and lower warfarin dose requirements with the -1639A allele.²⁰ The *CYP4F2* gene, which is involved in the metabolism of vitamin K, also affects warfarin dose requirements, with higher doses required in carriers of a 433Met allele.^{21,22} In addition to influencing dose requirements, the *CYP2C9* and *VKORC1* variants were recently associated with an increased risk for major bleeding events with warfarin.²³

Two prospective clinical trials examining the efficacy of genotype-guided warfarin dosing yielded disparate results. A European trial showed improved anticoagulation with genotype-guided dosing versus a traditional dosing approach.²⁴ In contrast, a U.S. trial in a diverse patient population showed no benefit in the time spent in the therapeutic International Normalized Ratio (INR) range using a pharmacogenetics algorithm including both genotype and clinical factors versus dosing with an algorithm containing clinical factors alone.²⁵ There were a number of differences between the two studies that have been postulated as contributors to the disparate results, including differences in study populations, comparator groups, loading-dose regimens, and pharmacogenetic algorithms, which are summarized elsewhere.²⁶ An important criticism of the U.S. trial is that approximately one third of the population was black, yet many of the common genetic alleles contributing to warfarin dose requirements in blacks were not tested. Specifically, both trials limited genotyping to the *VKORC1* -1639G>A and *CYP2C9*2* and *CYP2C9*3* alleles, which are the most common alleles contributing to warfarin dose requirements in whites. Failure to test for the *CYP2C9*5*, *CYP2C9*6*, *CYP2C9*8*, and *CYP2C9*11* alleles and other alleles contributing to warfarin dose requirements in blacks may have influenced the accuracy of genotype-guided warfarin dosing in this population.^{17,27,28} The pharmacogenetic algorithm used in the U.S. trial was significantly better than the clinical algorithm at predicting warfarin dose requirements in nonblacks but performed worse than the clinical algorithm in blacks.

Despite the inconsistencies in study results, genotype-guided dosing has entered clinical practice in some institutions, with preliminary evidence of improved anticoagulation-related outcomes with this approach, as described below.²⁹ CPIC guidelines recommend the use of genetic information to guide warfarin dosing when such information exists and the use of pharmacogenetic algorithms that incorporate clinical and genetic factors to assist with dosing.¹⁵

Operational elements

Pharmacogenetics implementation requires a multidisciplinary team approach. While the size of the team may vary by institution and complexity of the implementation, it usually consists of at least one individual with expertise in each of the following areas: pharmacogenetics, clinical care in the area of implementation, laboratory medicine, and health informatics. Pharmacists are important members of the multidisciplinary team, in some instances serving as champions of implementation efforts.^{30,31} In other instances, pharmacists play critical roles in establishing the processes to support genetic testing and facilitating incorporation of genetic test results into clinical decisions.³² Many pharmacists involved in the clinical implementation of pharmacogenetics have formal education and postdoctoral residency or fellowship training in pharmacogenetics or a related specialty area (e.g., oncology).³³ Specialized certificate training and continuing-education programs are also beginning to emerge to help prepare pharmacists without formalized education and training to provide genotype-guided therapy.^{34–36} In spite of an increased availability of such programs, postgraduate training and education opportunities for pharmacogenetics remain limited, and there is a significant need in this area.³³ Common steps for implementing pharmacogenetics in the inpatient setting are summarized in Figure 1, in addition to important questions to consider before implementation. The following sections summarize key considerations in the implementation process, including those unique to the inpatient setting.

Selection and institutional approval of pharmacogenetic tests for clinical use

The initial step in the implementation process is a review of the evidence to determine whether the data are sufficient to support clinical application of genetic test results. PharmGKB, a pharmacogenomics knowledge base, serves as a key resource in this regard. PharmGKB is a centralized resource for pharmacogenetic data and is publicly accessible through its website, www.pharmgkb.org.³⁷ PharmGKB has established a framework for evaluating the quality of pharmacogenetic evidence, with the strongest (high) evidence ranked as level 1 and the weakest (preliminary) as level 4. Levels 1 and 2 are further classified as A or B, with level 1A indicating that a gene–drug pair has a CPIC-endorsed or medical society–endorsed guideline or is supported by an existing clinical implementation within a major health system. Accordingly, most pharmacogenetics implementation efforts target gene–drug pairs with level 1A evidence. Each peer-reviewed, consensus-based CPIC guideline is published in *Clinical Pharmacology and Therapeutics* and indexed by the National Guidelines Clearinghouse, with select guidelines endorsed by ASHP.³⁸ In addition, the PharmGKB website houses additional clinical implementation resources for each guideline, including tools for interpreting genotype results, genotype translation and frequency tables, links to additional professional guidelines, and sample clinical decision support tools.³⁷ The goal of CPIC is not to recommend whether genetic testing should be done, leaving this to the discretion of the clinician. Rather, CPIC provides guidance on how to use existing genetic test results to optimize pharmacotherapy.³⁸

Although not always necessary, another important step in the implementation process may be to obtain appropriate administrative and institutional approval to establish testing as part

of clinical care. On the inpatient side, the pharmacy and therapeutics (P&T) committee and the medical executive committee often serve as the regulatory approval bodies for pharmacogenetics implementation, though additional approvals may be necessary from other regulatory bodies (e.g., anticoagulation task force, clinical decision support committee). Institutional endorsement of the program may also help to support the program's success. For example, in instances where genetic testing is not reimbursed by third-party payers, the hospital must be willing to assume this cost.

Establishing genotyping procedures

Genetic testing is offered through a number of commercial laboratories. For institutions choosing to establish genetic testing inhouse, selection of the genotyping methodology is another critical component in the implementation process. Examples of FDA-cleared platforms for pharmacogenetic testing are provided in the appendix.³⁹ Laboratories may also choose to develop their own tests. Genetic testing must be established in accordance with Clinical Laboratory Improvement Amendments (CLIA) licensure and be accredited by the College of American Pathologists (CAP) in order for test results to be integrated into the electronic health record (EHR) and used for clinical decision-making.⁴⁰ Genetic testing is considered high-complexity testing by CLIA, which prevents the use of bedside testing outside of a CLIA- or CAP-accredited process and creates a challenge when genetic test results are needed quickly to influence acute drug therapy decisions.⁴⁰

Key considerations in choosing genotype methodology are the complexity of the test procedure and the turnaround for test results. In the inpatient setting, efficient attainment of test results is warranted so that results are available quickly to influence drug decisions. Rapid turnaround of test results is not always possible; thus, there should be a process in place for communicating results to providers after the patient is discharged. For example, at University of Florida (UF) Health, where *CYP2C19* testing is clinically available to assist with the selection of anti-platelet therapy after PCI, the mean test turnaround time is two to four business days. Patients may be discharged by the time genotype results are returned, especially if the PCI is done electively. In this case, the clinical pharmacist notifies the provider caring for the patient after discharge and recommends an alternative antiplatelet agent if a loss-of-function variant is detected.³¹

Another important consideration is which genetic variants to test for, especially considering ethnic differences in genotype frequencies. For example, approximately 15–20% of African Americans have a *CYP2C9**5, *CYP2C9**6, *CYP2C9**8, or *CYP2C9**11 allele, whereas only about 6% have a *CYP2C9**2 or *CYP2C9**3 allele. If only the *CYP2C9**2 and *CYP2C9**3 alleles are tested for, then the 15–20% of African Americans with an alternative *CYP2C9* variant will be assumed to have the “normal” genotype. Warfarin dosing based on this assumption may result in significant overdosing in this population, placing patients at risk for bleeding.²⁸ At the University of Illinois Hospital and Health Sciences System (UI Health), approximately half of the patient population is black, so care was taken to choose a genotyping platform that captured variability unique to those of African ancestry.

Informatics considerations

There must be a process in place for ordering genetic tests, which may or may not include a process for recommending or suggesting genetic testing for a particular patient or patient population at the time of drug prescribing. For example, at UF Health, a *CYP2C19* genetic test order is included by default on the post-PCI order set so that every patient undergoing PCI receives genetic testing, unless the testing was conducted previously or the physician deselects the defaulted order.³¹

Further informatics support is needed to enter genotype results into the EHR. Genotype results reported in the format of nucleotide base calls (e.g., *VKORC1* AG genotype) or “star” allele nomenclature (e.g., *CYP2C19**1/*2) have little meaning to most clinicians. Therefore, a process must be in place to translate genotype data into clinically interpretable and actionable information. This is often done through the laboratory report accompanying each test result. In addition, clinical decision support tools may be developed to assist the clinician with interpreting results and their implications for drug therapy at the point of prescribing. For example, at UF Health, an alert appears within the EHR if the physician orders clopidogrel for a patient with a loss-of-function variant, notifying the clinician of the potential for reduced clopidogrel effectiveness and providing prescribing information, including contraindications, for alternative agents.³¹ The clinician may order an alternative agent by selecting this option within the alert or bypass the alert and continue clopidogrel if deemed appropriate. In other instances, a clinical pharmacist provides drug therapy recommendations to the primary medical team.^{30,32}

Education and consultative support

Before the implementation of pharmacogenetic testing, education is required to inform the clinical staff of the availability of testing, data supporting pharmacogenetic testing, the process for ordering and interpreting test results, and who to contact if questions arise. Clinician education may be oral or written and can occur in formal grand rounds presentations, less formal group or one-on-one conferences, or written clinical practice support tools (e.g., quick-reference charts to support genotype ordering or interpretation). Inservice programs may also be necessary to educate nursing, administrative, and laboratory staff and others involved in the patient’s care. Once testing is launched, additional ongoing education is required to provide information to new clinicians and reinforce information for others. A process should also be in place to assist clinicians with questions regarding genotype results or unique patient cases. The development of patient and community education support and materials is an important component of the implementation process. Pharmacists can play key roles in this regard, whether as part of multidisciplinary teams caring for the patient, as clinicians providing consultations for medication-related questions, or as members of a formal pharmacogenetic consultation service.

Quality metrics and outcomes assessment

Most pharmacogenetic clinical implementations also incorporate ongoing assessment of quality and safety metrics to evaluate continuous quality-improvement measures, patient and medication safety, and clinical, economic, or other outcomes. Important quality assessment metrics that are commonly reported include genetic test ordering rate, test turnaround time,

and action taken in response to the results.^{30–32,41,42} Patient and medication safety assessment metrics may be specific to the gene–drug pair being implemented (e.g., rate of alternative therapy use when indicated by genotype). In the case of genotype-guided warfarin dosing or antiplatelet selection, safety metrics might include clinical predictors (e.g., age, prior bleeding event, concomitant medications) or laboratory measures of bleeding risk. Additional documentation of outcomes with a pharmacogenetics program may be important to support continuation of the program, particularly if the hospital pays for the testing. In the case of genotype-guided warfarin dosing, such outcomes might include the time to achieve a therapeutic INR level, the number of INR levels extremely above or below goal, and the duration of low-molecular-weight heparin use.²⁹ Important outcomes with genotype-guided antiplatelet selection might include the occurrence of major adverse cardiovascular or bleeding events, especially in the early period after PCI when hospitals may be penalized for excess readmissions per the Centers for Medicare and Medicaid Services Hospital Readmissions Reduction Program.⁴³

Practice models of inpatient pharmacogenetics implementation

The following section describes pharmacogenetics implementation programs at three institutions and highlights the operational elements and contributions of pharmacists to each program. Additional information, including genotyping procedures, is provided in Table 1.

UF Health

The UF Health Personalized Medicine Program (PMP) was launched in 2012 as a pharmacist-led multidisciplinary team effort, with members including experts in pharmacogenetics, molecular pathology, clinical care, health informatics, and healthcare administration. The goal of the UF Health PMP is to develop, implement, study, and refine methods that allow genetic information to be used as a routine part of patient care. *CYP2C19* testing to predict patient response to clopidogrel after PCI was selected as the initial pharmacogenetics implementation based on the evidence described above.

A number of steps were taken to prepare for the implementation of the *CYP2C19* testing program, including establishing the genotype testing procedures, building clinical decision support (i.e., best-practice advisory) to provide test interpretation and clinical recommendations based on genetic information, and providing education to physicians and other healthcare professionals at UF Health.^{31,33} A multidisciplinary PMP subcommittee to the P&T committee was established to assist with many of these steps and provide oversight of the PMP initiative. The subcommittee includes clinical pharmacists with expertise in medication safety, pharmacogenetics, drug information, or informatics. The committee defined the population to be targeted for testing and the specific genotypes and metabolic phenotypes that would be the basis for pharmacogenetic recommendations. The committee also assisted with wording of pathology reports to accompany genotype results and the best-practice advisory. The PMP subcommittee continues to serve an important role by evaluating new evidence as it arises to determine whether any change in procedures is warranted. For example, while triple-dose clopidogrel (225 mg) was initially recommended as an option for alternative therapy in IMs, the subcommittee voted to remove this option due to the

emergence of data showing that this approach may be insufficient for overcoming the effects of this loss-of-function genotype.⁴⁴

When the program began in June 2012, the genotype test order was placed on the precatheterization order set, and genotyping was conducted preemptively for patients undergoing left heart catheterization with the expectation that many patients would proceed to PCI. When the program started billing for *CYP2C19* testing, the genotype test order was moved to the post-PCI order set, where it remains today. Because genotyping is included in the standard patient care procedures for this patient population, additional patient consent for genetic testing is not needed.

Patients with any combination of two loss-of-function alleles are assigned the PM phenotype, while those with a single loss-of-function allele (e.g., *CYP2C19**1/*2 or *CYP2C19**2/*17) are assigned the IM phenotype. Genotype and phenotype results are reported in the EHR under the laboratory reports tab and are accompanied by an interpretative laboratory report. A clinical pharmacist reviews *CYP2C19* test results and recommends alternative antiplatelet therapy with prasugrel or ticagrelor for PMs or IMs who underwent PCI in the absence of contraindications. Patient education materials about *CYP2C19* genotyping are provided to physicians and nurses in the clinical setting, are available to clinicians via a direct link in the EHR alert, and are accessible to clinicians and patients through the program's website (<http://personalizedmedicine.ufhealth.org>). Patients can also access their genotype results through the patient portal of the EHR.

Initial program metrics were published in 2013 and showed that the majority of patients undergoing PCI received a genetic test, with an increased rate of test adoption over the initial year of the program.³¹ Approximately 30% of the patients tested had the IM or PM phenotype, and 70% of these patients were switched to an alternative agent after PCI. The effect of genotype-guided antiplatelet drug selection on clinical outcomes has been reported elsewhere, revealing that patients with the IM or PM phenotype who remained on clopidogrel had significantly worse cardiovascular outcomes than those who were switched to alternative antiplatelet therapy (i.e., prasugrel or ticagrelor).⁴³

University of North Carolina

An algorithm that uses *CYP2C19* genotype and clinical factors to guide antiplatelet therapy in high-risk patients undergoing PCI was implemented at the University of North Carolina (UNC) in April 2012 as the standard of care.³² The development, approval, and implementation of this algorithm were driven by the physician director of the cardiac catheterization laboratory and completed in collaboration with the interventional cardiology attending physicians and clinical pharmacy specialists supporting the inpatient cardiology service. Clinical pharmacy also played a key leadership role in the education of physicians and other healthcare professionals on the available evidence to facilitate implementation of this practice model.

The 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions PCI guidelines state that a genotype-guided approach “might be considered” in high-risk patients, such as those with

an unprotected left main coronary artery or a bifurcating left main coronary artery or those undergoing PCI on the last patent coronary artery (class IIb, level of evidence: C).⁴⁵ In accordance with these guidelines, *CYP2C19* genotype testing is recommended in patients undergoing PCI at UNC for either acute coronary syndrome or stable coronary artery disease with high-risk anatomical findings. Consequently, the genotype test is not a defaulted order in the post-PCI order set and needs to be actively ordered after angiography-guided risk stratification by the interventional cardiologist (i.e., reactive strategy). Similar to UF Health, patient consent for genotyping occurs as part of the clinical consent process for the PCI and its associated care. Genotype results are uploaded into the molecular genetics laboratory section of the EHR and accompanied by an interpretation. The report also includes a brief description of clopidogrel clinical pharmacology and the relevance of the detected alleles.

After risk stratification, the physician initiates treatment with a loading dose of either prasugrel or clopidogrel based on patient-specific clinical factors (e.g., indication for PCI, risk factors for bleeding, prior use of a P2Y₁₂ inhibitor) and orders the *CYP2C19* genotype test if indicated. At UNC, approximately 30% of patients are initiated on prasugrel therapy before the genotype test results are available. Presentation with an acute myocardial infarction and prasugrel use on admission are the most common indications for this approach.³² Consistent with CPIC guidelines,⁸ prasugrel or ticagrelor is recommended if the patient is a *CYP2C19* IM or PM, while standard-dose clopidogrel (75 mg/day) is the recommended maintenance therapy in *CYP2C19* EMs, RMs, and UMs. Prasugrel is the most commonly prescribed alternative therapy, and triple-dose clopidogrel (225 mg/day) is not recommended.

After receiving the genotype test report, a clinical pharmacist follows up with the physician to recommend either continuation of or a change to the P2Y₁₂ inhibitor. Changes in therapy are communicated to the nursing staff and patient and occur either before discharge or after discharge via telephone follow-up. Based on the initial experience at UNC, approximately half of the genotype-driven changes in therapy occur before hospital discharge; the remaining half occur after discharge in the outpatient setting.

The UNC practice model has several unique features. First, genotype testing targets high-risk patients undergoing PCI following risk stratification by the interventional cardiologist. Second, this effort was not driven by a large, institutionalized PMP that spans multiple practice settings. In contrast, the development and implementation of this genotype-guided treatment algorithm were championed and driven by physician leadership in cardiology (most notably, the director of the cardiac catheterization laboratories) in collaboration with clinical pharmacy specialists. Third, the UNC practice model does not currently employ clinical decision support tools within the EHR. Thus, interdisciplinary collaboration and communication among physicians, clinical pharmacists, and nurses and rigorous follow-up with the patients and their providers have proven critical to effectively obtain, interpret, and use *CYP2C19* genotyping to guide P2Y₁₂ inhibitor selection in practice. Consequently, genotype test results can now be obtained and interpreted as routine laboratory test results and utilized to optimize therapeutic decision-making. This is particularly important because automated prompts within the EHR are not currently available to alert clinicians about the

genotype result. The sustainability of this practice model over time, as well as its impact on clinical outcomes, is being actively investigated.

University of Illinois

UI Health PMP is a clinical and research initiative with the primary goal of improving pharmacotherapy in patients by increasing personalization of drug selection and dosing. Central to the program is its consultation service, which uses both clinical and genetic information to provide dosing recommendations for the initiation of warfarin therapy as well as antiplatelet therapeutic selection in patients undergoing PCI. The service team is led by pharmacists but also includes members from UI Health molecular pathology laboratory, health informatics, department of medicine, and health system administration.

Pharmacogenetic testing at UI Health is currently optional, with the decision on whether to perform genetic testing left to the medication prescriber. However, when the warfarin pharmacogenetics program began in 2012, testing was automatically conducted for all patients newly starting warfarin.³⁰ This changed in early 2014, after the publication of clinical trial data led clinicians to question the added benefit of genotyping over warfarin dosing based on clinical information alone.²⁵ At that time, testing for warfarin dosing became optional. Since the switch from automatic to optional genotyping, genotype testing has been ordered for approximately 50% of patients starting warfarin.

When a genetic test is ordered, a consultation by the PMP is automatically generated. Simultaneously, a technician in the molecular pathology laboratory receives an electronic alert about the genetic test order. Once the blood sample arrives at the laboratory, the laboratory technician contacts the PMP pharmacist to confirm that genotyping is appropriate (e.g., the patient has no recent history of warfarin use) before proceeding with testing. Genotyping is performed at 10 a.m. each day of the week. Blood samples arriving at the laboratory before 10 a.m. are genotyped that day, with the results available by 4 p.m. Blood samples arriving in the laboratory after 10 a.m. are processed the following day. Warfarin is administered at 9 p.m. each day; thus, this model allows for genotype-informed dosing by the second dose for more than 90% of patients. The PMP pharmacist recommends a clinically informed dose (determined using the www.warfarindosing.org algorithm and clinical judgment) for the first dose (i.e., dose before the return of genotyping results) when possible. Otherwise, determination of the first dose is left to the discretion of the provider.

Once available, genotypes are entered into the laboratory results section of the EHR. The PMP pharmacist combines genotype data with clinical information retrieved from the EHR and determines an estimated effective dose using a combination of dosing algorithms available at www.warfarindosing.org and clinical judgment. Dose recommendations are communicated to the prescriber via a note in the patient's medical record and direct discussion. The patient is followed by the PMP pharmacist (with daily notes written) until the patient either achieves two consecutive therapeutic INRs or is discharged from the hospital. At the time of hospital discharge, the PMP pharmacist recommends that the patient be referred to the pharmacist-managed, outpatient UI Health antithrombosis clinic for follow-up.

Prescriber acceptance of warfarin dosing recommendations has steadily increased since pharmacogenetics implementation. Currently, approximately 95% of warfarin dose adjustments in patients followed by the service are within 0.5 mg of PMP pharmacist recommendations. In addition, preliminary results based on data collected from the first 16 months of implementation suggest that, compared with historical controls, patients receiving genotype-guided warfarin doses by the pharmacist-led UI Health PMP reach their targeted INR values at a faster rate and are more likely to have a therapeutic INR at discharge, fewer extreme INR values, and a shorter duration of low-molecular-weight heparin use during warfarin initiation.²⁹

Clopidogrel pharmacogenetic testing was implemented at UI Health in 2014 and, as with warfarin, is ordered at the discretion of the prescriber. The UI Health PMP strongly recommends *CYP2C19* testing for high-risk patients, as defined by the ACCF/AHA PCI guidelines discussed above, with testing targeted to those prescribed clopidogrel. Once an order is placed and the blood sample arrives in the molecular pathology laboratory, a laboratory technician contacts the PMP pharmacist to confirm that genotyping is appropriate. Clopidogrel genotyping and warfarin genotyping are conducted simultaneously, so genotyping results are usually available either the same day or the next day, allowing an antiplatelet recommendation to be made before most patients are discharged from the hospital. Once the results are available, they are placed in the same EHR laboratory results section as warfarin genotyping results. The PMP pharmacist then recommends to continue clopidogrel (for EMs, RMs, and UMs) or to consider another antiplatelet medication (for IMs or PMs) if no contraindications exist. This recommendation is communicated to the prescriber via a consultation note in the EHR as well as via direct discussion.

Discussion

All three programs currently use reactive versus preemptive genotyping, meaning that genotyping is done at the time of prescribing. While this is the only feasible approach under the current third-party payment structure, which only reimburses for reactive testing, it creates a challenge because test results are not readily available at the time of prescribing. All three sites also follow CPIC guidelines for drug therapy recommendations based on genetic test results. However, while CPIC guidelines for clopidogrel focus on patients who undergo PCI for an acute coronary event, the UF Health program targets all patients undergoing PCI; the UNC and UI Health programs target high-risk patients undergoing PCI, whether the procedure is done electively or for an acute coronary event. Genotype test turnaround time varies among programs, as shown in Table 1, with a longer turnaround time at UF Health where samples must be transported to an offsite laboratory. The latter may serve as a model for other institutions where genotyping facilities are not immediately available. There are some differences among programs in the use of clinical decision support tools, and while clinical pharmacists serve vital roles in each program, the nature of roles varies somewhat among programs. The UF Health and UI Health programs are championed by pharmacists who led the initial implementation efforts and continue to serve as program leaders. While the UNC model is a physician-led model, pharmacists serve as leaders of the educational efforts and have critical roles in facilitating test interpretation and prescribing decisions. While only three programs are highlighted in this article, there are examples of

additional programs implementing pharmacogenetics in the inpatient setting across the country.^{46–48}

Conclusion

Pharmacogenetics has emerged into clinical practice in the inpatient setting, with pharmacists assuming important roles in facilitating the application of genetic information to drug therapy decisions. Pharmacists are serving as important members of multidisciplinary teams in leading pharmacogenetics programs in hospitals, including *CYP2C19* testing to predict clopidogrel response and *CYP2C9* and *VKORC1* testing to predict warfarin dose requirements. Each implementation involves critical steps with which pharmacists may either lead or assist, including reviewing the evidence supporting implementation, obtaining necessary institutional approval, educating prescribers, building user-friendly clinical decision support tools to assist with interpreting genotype test results, and applying results to actionable prescribing decisions. Once implementation is in place, pharmacists can serve vital roles in providing genotype-guided therapy, assessing metrics to ensure patient safety and efficient delivery of therapy based on genotype, and examining important outcomes to evaluate the value of pharmacogenetics implementation. Therefore, it is important for pharmacists practicing in inpatient settings to be prepared to manage drug therapy in the age of pharmacogenetics. Moreover, given that genotype test results may not be available until after the patient is discharged from the hospital, pharmacists practicing in ambulatory care settings should also be prepared to adjust drug therapy according to genotype results.

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Appendix—Genotyping tests available for polymorphisms relevant to clopidogrel and warfarin dosing, as of March 2016

Clopidogrel/*CYP2C19*

- Spartan RX CYP2C19 Test System (Spartan Bioscience, Ottawa Ontario, Canada)
- TAG CYP2C19 Kit V3 (Luminex Corp., Madison, WI)
- INFINITI CYP2C19 Assay (AutoGenomics, Vista, CA)
- Roche AmpliChip CYP450 microarray (Roche Molecular Systems, Pleasanton, CA)

Warfarin/*CYP2C9* and *VKORC1*

- eSensor Warfarin Sensitivity Test (GenMark Diagnostics, Carlsbad, CA)
- eQ-PCR LC Warfarin Genotyping kit (TrimGen, Sparks Glencoe, MD)

- Gentris Rapid Genotyping Assay CYP2C9 & VKORC1 (ParagonDx, Morrisville, NC)
- INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin (AutoGenomics)

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KEY POINTS

- Evidence supports the incorporation of genotype information into prescribing decisions for a number of drugs commonly initiated in the inpatient setting.
- Pharmacists are serving as important members of multidisciplinary teams in leading pharmacogenetics programs in hospitals, including CYP2C19 testing to predict clopidogrel response and CYP2C9 and VKORC1 testing to predict warfarin dose requirements.
- Pharmacists must be prepared to optimize drug therapy for hospitalized patients in this age of pharmacogenetics.

Figure 1.

Operational elements of an inpatient models of pharmacogenetics programs and questions to consider. CPIC = Clinical Pharmacogenetics Implementation Consortium.

Table 1Comparison of Pharmacogenetic Practice Models at Three Institutions^a

Variable	University of Florida (UF)	University of Illinois (UI) at Chicago	University of North Carolina (UNC), Chapel Hill
Gene(s)/drug pair(s)	<i>CYP2C19</i> /clopidogrel	<i>CYP2C9</i> , <i>VKORC1</i> /warfarin; <i>CYP2C19</i> /clopidogrel	<i>CYP2C19</i> /clopidogrel
Regulatory bodies requiring approval	P&T committee and clinical decision support committee	P&T committee and anticoagulation task force for warfarin genetic testing; none for <i>CYP2C19</i> testing ^b	None ^b
Genotyping location	UF Health pathology laboratory located approximately 3 miles from the medical center	UI Health molecular pathology laboratory located within the medical center	UNC McLendon molecular genetics laboratory located within the medical center
Genotype platform and alleles detected	eSensor XT-8 (GenMark Diagnostics, Carlsbad, CA) <i>CYP2C19</i> *2, <i>CYP2C19</i> *3, <i>CYP2C19</i> *4, <i>CYP2C19</i> *5, <i>CYP2C19</i> *6, <i>CYP2C19</i> *8, <i>CYP2C19</i> *17	eSensor XT-8 (GenMark Diagnostics) <i>VKORC1</i> c.-1639G>A; <i>CYP4F2</i> 1347G>A (<i>V433M</i>); <i>CYP2C9</i> *2, <i>CYP2C9</i> *3, <i>CYP2C9</i> *5, <i>CYP2C9</i> *6, <i>CYP2C9</i> *11, <i>CYP2C9</i> *14, <i>CYP2C9</i> *15, <i>CYP2C9</i> *16; <i>CYP2C19</i> *2, <i>CYP2C19</i> *3, <i>CYP2C19</i> *4, <i>CYP2C19</i> *5, <i>CYP2C19</i> *6, <i>CYP2C19</i> *8, <i>CYP2C19</i> *17	TaqMan (Life Technologies, Foster City, CA) <i>CYP2C19</i> *2, <i>CYP2C19</i> *3, <i>CYP2C19</i> *17
Average genotype turnaround time	2–4 business days	24 hr	1 business day
Clinical decision support	Available in the form of a best-practice advisory in the EHR (Epic, Verona, WI) to alert prescriber when clopidogrel is ordered for a patient with a loss-of-function genotype	Alert in the EHR (Cerner Powerchart, Brooklyn, NY) about option of genetic testing that appears at the time warfarin is ordered for adult age ≥ 18 yr with no record of warfarin use within 6 mo; prescriber must respond “yes” or “no” to the option of genotyping to proceed with the order; no clinical decision support for clopidogrel	Not available

^aP&T = pharmacy and therapeutics, EHR = electronic health record, PCI = percutaneous coronary intervention.^bDeveloped in accordance with the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guidelines and approved by the cardiac catheterization laboratory attending physicians in collaboration with clinical pharmacy specialists supporting the inpatient cardiology service.