Annals of Internal Medicine

Cases in Precision Medicine: The Role of Pharmacogenetics in Precision Prescribing

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Pharmacogenetics may help physicians deliver individualized treatments based on how a person's genes affect a drug's effects and metabolism. This information can help prevent adverse events or improve drug efficacy by enabling the physician to optimize dosage or to avoid a medication with adverse reactions and to prescribe an alternative therapy. This article discusses the current clinical utility of pharmacogenetic testing in the context of a patient who requires anticoagulation with warfarin.

Ann Intern Med. 2019;170:796-804. doi:10.7326/M18-2357 **Annals.org**
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This article was published at Annals.org on 21 May 2019.

We present a hypothetical case to illustrate the potential use of pharmacogenetics in clinical practice.

A 70-year-old man of European descent receives a diagnosis of atrial fibrillation. The patient's height is 1.75 m, his weight is 90.7 kg, and his body mass index is 29.5 kg/m^2. He has a history of chronic hypertension along with hyperlipidemia. His daily medical regimen consists of hydrochlorothiazide, lisinopril, and atorvastatin, and he currently does not use any other medications. He quit smoking 20 years ago. The patient's internist prescribes the anticoagulant warfarin to decrease his risk for stroke. The therapeutic window for warfarin is narrow. In addition, the drug is more challenging to use safely in patients of advanced age, who have a lower capacity to metabolize drugs and an increased risk for falling, which elevates the risk for bleeding. With these concerns in mind, the internist considers using pharmacogenetics to determine the warfarin dosage.

What Is Pharmacogenetic Testing, and How Can It Be Helpful?

Pharmacogenetics can help physicians deliver individualized treatments based on how a person's genes affect a drug's effects and metabolism. Polymorphisms in the genes encoding the drug target pharmacodynamics, whereas genetic determinants of the drug's metabolism or excretion, such as the cytochrome P450 (CYP) enzyme superfamily, influence pharmacokinetics. In the United States, the 30 most commonly prescribed drugs with potential for pharmacogenetic utility account for more than 15% of all prescriptions (1).

Pharmacogenetics may help prevent adverse events or improve drug efficacy by enabling physicians to optimize dosage or to avoid a medication with adverse reactions and to prescribe an alternative therapy. In addition, such drugs as warfarin have a narrow therapeutic range, and genotype-based treatment may help minimize the risk for adverse events while maximizing time in the therapeutic window. Pharmacogenetic testing also can identify patients with variants who are responsive to certain drugs, such as those with cystic fibrosis who have the G551D *CFTR* (cystic fibrosis transmembrane conductance regulator) mutation, who may benefit from ivacaftor (2). Furthermore, pharmacogenetics has the most impact on populations in which the variant allele is found at high frequency. For instance, genetic testing for the HLA-B*15:02 variant to prevent associated Stevens–Johnson syndrome in Southeast Asians receiving carbamazepine is most beneficial because of the high HLA-B*15:02 allele frequency in the Southeast Asian population (2).

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Which Genes Influence Response to Warfarin?

The warfarin-specific genes and their effect on determining warfarin dosage are summarized in Table 1, along with specific recommendations regarding how much the dosage should be adjusted on the basis of genotype.

Vitamin K epoxide reductase, encoded by the gene *VKORC1*, reduces vitamin K and allows it to activate coagulation factors II, VII, IX, and X. *VKORC1* is the target of warfarin, and warfarin produces anticoagulation effects by inhibiting vitamin K epoxide reductase. The genetic polymorphism *VKORC1* − 1639G>A (guanine-to-adenine substitution at position −1639) is associated with increased sensitivity to warfarin, and patients with genotypes AA or GA require a lower dose of warfarin than those with genotype GG (5). This is a pharmacodynamic genetic difference.

CYP2C9 of the CYP superfamily is the hepatic enzyme responsible for the metabolism of warfarin or a pharmacokinetic genetic difference. Warfarin is a 50:50 racemic mixture of *R*-warfarin and *S*-warfarin enantiomers; *S*-warfarin is 5 times more active than *R*-warfarin. An asterisk after the CYP2C9 enzyme denotes the specific genetic variant or allele. CYP2C9*1 is the wild-type allele, whereas CYP2C9*2 and CYP2C9*3 are variant alleles that are associated with slower warfarin metabolism (5). Metabolism of *S*-warfarin is decreased by approximately 30% to 40% in patients with the *2 allele

Key Summary Points

Although evidence for the clinical utility of genotype-based warfarin therapy is conflicting, data exist to support the use of pharmacogenetic testing in persons of European ancestry. If genetic information is readily available, genotype-based warfarin therapy should be applied on the basis of recommendations from the Clinical Pharmacogenetics Implementation Consortium guidelines.

Warfarindosing.org provides a calculator in which physicians can enter a patient's genetic and clinical information to determine the appropriate warfarin dosage.

Because of the long turnaround times for pharmacogenetic testing, it is not feasible for patients with an emergent need for warfarin.

Pharmacogenetics currently is not recommended when prescribing warfarin for persons of African ancestry because of the lack of clinical studies in this population.

Evidence is available to support genotype-guided prescribing for a limited number of drugs, including abacavir, thiopurines, carbamazepine (Asian populations), allopurinol (Asian populations), and ivacaftor. Overall, however, the evidence is insufficient to support genotype-guided prescribing for most other medications with available pharmacogenetic tests.

and about 80% to 90% in those with the *3 allele (5). The *5, *6, *8, and *11 alleles are more frequent in African Americans. Inclusion of the rs12777823 polymorphism in the CYP2C cluster also is helpful in determining dosage in African Americans (5, 6).

The CYP4F2 enzyme oxidizes vitamin K to the inactive form, and carriers of the *CYP4F2* V433M polymorphism have a decreased ability to oxidize vitamin K and have higher hepatic levels of activated vitamin K. Therefore, V433M carriers require a higher dosage of warfarin (5).

What Evidence Is Available to Support the Clinical Utility of Pharmacogenetics for Warfarin and for Other Drugs?

For drugs with potential for pharmacogenetic implementation, randomized controlled clinical trials provide the highest level of evidence to assess clinical utility. These studies must be completed in each ethnic group for which testing is considered because clinical utility may differ among ethnic groups and the genetic variants assessed. For some drugs, evidence shows that most persons with a particular serious adverse event carry the same genotype; therefore, pharmacogenetic testing is recommended to avoid adverse events (Table 2). For most drugs with associations between genotype and drug dosing, only sparse case report data are available to demonstrate the clinical utility of pharmacogenetic testing. Some drugs, such as clopidogrel and tacrolimus, have been tested in randomized controlled trials, but results showing the benefit of pharmacogenetic testing are inconclusive (Table 2).

Three large randomized controlled trials evaluated the clinical utility of genotype-guided warfarin therapy, with somewhat conflicting results influenced by the patient population and genotypes tested in the studies. In the COAG (U.S Clarification of Optimal Anticoagulation Through Genetics) trial (8), patients received treatment based on either a clinically derived algorithm without pharmacogenetics or a genotype-based algorithm incorporating the genotype data for CYP2C9*2, CYP2C9*3, and *VKORC1* polymorphisms together with clinical factors. The COAG trial found no significant difference in the primary outcome of percentage of time in therapeutic range between the genotype-guided group (45.2%) and the clinically guided group (45.4%). No significant difference was observed in the rate of adverse bleeding events. Of the 27% of COAG participants who were African American, those in the genotype-guided group spent significantly less time within the therapeutic range than those in the clinically guided group (35.2% vs. 43.5%). The trial did not include all the relevant alleles for the African American population (CYP2C9*5, *6, *8, and *11 and rs12777823), which might partially explain the failure of the genotype-based algorithm to affect overall outcome.

The EU-PACT (European Pharmacogenetics of Anticoagulant Therapy) trial used the same genetic polymorphisms and primary outcome measures as the COAG study (9). Overall, EU-PACT demonstrated that the genotype-guided group was within the therapeutic international normalized ratio (INR) range 7% longer than the control group (67.4% vs. 60.3%), which used an empirical dosing algorithm without incorporating any clinical factors. As in the COAG trial, no significant difference was observed in adverse bleeding events. However, 98.5% of the EU-PACT population was of European ancestry, and the difference in ethnic composition between EU-PACT and COAG may partially explain the difference in findings between the 2 trials. Another possibility is that the success of the pharmacogenetic intervention in the EU-PACT trial may have been attributable to the other clinical factors used in the genetic dosing algorithm (age, height, weight, amiodarone use), which were not included in dosing for the control group.

The GIFT (Genetic Informatics Trial), designed to study the incidence of warfarin-related bleeding, found a 3.9% reduction (10.8% vs. 14.7% absolute difference) in the primary end point of major bleeding, INR of 4 or greater, venous thromboembolism, or death in the genotype-guided versus the clinically guided group, for which dosing was based only on clinical factors (10). The genotype-guided group also had a 3.4% absolute improvement in the percentage of time within the therapeutic window, with the greatest progress in patients who were genetically most sensitive to warfarin. Similar

Table 1. Genetic Polymorphisms Affecting Warfarin Dosage

Variant Allele, by Gene	Allele Frequency, by Ethnic Group†‡	Effect on Warfarin Dosing
VKORC1		
−1639G>A	East Asian: 88% European descent: 41% African American: 10%	Decrease dose by 28% per variant allele
CYP2C9		
CYP2C9*2	East Asian: 0.06% European descent: 13% African American: 2.3%	Decrease dose by 19% per variant allele‡
CYP2C9*3	East Asian: 3.4% European descent: 7.1% African American: 1.2%	Decrease dose by 33% per variant allele‡
CYP2C9*5	East Asian: 0% European descent: 0% African American: 1.3%	Decrease dose by 15%–30% per variant allele§
CYP2C9*6	East Asian: 0% European descent: 0% African American: 0.77%	Decrease dose by 15%–30% per variant allele§
CYP2C9*8	East Asian: 0% European descent: 0.14% African American: 6.7%	Decrease dose by 15%–30% per variant allele§
CYP2C9*11	East Asian: 0% European descent: 0.17% African American: 1.4%	Decrease dose by 15%–30% per variant allele§
rs12777823 A	African American: Approximately 25%	Decrease dose by 10%–25%§
CYP4F2		
V433M	East Asian: 22% European descent: 30% African American: 7.7%	Increase dose by 5%–10%§

CYP2C9 = cytochrome P450 2C9; *CYP4F2* = cytochrome P450 4F2; *VKORC1* = vitamin K epoxide reductase complex subunit 1.
† All data are from reference 3 (www.pharmgkb.org/page/pgxGeneRef).
‡ Reference 4.
§ Reference 5.

to the EU-PACT trial, 91.0% of participants in GIFT were of European ancestry.

Randomized controlled clinical trials provide the highest level of evidence to assess the utility of pharmacogenetic testing. On the basis of results from these studies, pharmacogenetic testing for warfarin may be helpful in determining the initial dosage for persons of European descent. However, evidence is not yet available to support pharmacogenetic testing for patients of African ancestry. Although pharmacogenetic testing helps determine the initial warfarin dosage, INR still must be monitored, with appropriate dosage adjustments due to changes in diet and other factors that vary over time.

Single-gene pharmacogenetic testing has clinical utility for a limited number of medications associated with high risk for adverse events, and U.S. Food and Drug Administration (FDA) labeling for a subset of these drugs requires pharmacogenetic testing (**Table 2**). Thiopurine methyltransferase (*TPMT*) genetic testing is used to screen for patients at risk for bone marrow toxicity, gastrointestinal symptoms, hepatotoxicity, pancreatitis, arthralgia, and rashes due to their reduced ability to metabolize thiopurines (2, 11). The HLA allele (HLA-B*57:01) predicts hypersensitivity to the anti-HIV drug abacavir (2, 11). *CFTR* testing identifies persons with the G551D *CFTR* mutation, who might benefit from ivacaftor (2). Most pharmacogenetic tests are currently done in a targeted manner immediately before the start of treatment with a single, specifically indicated medication. We provide key summary points highlighting recommendations for warfarin and other drugs for which high-quality evidence supports pharmacogenetic testing.

In Addition to High-Quality Evidence, What Infrastructure Is Necessary to Support Pharmacogenetics to Guide Prescribing in Clinical Settings?

Implementation of pharmacogenetic testing in the clinic has been challenging, partly because of the infrastructure necessary to carry it out. **Table 3** lists resources that can guide physicians in using pharmacogenetic information. The FDA has added genotype-based dosage recommendations to the labeling for some drugs. The Pharmacogenomics Knowledgebase (PharmGKB) curates the information needed to use pharmacogenetics in prescribing medications (3). Together, PharmGKB and the Pharmacogenomics Research Network founded the Clinical Pharmacogenetics Implementation Consortium (CPIC) to advance the use of pharmacogenetics by publishing peer-reviewed, evidence-based practice guidelines for specific drugs. After reviewing the current state of research, CPIC assigns each gene–drug pair a level of evidence (high, moderate, or weak) linking genotype to phenotype and

Table 2. CPIC Level A Gene–Drug Pairs†

Drug	Genetic Variants‡	Potential Pharmacogenetic Benefit‡	Level of Evidence to Assess Clinical Utility	FDA Labeling Requirement for Testing‡
Antithrombotics				
Clopidogrel	CYP2C19*1, *2, *3, *17	Prevents cardiovascular events in patients with acute coronary syndromes undergoing percutaneous coronary intervention	6 RCTs§; conflicting evidence for pharmacogenetics	Not required
Warfarin	CYP2C9*1, *2, *3, *5, *6, *8, *11; rs12777823; *VKORC1* −1639G>A; CYP4F2*3	Achieves therapeutic INR faster, increases time within therapeutic INR, reduces adverse bleeding events	3 large RCTs‖; conflicting evidence for pharmacogenetics	Not required
Narcotics				
Codeine	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Identifies patients at high risk for drug toxicity (respiratory depression, nausea, vomiting, constipation) or ineffective response	No studies	Not required
Oxycodone (refer to CPIC codeine guideline)	CYP2D6*1, *2, *3, *4, *5, *6	Identifies patients at high risk for drug toxicity (respiratory depression, nausea, vomiting, constipation) or ineffective response	No studies	Not required
Tramadol (refer to CPIC codeine guideline)	CYP2D6*1, *2, *3, *4, *5, *6, *10	Prevents adverse events (respiratory depression, cardiotoxicity, or nausea) and maintains drug efficacy	No studies	Not required
Antidepressants				
Amitriptyline	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41; CYP2C19*1, *2, *3, *17	Prevents adverse effects (anticholinergic, CNS, gastrointestinal, cardiovascular) and increases likelihood of drug efficacy	No studies	Not required
Nortriptyline	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Prevents adverse effects (anticholinergic, CNS, gastrointestinal, cardiovascular) and increases likelihood of drug efficacy	No studies	Not required
Fluvoxamine	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Prevents adverse effects (CNS, gastrointestinal, sexual)	No studies	Not required
Citalopram	CYP2C19*1, *2, *3, *17	Prevents adverse events (CNS, gastrointestinal, sexual, arrhythmias) and increases likelihood of drug efficacy	No studies	Not required
Escitalopram	CYP2C19*1, *2, *3, *17	Prevents adverse events (CNS, gastrointestinal, sexual, arrhythmias) and increases likelihood of drug efficacy	No studies	Not required
Paroxetine	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Prevents adverse effects (CNS, gastrointestinal, sexual)	No studies	Not required
Anticonvulsants				
Carbamazepine	HLA-B*15:02, HLA-A*31:01	Reduces incidence of Stevens–Johnson syndrome, toxic epidermal necrolysis, maculopapular exanthema, and other cutaneous adverse reactions; greater benefit in Southeast Asian populations (HLA-B*15:02 allele frequencies: East Asian, 6.9%; Oceanian, 5.4%; South/Central Asian, 4.6%)	Prospective screening study of HLA-B*15:02 in Taiwan¶; supportive evidence for pharmacogenetics	Required for HLA-B*15:02
Phenytoin	HLA-B*15:02; CYP2C9*1, *2, *3	Reduces risk for Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with HLA-B*15:02, avoids adverse events (sedation, ataxia, dizziness, nystagmus, nausea, cognitive impairment) in patients who are poor CYP2C9 metabolizers; high frequency of benefit in Southeast Asian populations (HLA-B*15:02 allele frequencies: East Asian, 6.9%; Oceanian, 5.4%; South/Central Asian, 4.6%)	No studies	Not required
Oxcarbazepine	HLA-B*15:02	Reduces risk for Stevens–Johnson syndrome and toxic epidermal necrolysis; high frequency of benefit in Southeast Asian populations (HLA-B*15:02 allele frequencies: East Asian, 6.9%; Oceanian, 5.4%; South/Central Asian, 4.6%)	No studies	Not required

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Table 2–Continued

Drug	Genetic Variants‡	Potential Pharmacogenetic Benefit‡	Level of Evidence to Assess Clinical Utility	FDA Labeling Requirement for Testing‡
Antiemetics				
Ondansetron	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Identifies patients who do not respond effectively	No studies	Not required
Tropisetron	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *41	Identifies patients who do not respond effectively	No studies	Not required
Anticancer/immunosuppressive agents				
Capecitabine	DPYD*2A, *13; rs67376798; rs75017182	Reduces risk for drug toxicity (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand–foot syndrome)	No studies	Not required
Fluorouracil	DPYD*2A, *13; rs67376798; rs75017182	Reduces risk for drug toxicity (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand–foot syndrome)	No studies	Not required
Thioguanine	TPMT*1, *2, *3A, *3B, *3C, *4	Reduces risk for acute myelosuppression and maintains drug efficacy	No studies	Not required
Azathioprine	TPMT*1, *2, *3A, *3B, *3C, *4	Reduces risk for acute myelosuppression and maintains drug efficacy	2 RCTs**; supportive evidence for pharmacogenetics	Not required
Mercaptopurine	TPMT*1, *2, *3A, *3B, *3C, *4	Reduces risk for acute myelosuppression and maintains drug efficacy	1 RCT**; supportive evidence for pharmacogenetics	Not required
Tacrolimus	CYP3A5*1, *3, *6, *7	Achieves target concentrations faster to reduce risk for graft rejection after transplantation and to reduce risk for drug toxicity (nephrotoxicity, hypertension, neurotoxicity, hyperglycemia)	2 RCTs††; conflicting evidence for pharmacogenetics	Not required
Tamoxifen	CYP2D6*1, *2, *3, *4, *5, *6, *9, *10, *17, *41	Optimizes dosage or identifies patients who do not respond effectively	No studies	Not required
Irinotecan (CPIC guideline not yet available)	UGT1A1*1, *28	Reduces risk for neutropenia, diarrhea, and asthenia	No studies	Not required
Anesthetics				
Isoflurane (CPIC guideline not yet available)	*CACNA1S* and *RYR1*	Reduces risk for malignant hyperthermia	No studies	Not required
Desflurane (CPIC guideline not yet available)	*CACNA1S* and *RYR1*	Reduces risk for malignant hyperthermia	No studies	Not required
Sevoflurane (CPIC guideline not yet available)	*CACNA1S* and *RYR1*	Reduces risk for malignant hyperthermia	No studies	Not required
Antivirals				
Abacavir	HLA-B*57:01	Reduces risk for hypersensitivity reactions	RCT with prospective screening for HLA-B*57:01**; supportive evidence for pharmacogenetics	Required
Atazanavir	UGT1A1*28, *37, rs887829	Identifies patients at high risk for hyperbilirubinemia	No studies	Not required
Peginterferon-α2a	*IFNL3* rs12979860 and rs8099917	Predicts drug response and eligibility for shorter durations of therapy when used in combination with protease inhibitors	No studies	Not required
Peginterferon-α2b	*IFNL3* rs12979860 and rs8099917	Predicts drug response and eligibility for shorter durations of therapy when used in combination with protease inhibitors	No studies	Not required
Ribavirin	*IFNL3* rs12979860 and rs8099917	Predicts drug response and eligibility for shorter durations of therapy when used in combination with protease inhibitors	No studies	Not required
Antifungals				
Voriconazole	CYP2C19*1, *2, *3, *17	Prevents adverse effects (hepatotoxicity, visual disturbances, visual hallucinations) or identifies patients who do not respond	No studies	Not required

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Table 2–Continued

Drug	Genetic Variants‡	Potential Pharmacogenetic Benefit‡	Level of Evidence to Assess Clinical Utility	FDA Labeling Requirement for Testing‡
Antigout agents				
Allopurinol	HLA-B*58:01	Reduces risk for hypersensitivity syndrome, Stevens–Johnson syndrome, and toxic epidermal necrolysis; high frequency of benefit in Han Chinese and Thai populations (HLA-B*58:01 allele frequency: Han Chinese, 11%)	Prospective screening trial for HLA-B*58:01 in Taiwan¶; supportive evidence for pharmacogenetics	Not required
Rasburicase	*G6PD* I, II, III, IV	Reduces risk for acute hemolytic anemia; high frequency of benefit in Asian, European, African, and Middle Eastern populations	No studies	Required
Cystic fibrosis agents				
Ivacaftor	G551D *CFTR* (rs75527207)	Identifies patients who may benefit from ivacaftor treatment	Clinical trials provide supportive evidence for pharmacogenetics¶	Required
Paralytics				
Succinylcholine (CPIC guideline not yet available)	*CACNA1S* rs1800559 and rs772226819	Reduces risk for malignant hyperthermia	No studies	Not required
Lipid-lowering agent				
Simvastatin	SLCO1B1*1, *5, *15, *17	Reduces risk for myopathies and rhabdomyolysis	No studies	Not required

CACNA1S = calcium voltage-gated channel subunit-α_1; CFTR = cystic fibrosis transmembrane conductance regulator; CNS = central nervous system; CPIC = Clinical Pharmacogenetics Implementation Consortium; CYP2C19 = cytochrome P450 2C19; CYP2C9 = cytochrome P450 2C9; CYP2D6 = cytochrome P450 2D6; CYP3A5 = cytochrome P450 3A5; CYP4F2 = cytochrome P450 4F2; DPYD = dihydropyrimidine dehydrogenase; FDA = U.S. Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; IFNL3 = interferon-λ3; INR = international normalized ratio; RCT = randomized controlled trial; RYR1 = ryanodine receptor 1; SLCO1B1 = solute carrier organic anion transporter family member 1B1; TPMT = thiopurine *S*-methyltransferase; UGT1A1 = UDP glucuronosyltransferase family 1 member A1; VKORC1 = vitamin K epoxide reductase complex subunit 1.
† The CPIC considers all level A drugs to have high or moderate evidence in favor of using available genetic information when treatment is prescribed, and ≥1 moderate or strong clinical action is recommended in the CPIC guidelines. The common genetic variants that influence drug response are included along with a description of the potential benefit of using pharmacogenetics to prescribe medications and the level of evidence to assess the clinical utility of pharmacogenetic testing.
‡ References 2 and 3.
§ Reference 7.
|| References 8–11.
¶ Reference 2.
** References 2 and 11.
†† References 11 and 12.

determines the strength of recommendations (strong, moderate, or optional) for specific clinical actions. The gene–drug pairs are graded as A, B, or C, with level A having the highest potential evidence for pharmacogenetic utility, although clinical usefulness has not yet been demonstrated in all cases. The consortium has published guidelines for 15 genes and prescription recommendations for more than 30 medications (2). The CPIC guidelines currently are limited by a lack of evidence for most drugs regarding whether use in genotype-guided therapy improves clinical outcomes for patients; therefore, these guidelines are not intended to justify clinical utility but to help guide the use of genotype information when the genotype is available. We summarize all level A gene–drug pairs in Table 2, providing their potential pharmacogenetic benefits and the current degree of evidence available to support clinical utility.

A need exists for real-time clinical decision support in the electronic health record to facilitate implementation. Pop-ups alerting clinicians of actionable genetic variants and providing guideline-recommended dosages or medication alternatives will help guide prescribing decisions. To facilitate the integration of pharmacogenetics into clinical practice, the Pharmacogenomics Research Network established the Translational Pharmacogenetics Program (TPP). Through the TPP, multigene array testing is performed at baseline in patients at several academic health care centers, and the results are incorporated into the patients' electronic health records for future drug prescribing decisions (13). As of June 2015, more than 20 000 persons had been evaluated through the TPP, with an average turnaround of 14 days for preemptive testing. Nearly 100 000 test results have been added to patients' electronic health records, and about 1 in 4 pharmacogenetic tests produced results that were actionable under CPIC guidelines (14). Laboratories that performed the *CYP2C19* test to assist in prescribing clopidogrel received an 85% reimbursement rate for outpatient claims (15). The TPP has developed clinical decision support tables for the genes *CYP2C19*, *SLCO1B1* (solute carrier organic anion transporter family member 1B1), *TPMT* (thiopurine *S*-methyltransferase), and *CYP2D6*.

The Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) is a database of available genetic tests and

Table 3. Resources for the Application of Pharmacogenetics in Clinical Practice

Resource (URL)	Description
FDA table of pharmacogenetic biomarkers (www.fda.gov/Drugs/ScienceResearch/ucm572698.htm)	List of medications with pharmacogenetic biomarkers on the drug label; some labels recommend specific actions to be taken on the basis of genetic testing outcomes
PharmGKB (www.pharmgkb.org)	Annotations of the CPIC guidelines and freely accessible resources to advance the implementation of pharmacogenetics in the clinic, such as summaries of genetic pathways and gene–drug information tables
TPP tables (www.pharmgkb.org/page/tppTables)	Tables containing information on the genes currently implemented by TPP participating institutions and CDS information that can be accessed by providers
Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr)	Resource for ordering pharmacogenetic tests from specific laboratories
CPIC gene–drug table (https://cpicpgx.org/genes-drugs)	List of the gene–drug pairs reviewed by CPIC, including evaluations on the level of pharmacogenetic evidence and links to CPIC guidelines; the current table contains 127 unique genes and 223 unique drugs
Warfarin dosing calculator (www.warfarindosing.org/Source/Home.aspx)	Online warfarin dosage calculator that physicians can use to estimate drug dosages for patients with available genotype information

CDS = clinical decision support; CPIC = Clinical Pharmacogenetics Implementation Consortium; FDA = U.S. Food and Drug Administration; PharmGKB = Pharmacogenomics Knowledgebase; TPP = Translational Pharmacogenetics Project.

the laboratories that perform them. Currently, the pharmacogenetic tests listed in the registry include 32 genes that can provide predictive information for 188 drug responses. The price of pharmacogenetic testing ranges from $33 to $710, with a median cost of $175 (16). From 2012 to 2013, testing for the 3 CYP genes with the greatest influence on drug metabolism (*CYP2D6*, *CYP2C19*, and *CYP2C9*) was billed to Medicare at an average of $260 per test (17). Turnaround for genetic testing ranges from 1 to 2 days to 4 to 6 weeks, which is problematic if a patient requires immediate therapy. Until randomized clinical trials provide evidence of clinical utility, payers remain cautious about the economic benefit of universal testing among adults to inform prescribing decisions at an unknown point in the future. Although pharmacogenetic variants are an independent risk factor for hospitalization in older adults (aged ≥65 years), the average age at which universal testing would be most cost-effective and beneficial remains to be determined (17, 18).

How Should the Results of Testing Guide Warfarin Prescribing?

The International Warfarin Pharmacogenetics Consortium (IWPC) developed a consensus model for warfarin dosing. Algorithms incorporating clinical and genetic factors to be used to calculate the warfarin dosing were published by both the IWPC and Gage and colleagues (4, 19). The 2 algorithms are similar and contain like variables, including *VKORC1* − 1639G>A, CYP2C9*3, and CYP2C9*2 genotypes; height; weight; age; target INR; amiodarone use; smoking status; and race. Both were created before substantial evidence was discovered for African-specific polymorphisms. Collaboration between the IWPC and Gage and colleagues led to the creation of www.warfarindosing.org, a Web site where physicians can enter a patient's variables into the algorithms to determine the appropriate dose of medication. More recent cohort studies showed that accounting for CYP2C9*5, *6, *8, and *11 and rs12777823 improved both the IWPC and Gage algorithms (6, 20). The CPIC guideline has incorporated recommendations for CYP2C9*5, *6, *8, and *11 and rs12777823 polymorphisms.

The CPIC 2017 warfarin dosing guideline may be accessed at https://cpicpgx.org/content/guideline/publication/warfarin/2017/28198005.pdf. It provides strong recommendations for using either the Gage or IWPC algorithm for warfarin dosing if genotype data for *VKORC1*, CYP2C9*2, and CYP2C9*3 polymorphisms are available for patients of non-African ancestry, with the best evidence for those of European and East Asian descent (5). The online calculator at warfarindosing.org allows physicians to estimate warfarin dosages for patients who either are beginning therapy or have received warfarin for no more than 5 days. The Web site also includes dose-refinement calculations based on existing INR. In addition to the factors in the original Gage or IWPC algorithm, the calculator also accounts for *GGCX* rs11676382, a variant in γ-glutamyl carboxylase that leads to a decrease in warfarin dosage. Furthermore, because of accumulating evidence in support of African-specific alleles, warfarindosing.org included CYP2C9*5 and CYP2C9*6 to the list of alleles that physicians can enter.

Should the Case Patient Have Pharmacogenetic Testing Before Starting Warfarin Therapy?

Randomized controlled trial outcomes suggest that genetically guided warfarin dosing may be most beneficial to persons who already have genotype data available before receiving the initial warfarin dose. The algorithms for genotype-based warfarin dosing are designed to help predict the initial treatment response for patients who have not yet received more than 5 warfarin doses. Because of the variable turnaround time for test results, as previously discussed pharmacogenetic testing is best suited for patients who do not need to begin warfarin therapy emergently or who already have genotypes available and deposited in their electronic health record.

Because our patient does not have pharmacogenetic data available, postponing the start of warfarin treatment is not feasible, and initial dosing should be based on available clinical variables alone. However, if genetic results were readily available and clinical decision support pop-ups showed that the patient carries the AG genotype for *VKORC1* and the *3/*3 *CYP2C9* variant, then his internist should refer to the CPIC 2017 guideline, which strongly recommends genotype-based warfarin dosing for patients of non-African ancestry who have the *VKORC1* and *CYP2C9* variants. After the genotype information and relevant clinical variables (age, 70 years; male; European descent; height, 1.75 m; weight, 90.7 kg; nonsmoker; atrial fibrillation; atorvastatin use with target INR, 2.5) are entered into the warfarindosing.org calculator, the Gage algorithm estimates a therapeutic dosage of 2.1 mg/d and the IWPC estimates a dosage of 1.5 mg/d. A mini-loading dose of 4.6 mg also is recommended to help the patient reach his therapeutic INR faster. The site recommends recalculating INR after 3 warfarin doses to obtain an improved estimate.

SUMMARY

Evidence of the clinical utility of pharmacogenetic testing is available for a few medications. The FDA labels for some drugs require pharmacogenetic testing to avoid genetically associated adverse events or, less often, to identify molecular disease subtypes for which a medication has clinical efficacy. Data from randomized controlled trials conflict but support the benefit of pharmacogenetic testing before warfarin is prescribed for persons of European ancestry. Although the cost of genetic testing is decreasing, routine preemptive pharmacogenetic assessment has yet to be widely adopted because of insufficient evidence to support it and inadequate infrastructure to help physicians make prescribing decisions based on complicated algorithms.

Pharmacogenetics currently is used routinely for only a few medications and, in some cases, for specific ethnic groups. Nevertheless, if pharmacogenetic testing is shown to have clinical benefit in the future, it may increasingly be covered by Medicare and private insurance. As more insurers pay for pharmacogenetic testing and as pharmacogenetic decision support is built into electronic health records, pharmacogenetic information for certain medications will become more widespread.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Grant Support: By the National Center for Advancing Translational Sciences, National Institutes of Health (grant UL1TR001873).

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-2357.

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2018 *ANNALS* POETRY PRIZE

Congratulations to Sylvia S. Villarreal, MEd, MPH, winner of the 2018 *Annals* Poetry Prize. Her poem "Provisions" was published in the 3 April 2018 issue (vol. 168, no. 7, page 497). Ms. Villarreal is Associate Faculty and Program Manager for the Sacred Vocation Program at McGovern Center for Humanities & Ethics.

Ms. Villarreal's poem was selected from poetry published in *Annals* in 2018 by 3 judges: Daniel Bosch of Emory University; Jack Coulehan, poet/physician of Stony Brook; and Abigail Zuger, who writes for *The New York Times*.

For information on the Poetry Prize contest, visit www.annals.org/aim/pages/poetry-prize.

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Final approval of the article: B. Lin, W.K. Chung.
Obtaining of funding: W.K. Chung.
Administrative, technical, or logistic support: W.K. Chung.
Collection and assembly of data: B. Lin, W.K. Chung.