An increasingly robust body of knowledge indicates that human genetic variation modulates disease susceptibility and drug responses. Compelling arguments have been put forward in support of using information on genetic variation to guide the choice of medications and dosages.1,2 The US Food and Drug Administration (FDA) now includes pharmacogenomics data in drug labels,3 and some of these data have acquired “black box” status. Although the use of information about individual genomic variability can improve health care,1 there are challenges to implementing this vision, and therefore the fundamental idea remains largely untested.

The conventional approach to using genetic information to guide prescribing is reactive and often labor-intensive—for instance, a practitioner must first recognize the potential utility of knowing a patient’s genetic variant status when considering a therapeutic; the practitioner must then order the test, receive and interpret the result, and recontact the patient to relay the treatment decision or alter a prescription if it has already been dispensed. Unfortunately, although knowledge relating genomic data to health care has been expanding, the systems to deliver information have not kept pace; the current approach is therefore becoming increasingly impractical, even with respect to a limited number of drugs.

An alternative strategy is to deposit genomic information in patient records preemptively—that is, prior to its being needed in making health-care decisions.1,4 In this scenario, when a drug is being considered for a patient with known genetic variants that could modulate response, the electronic decision-support system would alert the practitioner to the potential for decreased efficacy or adverse effects and would recommend alternative therapies as appropriate. Implicit in this idea is that genetic information can influence health-care decision-making prior to the need for treatment.

The promise of “personalized medicine” guided by an understanding of each individual’s genome has been fostered by increasingly powerful and economical methods to acquire clinically relevant information. We describe the operational implementation of prospective genotyping linked to an advanced clinical decision-support system to guide individualized health care in a large academic health center. This approach to personalized medicine entails engagement between patient and health-care provider, identification of relevant genetic variations for implementation, assay reliability, point-of-care decision support, and necessary institutional investments. In one year, approximately 3,000 patients, most of whom were scheduled for cardiac catheterization, were genotyped on a multiplexed platform that included genotyping for CYP2C19 variants that modulate response to the widely used antiplatelet drug clopidogrel. These data are deposited into the electronic medical record (EMR), and point-of-care decision support is deployed when clopidogrel is prescribed for those with variant genotypes. The establishment of programs such as this is a first step toward implementing and evaluating strategies for personalized medicine.

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information is stored and advice is provided in an advanced health information technology environment: no health-care provider can reasonably be expected to have a personal fund of knowledge large enough to take appropriate action in an era of genomically enabled personalized medicine without automated clinical decision support. The preemptive approach presents substantial challenges, such as selecting the genetic variants for prospective testing and identifying patients who would benefit from such testing. Test results must be aligned with synthesized evidence, formatted to be acted on by decision-support algorithms and rules, and presented as clearly actionable guidance to prescribers.

Addressing these challenges is the key goal of a pharmacogenomics implementation project at Vanderbilt University Medical Center (VUMC) launched in September 2010. We describe the elements of this program and the findings of a 1-year report that focused on implementation of the program in the setting of antiplatelet therapy after placement of cardiovascular stents. We also explore the potential generalizability of these findings. The present implementation, which focuses on prospective assessment of genomic variants that have relevance for drug prescribing, is designated

### Results

#### Overview

The PREDICT team established as the overall goal of the program the prospectively genotyping of patients for “high-value” genetic variants to provide information that could guide drug selection and dosing so as to decrease medication-related adverse events. The evidence-review process identified the relationship between variant CYP2C19 genotypes and reduction in clopidogrel efficacy (included in the FDA’s March 2010 relabeling of the drug) as the first focus of implementation of the program.

#### Table: Program Components and Milestones

<table>
<thead>
<tr>
<th>4Q09</th>
<th>1Q10</th>
<th>2Q10</th>
<th>3Q10</th>
<th>4Q10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics/regulatory/community</td>
<td>Assess ethical landscape</td>
<td>Determine options for genotyping</td>
<td>Research execution and legal authorization</td>
<td>Create patient notification mechanisms</td>
</tr>
<tr>
<td>Bioinformatics and IT infrastructure</td>
<td>Identify EMR-derived, drug outcome phenotypes and incorporate information into decision support</td>
<td>Outpatient Rx system and inpatient order system preparation for logic/rules engine</td>
<td>Development/testing of new decision support logic, integration with existing systems/order sets</td>
<td>Clinical information systems move to production</td>
</tr>
<tr>
<td>Pharmacogenomics and clinical relevance</td>
<td>Validate genetic-based drug outcome phenotypes in the patient population and model relative contributions to clinical event prediction</td>
<td>Create/implement genomic evidence review procedures and committee to assess additive value of genotypes in AE prediction and strength of the evidence</td>
<td>Select initial SNP panel and obtain P&amp;T approval</td>
<td>Initial SNP finalization: move to pt care</td>
</tr>
<tr>
<td>Clinical outcomes and health economics</td>
<td>Determine desired process and outcomes measures for each drug–gene interaction</td>
<td>Implement mechanisms to capture the impact of genetic information on drug ordering</td>
<td>Health-care outcomes study design</td>
<td>Determine cost-effectiveness study needs</td>
</tr>
<tr>
<td>Implementation/logistics/operations</td>
<td>Patient stratification and selection for testing</td>
<td>Develop long-range plan for genotyping and compliant procedures for blood sample collection</td>
<td>CLIA-approved laboratory location prepared and equipment acquired/installed</td>
<td>Identification of initial pt pop: implementation of consent and collection procedures</td>
</tr>
<tr>
<td>Provider and patient communication and education</td>
<td>Determine awareness and education levels/gaps for various audiences</td>
<td>Create and test printed educational material for patients and evidence synthesis for providers</td>
<td>Go-live announcement</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Large-scale real-world pilot of personalized prescribing. Program components: overview and timeline, with key milestones. AE, adverse event; CLIA, Clinical Laboratory Improvement Amendments; EMR, electronic medical record; IT, information technology; P&T, Pharmacy and Therapeutics committee; pop, population; pt, patient; Rx, prescription; SNP, single-nucleotide polymorphism.
The evidence for a pharmacogenomic contribution to clopidogrel response was considered strong enough to justify this first implementation as a quality improvement initiative. This report describes the multiplexed genotyping that was undertaken and also discusses the process for moving CYP2C19 genotype information into routine health-care processes at VUMC.

**Pilot survey of patients’ attitudes**

An initial step was to take advantage of the patient portal MyHealthAtVanderbilt.com (currently used by more than 140,000 patients at our medical center) to survey patients’ attitudes. An optional survey link was placed on the portal and was available for 4 days in May 2010; it elicited responses from 644 patients. The demographic characteristics of these patients are shown in Table 1. Although 84% of respondents found prospective genotyping for use in future care acceptable, they also felt that the practice is not yet routine relative to other common laboratory tests (Table 2): 87% identified cholesterol level testing as being routine, whereas only 20% felt similarly about genetic tests conducted to avoid adverse drug outcomes ($P < 0.0001$ per $\chi^2$ test). The respondents were not given a prespecified definition of “routine,” and the goal was to elicit relative perspectives.

**Patient focus groups**

Focus-group discussions generated a wide range of findings related to clinical pharmacogenomics. Patients expressed a preference for brief verbal notification of testing from their provider rather than a process requiring them to sign a formal patient-consent document. They expressed a wide range of preferences regarding the issue of being informed about the ancillary findings relating to their genetic susceptibility to disease. The overall consensus was that (i) patients should have a choice about how much and which types of ancillary findings they would receive, (ii) providers should not be given any test results that are not also communicated to patients, and (iii) work to implement PREDICT should not be delayed by differences of opinion regarding issues related to ancillary findings.

**Patient notification of test ordering**

To raise awareness of the program, information related to PREDICT has been included in the standard “Consent to Treatment” forms that all patients sign upon registration. Electronic prompts within the patient chart remind providers and other members of the care team to discuss the testing program verbally, document the conversation, record preferences, and provide the brochure. In this way, patients are notified of the PREDICT program and have the opportunity to have questions addressed. (A copy of the brochure is provided in Supplementary Figure S1 online.)

**Synthesis and review of evidence of drug–gene interactions**

In 2009, clopidogrel was the third most commonly prescribed drug in the United States. The primary indication for its use is in patients with coronary artery disease, particularly in the prevention of stent thrombosis in patients who have received drug-eluting stents. Clopidogrel entered the market in 1997, but it was not until 2006 that bioactivation by CYP2C19 was identified as a major factor in its antiplatelet efficacy. In 2009, several single centers reported that individuals homozygous for CYP2C19*2, a loss-of-function allele, displayed increased rates of adverse cardiovascular events while on clopidogrel therapy after coronary stenting. More recently, meta-analyses have confirmed this risk and have extended it to include individuals who are heterozygous (termed CYP2C19*1/*2) for this variant, and they have suggested that variants in the intestinal transporter encoded by ABCB1 may also contribute...

### Table 1  Demographics of patient pilot survey respondents

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>No. of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 20–39</td>
<td>202</td>
</tr>
<tr>
<td>Age 40–59</td>
<td>292</td>
</tr>
<tr>
<td>Age 60–79</td>
<td>143</td>
</tr>
<tr>
<td>Age 80+</td>
<td>8</td>
</tr>
<tr>
<td>Caucasian</td>
<td>521</td>
</tr>
<tr>
<td>African American</td>
<td>44</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
</tr>
<tr>
<td>American Indian</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>71</td>
</tr>
<tr>
<td>Male</td>
<td>224</td>
</tr>
<tr>
<td>Female</td>
<td>421</td>
</tr>
</tbody>
</table>

### Table 2  Responses as to whether a specific test was viewed as routine

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage of responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Routine</td>
</tr>
<tr>
<td>Cholesterol levels</td>
<td>87</td>
</tr>
<tr>
<td>Blood counts used to detect anemia or infection</td>
<td>73</td>
</tr>
<tr>
<td>Hemoglobin A1c (for diabetes management)</td>
<td>59</td>
</tr>
<tr>
<td>Urine test for drug abuse</td>
<td>18</td>
</tr>
<tr>
<td>Testing for HIV/AIDS</td>
<td>24</td>
</tr>
<tr>
<td>Information in genes to avoid bad side effects from medicines</td>
<td>20</td>
</tr>
<tr>
<td>Information in genes to test risk for specific diseases</td>
<td>24</td>
</tr>
</tbody>
</table>
to the risk.\textsuperscript{10,11,16–17} CYP2C19*17 is a "gain-of-function" allele that has been associated with increased bleeding during clopidogrel treatment.\textsuperscript{18} However, the evidence for this outcome is not as strong as for the *2 allele, and the FDA label does not recommend any action in the presence of this genotype. Accordingly, the initial implementation described here does not consider any difference in management of subjects carrying this variant. The development of an implementation plan started with a review of these data by a subcommittee of the standing Pharmacy and Therapeutics (P&T) committee (described more fully in the Materials and Methods section). The review results were in agreement with the FDA’s label and with consensus statements from professional societies\textsuperscript{12} to the effect that there is substantial individual variability in response to clopidogrel and that individuals with decreased CYP2C19 activity display an increased incidence of stent thrombosis and other adverse cardiovascular events. In addition, a retrospective case–control validation study using data from BioVU, a resource that links the DNA extracted from discarded blood samples to de-identified medical records,\textsuperscript{19} found a statistically significant increase in coronary events in patients with variant CYP2C19 genotypes receiving treatment with clopidogrel after coronary stenting (hazard ratio 1.54, 95% confidence interval 1.16–2.06, \(P = 0.003\)).\textsuperscript{20} At VUMC, approximately 4,000 patients underwent coronary angiography in 2008, and clopidogrel was ultimately prescribed in 1,735 (42.5%). Accordingly, the initial group of patients targeted for preemptive genotyping in PREDICT were those scheduled for coronary arteriography, before any decision to prescribe clopidogrel.

**Assay performance**

The VeraCode ADME Core Panel, which includes 184 variants known to have relevance to drug responses, was selected as the initial genotyping platform for the program. To maximize reporting efficiency, patient call rates (the call rate for a patient sample is the proportion of variants that are assigned a genotype out of all variants tested) were established at 97.30%. The average of the observed call rates for controls was 98.6%. After implementation of the assay for patient testing, repeat testing was performed on 150 patients to measure the concordance among the results. The loci showing the highest levels of discordance were GSTT1 CNV and DPYD*9B, and SLC22A6 and CYP2D6*9. However, the CYP2C19 genotype results demonstrated 100% concordance in all the patients. Seven subsequent monthly quality control (QC) plates have shown similar findings, with GSTT1 CNV and DPYD*9B showing the highest level of discordance, thereby indicating that these results should not be used in making decisions concerning patient management. By contrast, no discordant results were observed on these QC plates for CYP2C19 in an additional 200 patient specimens tested in duplicate. Importantly, CYP2C19 allele frequencies for *2/*2 and *17/*17 homozygotes and *2 and *17 heterozygotes are the expected values as compared with the National Center for Biotechnology Information dbSNP (Table 3). There are 10 loci that display poor performance as markers, with locus call rates <95%: CYP1A2*1C (94.47%); ABCB1-2349I (94.4%); SLC22A2-M165I (94.19%); DPYD*9B (92.97%); UGT2B17-CNV (91.68%); CYP1A2*3 (91.65%); UGT2B15*2 (91.43%); TPMT*4 (88.65%); GSTM1*2 (50.42%), and GSTT1 (46.51%).

**Clinical decision-support systems/architecture**

After genotype results are generated, they are stored in a database that is separate from the EMR. The data are archived to a privately owned path on the secure PREDICT application server to protect patient confidentiality. Genetic data that have not been approved for use are stored in a sequestered Oracle database, which resides at the VUMC data center behind its firewall. These data are not accessible by patients or providers but are linked to the patient. The data will be stored long term and will not be released until appropriate, i.e., until a new genotype is deemed actionable. The genotyping data of patients are also protected through the Genetic Information Nondiscrimination Act of 2008, a federal law that prohibits discrimination in health coverage and employment based on genetic information.

Genotypes that have been validated by the established QC metrics and that have been reviewed and approved for clinical implementation by the P&T committee process are deemed “actionable.” After an actionable genotype is recorded, it is converted into a standard notation and interpretation (e.g., CYP2C19*2, “Poor Metabolizer: Reduced anti-platelet effect”), stored in the EMR as a molecular diagnostic laboratory report, and displayed within a “Drug–Genome Interaction” section of the patient summary page of the EMR (Figure 2A). Decision-support modules were developed in collaboration with informatics specialists, medical geneticists, clinical pharmacologists, clinicians practicing in relevant fields, and the P&T committee. Current decision-support modules are integrated with inpatient computerized provider order entry and the outpatient electronic prescribing application.

The data implicating CYP2C19*2 as a modulator of response to clopidogrel did not translate unambiguously into standardized clinical recommendations.\textsuperscript{21,22} However, the approach that our program ultimately adopted was to recommend the use of prasugrel for patients with genotypes associated with

### Table 3  Genotype data and dosing recommendation

<table>
<thead>
<tr>
<th>Category</th>
<th>Genotypes</th>
<th>Recommendation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>CYP2C19*2/*2</td>
<td>Alternative therapy</td>
<td>82 (2.6%)</td>
</tr>
<tr>
<td>Rapid metabolizer</td>
<td>CYP2C19*17/*17</td>
<td>Usual care</td>
<td>154 (4.9%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>CYP2C19<em>2 Heterozygote, CYP2C19</em>3 Heterozygote</td>
<td>Alternative therapy</td>
<td>601 (19.1%)</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>CYP2C19<em>1/<em>1, CYP2C19</em>17 Heterozygote, CYP2C19</em>4 Heterozygote</td>
<td>Usual care (e.g., clopidogrel 75 mg)</td>
<td>2,059 (65.5%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>CYP2C19<em>5 Heterozygote, CYP2C19</em>6 Heterozygote, CYP2C19<em>8 Homozygote, CYP2C19</em>8 Heterozygote, CYP2C19*12 Heterozygote</td>
<td>Usual care</td>
<td>249 (7.9%)</td>
</tr>
</tbody>
</table>
decreased effectiveness of clopidogrel. (The option of recommending a higher dose of clopidogrel was not supported by any data at the time, or since.23) Use of prasugrel in patients with acute coronary syndrome has been associated with a 20% reduction in adverse cardiovascular events at 12 months as compared with clopidogrel, but at the expense of an increased risk of major bleeding.24 In patient subgroups with elevated rates of bleeding events (e.g., those aged >75 years), prasugrel is contraindicated; therefore, in PREDICT, the drug is not recommended in these patients.

Figure 2b shows the point-of-care decision-support guidance triggered when a prescription order is initiated for a patient with a variant CYP2C19 genotype. The guidance implemented in September 2010 focused on CYP2C19*2/*2 homozygotes only; with the availability of data from subsequent meta-analyses,10,11 the guidance was later extended to CYP2C19*1/*2 heterozygotes in 2011. Provider behavior in response to genotypes and outcomes in individuals are being followed for quality-improvement program evaluation at a later date.

Initial uptake and CYP2C19 variant assay results
The program was launched on 15 September 2010. As of 1 August 2011, 3,449 patients had undergone left heart catheterization, and genotyping was ordered in 2,165 (63%). The results of CYP2C19 genotyping are shown in Table 3; as expected in this largely Caucasian patient population, 19% were heterozygous for the *2 allele and 3% were homozygous for the *2 allele. Genotypes are classified as “normal metabolizer” (two copies of the CYP2C19*1 allele), “intermediate metabolizer” (one copy of any one of the *2, *3, or *4 alleles), “poor metabolizer” (two copies of any one of the *2, *3, or *4 alleles), or “rapid metabolizer” (two copies of the *17 allele). “Indeterminate” is used to denote variants for which there is insufficient evidence to warrant being clinically actionable and...
variants that could not be called because of low genotyping performance or low signal.

DISCUSSION

We have gleaned lessons that might be beneficial for other sites that may be considering implementing such a program:

- Commitment is necessary across multiple disciplines as well as by institutional leadership. Clinicians, geneticists, informatics specialists, user-interface experts, pharmacists, pharmacologists, clinical pathologists, and program managers must be committed to implementing the program. Institutional support is critical for salary support for faculty and staff, purchase of new equipment for clinical genotyping, and funding for genotyping of the initial set of patients. The estimated total expense is ~$5 million in the first 2 years. Seeking payer reimbursement for genetic screening to guide drug therapy as specified in approved FDA labels is the next phase of the program. With this in place, we expect the program to ultimately generate cost savings to payers and patients through reduction in adverse outcomes associated with lack of efficacy and toxicity.

- Collaboration with the interventional cardiology team is essential. This involves specific domain expertise as well as buy-in to the program by users. We anticipate that each new drug–genotype rollout will require expertise in terms of pharmacogenomic content as well as domain expertise from physicians who work within the specific targeted practice settings. The initial testing rate was ~75%, and it is possible that the mechanics of ordering a new test or uncertainties over how to interpret the result may have resulted in some clinicians omitting the test order from the precatheterization protocol.

- A key initial step in implementation is to establish appropriate attitudes in the patient population. To accomplish this goal, we leveraged the MyHealthAtVanderbilt.com portal and conducted patient focus groups. We recognize that this group of patients may differ in some ways from the general VUMC population; for example, our survey participants are likely to be more familiar with diagnostic testing because receipt of laboratory test results is a common reason to access the portal. However, this population represents 27% of the current VUMC population and is growing. These methods provided strong support for using genetic information to guide the choice of drugs and dosages, and they provided invaluable input for the implementation of PREDICT.

- The procedure for developing and refining decision-support rules is time-consuming. This process required careful review of the literature and input from multiple constituencies, including clinicians, pharmacy, informatics, and genomics, and repetitive iterations of the formats in which it would be provided (Figure 1). There were advantages to starting the program with clopidogrel: the drug is widely used; there was good evidence that failure of the drug’s efficacy confers risk of substantial morbidity; there is a single common risk allele in subjects of European descent; and the assay is reliable. The drug prescribing information also has a “black box” warning from the FDA. However, even this “simple” example highlighted the nuances and complexities of an implementation program. For example, there is an evolving set of data relating genotypes to outcomes: since initiating PREDICT in September 2010, more than 60 articles have been published that might influence the approach to clopidogrel and CYP2C19. These include articles on clinical outcomes in poor metabolizers,11,26 interaction with proton pump inhibitors,27,28 evaluations of other antiplatelet therapies,29 dose adjustments based on genotype,23,30,31 comparison with ticagrelor,32 further characterization of rare 2C19 alleles,33 use of platelet aggregometry testing,34 and platelet inhibition response.11,26–33,35 Indeed, our initial implementation focused on patients with the *2/*2 genotype and was extended to those with the *1/*2 genotype in March 2011 after publication of a large meta-analysis describing poorer outcome in both homozygotes and heterozygotes.11 Maintaining ongoing awareness of evolving pharmacogenetic evidence for purposes of translation to practice is a daunting task, and with the ever-increasing number of genetic tests and medications approved for pretreatment genetic tests, additional program staff may be necessary to keep up with the field. An increase in institutional funding may be necessary to achieve this.

- Although the evidence for a genetic predictor to clopidogrel response is strong, there is controversy over the utility of genotyping.22 For instance, there are patients who have allele(s) indicating increased risk for drug failure but who are not eligible for alternative therapy (such as prasugrel). The best approach to the management of such patients is as yet unclear. Also, the role of genomic variants in other settings in which clopidogrel is used, such as in neurovascular disease, is unknown.

- There is a need to perform and continuously monitor assay performance in a Clinical Laboratory Improvement Amendments setting. The initial platform that we chose performed well in determining CYP2C19*2 phenotype, but, as described above, there were a number of assays that did not meet clinical performance expectations. Also, with rapidly emerging genotyping technologies, the future use of DNA samples for additional testing is a possibility given that leftover DNA is currently stored. This aspect has not been explored in detail by PREDICT implementation teams and warrants further examination.

We are in the process of adding additional drug–gene pairs, including warfarin–CYP2C9-VKORC1 and simvastatin–SLCO1B1, to PREDICT. Each new drug–gene pair presents issues analogous to those we encountered with clopidogrel: an evolving set of evidence and single-nucleotide polymorphisms, variability across ancestries, newer drugs in the same therapeutic class, and changing regulatory advice. Nevertheless, the principles we have described
here represent important starting points for any program that proposes to implement genotype data into clinical workflow. The fundamental design principle that we embrace is that genotype data are best used in such an effort when they are available in the EMR before drug prescription, that is, “preprescription genotyping.”

**MATERIALS AND METHODS**

**Synthesis and review of evidence of drug–gene variant interactions.** The selection of drug–gene variant pairs to be implemented started with consideration of the available published evidence, followed by formulation of an initial implementation plan. The criteria for including a drug–genome interaction in the program included an established body of evidence in the biomedical literature linking the drug–genome interaction to patient outcomes, therapeutic guidance from the FDA, frequency of the risk-associated allele, and the severity and costs of adverse events that could be averted by genome-tailored prescribing. The decision for initial implementation was also guided by practical considerations such as whether the genotyping platform selected for initial implementation contained the genotypes of interest, the potential complexity of decision-support rules, the number of providers involved, and the availability of faculty with content expertise. Our initial implementation plan also included local validation of drug–genome associations in BioVU, the resource that links DNA samples to de-identified clinical data from VUMC EMR, so that we had confidence that the conditions of interest did indeed exist in the patient population that would be affected by the intervention.

The original implementation plan was developed by a multidisciplinary team that included individuals with expertise in pharmacy operations, clinical laboratory operations, pharmacogenomics, biomedical informatics, and ethics, as well as clinicians with content expertise. In the case of clopidogrel, interventional cardiologists were involved with the design and implementation of the program. The review process was facilitated by a Clinical and Translational Science Awards studio, and final approval was given by the P&T committee. A therapeutics subcommittee of the P&T committee, comprising a cross-section of VUMC clinicians, pharmacogeneticists, and pharmacists, was organized to perform a preliminary review of any drug–genotype variant proposed for consideration. For each actionable genotype, the entire process of genotype validation, review, and approval for clinical implementation took ~1 year.

**Communication with clinicians.** Because the primary clinical site of the initial PREDICT initiative was the cardiac catheterization laboratory, the primary providers were the 13 interventional cardiologists per- mission Amendments–approved high-complexity molecular diagnostics laboratory required additional institutional investments, including space for designated pre- and post–polymerase chain reaction work stations, personnel, laboratory informatics system work stations, specific instrument requirement for the assay, and an automated DNA extractor. To accommodate the anticipated workflow, four medical technologists were trained to perform the assay, with other laboratory staff providing assistance as needed for DNA extraction. General workflow was designed to process samples and return results within three business days after the sample draw.

**Patient attitudes—focus groups.** Previous studies to evaluate patients’ perceptions of pharmacogenetics have focused on general concerns related to privacy and management of ancillary findings but have not attended closely to the practical issues of implementing clinical pharmacogenomics. We conducted 10 focus-group sessions (including two in Spanish) with Vanderbilt patients to elicit input for the design and implementation of PREDICT. The discussions addressed such issues as preferences on how patients would like to be informed of PREDICT; how they would like to provide their consent for pharmacogenomic testing, what they would need to learn from their health-care provider, and how they would like ancillary findings to be managed.

**Ethics review and patient notification of test ordering.** The initial deployment of the PREDICT program was undertaken as a health-care quality improvement initiative based on the program objective to implement FDA regulatory guidance for prescribing, therefore, there is no process to obtain informed consent for research as there would be for a study involving human subjects. However, given the seminal nature of the program, the Medical Center Ethics Committee reviewed the overall program plan before implementation in order to provide guidance. Pilot surveys, focus-group findings, and committee recommendations were used to develop consent procedures, bro- chures, other patient-notification approaches, and policies relating to ancillary findings. Brochures were subsequently developed at a seventh-grade reading level based on the Fry Readability measurement.

**Genotyping assay.** The VeraCode ADMET Gene Core Panel (Illunima, San Diego, CA) was chosen for genotyping studies. The assay targets 184 variants in 34 genes involved in drug absorption, distribution, metabolism, and excretion. Given the highly polymorphic nature of many of the regions assayed, a patient’s sample is analyzed in three separate reactions to optimize the assays and prevent competition from adjacent polymorphic regions within the same gene. Thus, a 96-well plate enables analysis of 32 specimens; the VUMC implementation includes 30 patient specimens as well as a control DNA specimen (with known genotypes for the 184 variants) and a negative control reaction tube with all reagents but no template DNA. Polymorphisms in CYP2C19 analyzed in this panel include common variants (*2 and *17) as well as rarer ones (*3, *4, *5, *6, *7, *8, and *12). Implementation within the institution’s Clinical Laboratory Improv- ement Amendments–approved high-complexity molecular diagnostics laboratory required additional institutional investments, including space for designated pre- and post–polymerase chain reaction work stations, personnel, laboratory informatics system work stations, specific instrument requirement for the assay, and an automated DNA extractor. To accommodate the anticipated workflow, four medical technologists were trained to perform the assay, with other laboratory staff providing assistance as needed for DNA extraction. General workflow was designed to process samples and return results within three business days after the sample draw.

**Assay validation.** Before implementation for patient testing, the assay was validated by the laboratory by comparing the observed genotypes for all 184 variants with the previously reported genotypes for these variants in 54 control DNA cell line samples repeatedly tested on training plates by several technologists. The average concordance was 99.58% (SD = 0.4844%) from 23 cell lines (ParagonDx, Jacksonville, WY) and 98.36% (SD = 1.91%) from 31 additional cell line samples (Coriell, Camden, NJ).

**Assay QC.** In addition to control parameters included by the manufacturer to monitor the performance of each run, a previously validated control specimen was included on each plate to enable measurement of the performance and reproducibility of each variant. Other QC indicators established and monitored include locus call rate, patient and control call rates, frequencies of variant alleles, and monthly QC plates containing specimens tested and reported during the previous month. The locus call rate represents the percentage of patients for whom a result is obtained at a given marker and indicates the overall
performance of an individual variant. A “no call” result can indicate either complete failure of the assay at that site or potentially reduced stringency within a particular run and the consequent inability of the assay to discriminate among possible variants. The patient and control call rates indicate the percentages of variants for which a result was obtained for a given patient. The variant allele frequencies found are compared with those listed in the National Center for Biotechnology Information dbSNP, and the monthly QC plates assess the reproducibility of the assay. Because of the amount of data collected, reports were generated using bioinformatics tools and submitted to laboratory personnel for review.

Quality assurance of implementation. To monitor the initial clinician response to PREDICT and ensure the timely transmission of information, we deployed a multiuser Web-based application to allow a team of nurses and pharmacists to see which of the patients were carriers of an actionable genotype. Prescribing providers who had not yet received clinical decision support or had not reacted to a variant genotype (for example, if the patient’s genetic test result was available only after he or she was discharged) were notified through an electronic message via the EMR, which is a standard means of communication of clinical information within the institution. The quality assurance mechanism enabled the follow-up of genetic results that became available only after the discharge of a patient and before a follow-up visit with a Vanderbilt provider.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS
J.M.P., J.C.D., and D.M.R. designed and performed research and analyzed data. J.F.P., C.L.V.-J., and E.B. designed and performed research and analyzed data. A.H.R. designed and performed research and analyzed data. E.W.C. and J.M. designed and performed research and analyzed data. A.R.W. designed and performed research. K.J. designed research and analyzed data. G.R.B., D.C.C., D.R.M., and E.W.C. designed research.

CONFLICT OF INTEREST
The authors declared no conflict of interest.

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