Ten years ago, the development of genome-based approaches to predict drug response was proposed as one of the “grand challenges” in the future of genomics research. Since that time, evidence for implementation in a clinical setting has been established for a number of drug–gene interactions (DGIs). Implementation of pharmacogenomics into clinical practice, however, has not yet become widely adopted. One reason is the significant challenges associated with implementation, including assessment of the potential benefits of clinical pharmacogenomic testing; definition of the target populations; designation of anticipated scope of pharmacogenomic testing; determination of diagnostic methodologies; development of infrastructure to support reporting, interpretation, and use of results; and establishment of reimbursement for testing. A major source of uncertainty surrounding the feasibility of panel-based genotyping programs is whether pharmacogenomic test results will become “actionable” within a patient’s lifetime and provide clinical benefit given the initial investment in genotyping. The opportunities to use pharmacogenomic information and the number of individuals who will have actionable variants are unknown.

Since September 2010, more than 10,000 patients have undergone preemptive, panel-based pharmacogenomic testing through the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment program. Analysis of the genetic data from the first 9,589 individuals reveals that the frequency of genetic variants is concordant with published allele frequencies. Based on five currently implemented drug–gene interactions, the multiplexed test identified one or more actionable variants in 91% of the genotyped patients and in 96% of African-American patients. Using medication exposure data from electronic medical records, we compared a theoretical “reactive,” prescription-triggered, serial single-gene testing strategy with our preemptive, multiplexed genotyping approach. Reactive genotyping would have generated 14,656 genetic tests. These data highlight three advantages of preemptive genotyping: (i) the vast majority of patients carry at least one pharmacogenetic variant; (ii) data are available at the point of care; and (iii) there is a substantial reduction in testing burden compared with a reactive strategy.
the five DGIs has been serially deployed as they were locally approved. On the basis of this patient cohort, we report here a profile of the genotyped patients, including the genotypes identified, the frequency of actionable variants, and the medication exposures among genotyped patients. We also compare the preemptive, multiplexed genotyping model used for PREDICT with a “reactive” strategy, in which genetic testing would be ordered for individual genes as indicated by medication exposure. Our goal is to begin to quantify benefits of a multiplexed, preemptive approach to pharmacogenomic testing and to thereby inform evaluation of potential implementation at other centers.

RESULTS

Of the first 10,044 patients genotyped, 455 (4.5%) had one or more “no call” results among the five genes implemented and were excluded from analysis. Table 1 includes demographic and descriptive data for the remaining 9,589 patients with complete genotype data for the five currently implemented DGIs. Supplementary Table S1 online includes data for all 10,044 individuals. The median age (63 years) and overrepresentation of men (59%) are no different with inclusion of individuals with no calls. The PREDICT prognostic score represents the estimated likelihood of a patient’s exposure to clopidogrel, warfarin, or a 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) within 3 years. Internally, providers have been encouraged to order PREDICT testing for individuals with scores of at least 40%, although they are free to order the test for other patients as well. We found that the median was just higher than this threshold, at 45%. In total, 5,764 (60%) of those genotyped were in the PREDICT preemptive model target population of patients (prognostic scores ≥40% or with a history of coronary artery stent placement), and this subset had more exposures to antiplatelet and cholesterol medications than the genotyped cohort as a whole (Table 1). Among the entire cohort, the race/ethnicity of the majority of the cohort was primarily identified as European American, not Hispanic (EA) n = 6,986; 953 African American, not Hispanic (AA) individuals were also included, among whom women were overrepresented (n = 520, 55%). A total of 268 (3%) individuals were of unknown race, 105 (1%) were Asian, and 31 (0.3%) were Alaskan, Indian, or Pacific Islander. With respect to ethnicity, 110 (1%) individuals were identified as Hispanic, and 1,360 (14%) were of unknown ethnicity.

Table 2 describes the genotype data obtained for actionable SNPs in the genes of interest. The frequency of variant genotypes did not differ between the cohort as a whole and the PREDICT preemptive model target population. The proportion of individuals with variants in genes relevant to simvastatin (SLCO1B1), warfarin (CYP2C9 and VKORC1), and tacrolimus (CYP3A5) differed between EA and AA patients, as expected on the basis of reported differences in minor allele frequencies between these populations (Table 2). Using the definitions described in Supplementary Table S2 online, the number of individuals with “actionable” (prompting CDS to suggest a change in dose or medication) and “high-risk” (homozygous for variants in CYP2C19, SLCO1B1, CYP2C9, or TPMT, known to greatly increase the likelihood of a severe adverse outcome) genotypes for each DGI was determined (Figure 1 and Supplementary Table S3 online). For example, identification of either heterozygosity or homozygosity for the SLCO1B1*5 variant leads to genotype-guided advice if a provider orders or prescribes simvastatin, so both genotypes are “actionable,” a finding identified in 26% of all patients. However, individuals homozygous for this variant are at far higher risk than heterozygous or wild-type individuals (20-fold increased risk for homozygotes vs. 4-fold for heterozygotes, as compared with noncarriers);
only homozygosity is considered “high risk” and was found in 2% of patients. As discussed in the Methods section, the predefined high-risk alleles are CYP2C19*2/*2, SLC01B1*5/*5, and CYP2C9*3/*3, in addition to homozygosity or compound heterozygosity for TPMT*2 or *3.

The CYP3A5*1 genotype codes for a functional CYP3A5 enzyme and is the most common allele among AAs, but not among EAs. However, standard dosing recommendations for tacrolimus are based on individuals with the CYP3A5*3 (non-functional) genotype, the most common genotype in EAs. In our system, actionability is based on CYP3A5*1; having one or no copy of CYP3A5*3, indicating one or two copies of functional CYP3A5*1, respectively, is actionable and was identified in 24% of patients. Analysis of the cumulative frequency of

### Table 1: Frequency of Genetic Variants

| Gene     | Allele | All (N = 9,589) | European American, not Hispanic (n = 6,986) | African American, not Hispanic (n = 953) | PREDICT preemptive model target population (n = 5,764)
|----------|--------|----------------|---------------------------------------------|------------------------------------------|---------------------------------------------|
| CYP2C19  |        |                |                                              |                                          |                                             |
| rs4244285 (*2) Heterozygote | 2,398 (25%) | 1,751 (25%) | 235 (25%) | 1,431 (25%) |
| rs4244285 (*2) Homozygote | 238 (2%)  | 170 (2%)   | 25 (3%)  | 123 (2%)  |
| rs4986893 (*3) Heterozygote | 14 (0%)  | 2 (0%)     | 1 (0%)   | 3 (0%)    |
| rs4986893 (*3) Homozygote | 2 (0%)   | 0          | 0        | 1 (0%)    |
| rs28399506 (*4) Heterozygote | 46 (0%)  | 36 (1%)    | 1 (0%)   | 26 (0%)   |
| rs28399506 (*4) Homozygote | 0        | 0          | 0        | 0         |
| rs56337013 (*5) Heterozygote | 1 (0%)   | 1 (0%)     | 0        | 1 (0%)    |
| rs56337013 (*5) Homozygote | 0        | 0          | 0        | 0         |
| rs72552267 (*6) Heterozygote | 6 (0%)   | 5 (0%)     | 1 (0%)   | 4 (0%)    |
| rs72552267 (*6) Homozygote | 0        | 0          | 0        | 0         |
| rs41291556 (*8) Heterozygote | 52 (1%)  | 44 (1%)    | 1 (0%)   | 34 (1%)   |
| rs41291556 (*8) Homozygote | 1 (0%)   | 1 (0%)     | 0        | 0         |
| SLC01B1  |        |                |                                              |                                          |                                             |
| rs4149056 (*5) Heterozygote | 2,279 (24%) | 1,805 (26%) | 66 (7%)  | 1,346 (23%) |
| rs4149056 (*5) Homozygote | 181 (2%)  | 147 (2%)   | 3 (0%)   | 104 (2%)  |
| CYP2C9   |        |                |                                              |                                          |                                             |
| rs1799853 (*2) Heterozygote | 1,998 (21%) | 1,622 (23%) | 42 (4%)  | 1,229 (21%) |
| rs1799853 (*2) Homozygote | 156 (2%)  | 129 (2%)   | 1 (0%)   | 92 (2%)   |
| rs1057910 (*3) Heterozygote | 1,046 (11%) | 831 (12%)  | 31 (3%)  | 644 (11%) |
| rs1057910 (*3) Homozygote | 29 (0%)   | 23 (0%)    | 1 (0%)   | 14 (0%)   |
| VKORC1   |        |                |                                              |                                          |                                             |
| rs9923231 Heterozygote | 4,170 (43%) | 3,305 (47%) | 182 (19%) | 2,507 (43%) |
| rs9923231 Homozygote | 1,185 (12%) | 943 (13%)  | 10 (1%)  | 687 (12%) |
| TPMT     |        |                |                                              |                                          |                                             |
| rs1800462 (*2) Heterozygote | 52 (1%)   | 44 (1%)    | 2 (0%)   | 32 (1%)   |
| rs1800462 (*2) Homozygote | 0       | 0          | 0        | 0         |
| rs1800460 (*3B) Heterozygote | 1 (0%)   | 0          | 0        | 0         |
| rs1800460 (*3B) Homozygote | 0       | 0          | 0        | 0         |
| rs1142345 (*3C) Heterozygote | 171 (2%)  | 68 (1%)    | 81 (8%)  | 107 (2%)  |
| rs1142345 (*3C) Homozygote | 2 (0%)   | 0          | 2 (0%)   | 2 (0%)    |
| rs1800460+rs1142545 (*3A, 3D, 3E) Heterozygote | 649 (7%)  | 514 (7%)   | 20 (2%)  | 380 (7%)  |
| rs1800460+rs1142545 (*3A, 3D, 3E) Homozygote | 9 (0%)   | 6 (0%)     | 0        | 4 (0%)    |
| CYP3A5   |        |                |                                              |                                          |                                             |
| rs776746 (*3) Heterozygote | 1,663 (17%) | 918 (13%)  | 402 (42%) | 1,003 (17%) |
| rs776746 (*3) Homozygote | 7,332 (76%) | 6,022 (86%) | 98 (10%) | 4,357 (76%) |

PREDICT, Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment.

*PREDICT preemptive model target population, including those with history of coronary artery stent and/or with PREDICT risk score >40, indicating a 40% likelihood of exposure to clopidogrel, warfarin, or a statin within 3 years. High-risk genotype (not all-inclusive, as compound heterozygosity for TPMT variants is also of high risk).
Actionable genotypes (e.g., at least one actionable variant identified) revealed that of the 9,589 individuals with complete genotype data for these five DGIs, 8,760 (91%) have at least one actionable genotype (Figure 1), whereas 5% have at least one high-risk genotype (see Supplementary Table S3 online).

Each of the genes of interest has been studied in large populations, enabling the comparison of the observed frequency of actionable variants in each population with the expected frequency based on published minor allele frequencies for EA and AA populations. The frequencies of predicted and observed actionable and high-risk genotypes for each of the five DGIs are depicted in Figure 2a–c. For each of the five DGIs, observed frequencies closely approximate the expected frequencies.

EMR data were searched to determine the number of individuals with actionable genotypes who had evidence of exposure to the associated medication or medication class at any time in their history. Due to the recent implementation of the PREDICT program, medication initiations may have predated genotyping and incorporation of genotype-guided CDS into the EMR. More than half of the patients with actionable genotypes affecting clopidogrel and simvastatin response have been exposed to these medications at some point, and nearly one-fourth of those with actionable warfarin genotypes have evidence of warfarin exposure (Figure 2a–c). Among those with high-risk genotypes, no individuals with high-risk $\text{TPMT}$ genotypes (homozygous variant) have been exposed to date to thiopurine medications ($n = 0/19$). Of the 181 individuals homozygous for $\text{SLCO1B1}$ variation, 110 (61%) had evidence of simvastatin exposure, and an additional 32 (18%) have been exposed to a different statin. Of these 110, the last statin mentioned in the EMR was a simvastatin alternative in 55 (50%) individuals. Because the program has only recently started, the frequency with which the data will be used will increase with time.

Analysis of the cumulative frequency of actionable genotypes among AA individuals revealed that all but 40 of the 953 (96%) had at least one actionable genotype (Figure 2f). Using published minor allele frequencies for variants in six additional genes with known pharmacogenomic associations ($\text{CYP2D6}$, $\text{HLA-B}$, $\text{DPYD}$, $\text{G6PD}$, $\text{IL28B}$, and $\text{UGT1A1}$; see Supplementary Table S4 online), we estimate that implementation of these next pharmacogenomic target DGIs will increase the proportion of EA individuals with at least one actionable variant to 96% (Figure 2e).2,14–22 EA individuals with two or more actionable genotypes would increase from 49 to 74% with the addition of six more genes, and the proportion with three or more would increase from 14 to 39% (Figure 2e).

Among the individuals with one or more actionable genotypes, 4,018 (42% of the entire cohort) had evidence of exposure to the risk-associated medication or medication class (Figure 2d–f). In AA patients, 217 (23% of all AA patients) had actionable genotypes and evidence of an actionable medication exposure. In the PREDICT preemptive model target population, 2,744 (48%) were exposed to one or more medications for which they had actionable genotypes, reflecting the higher medication exposure rates in this subgroup. Medication exposure rates were further elevated when looking at the specific subgroups of patients with PREDICT risk score $>70$—among which 813 of 846 (96%) patients were exposed to one or more of the target medications—and at those who had been treated with a coronary artery stent—among which all but 12 of the 2,410 patients were exposed (see Supplementary Table S5 online). Patients receiving any one of the five target medications had a high likelihood of receiving an additional target medication. Among those who had received antiplatelet therapy with clopidogrel or prasugrel, 93% received a second PREDICT medication. Rates for second target medication exposure for those receiving thiopurine, tacrolimus, warfarin, and statin drugs were 91, 87, 84, and 69%, respectively.

The documented exposures to drugs and drug classes with established DGIs provide the opportunity to compare the preemptive, panel-based genetic test model used for PREDICT with a theoretical reactive genotyping model based on serial single-gene testing as indicated by patient prescription for each medication (Figure 3). As compared with the 9,589 panel-based genetic tests performed on patients through PREDICT, determination of genotype using a reactive strategy would have resulted in 14,656 tests (1.7-fold more tests). Within the PREDICT preemptive model target population, in which medication exposures occurred at a higher rate, reactive testing would have required nearly twice as many tests to be conducted (10,269 tests vs. 5,764 panel-based tests completed).

**DISCUSSION**

In this study analyzing the first ~10,000 individuals clinically genotyped through the PREDICT program, the vast majority of individuals (91%) have at least one actionable genotype...
Figure 2  Predicted and observed actionable genotypes and associated medication exposures. In panels a–c, for each drug–gene interaction (DGI), the frequencies of expected actionable genotypes based on reported minor allele frequencies (open triangles), observed actionable genotypes (open circles), expected frequency of medication exposures among patients with actionable genotypes (filled triangles), and observed actionable genotype with exposure to the associated medication (filled circles) are shown for (a) all 9,589 genotyped patients, (b) 6,986 patients of European American (EA) descent, and (c) 953 patients of African American (AA) descent. Clopidogrel exposure includes clopidogrel and/or prasugrel, the alternative agent. Statin exposure includes simvastatin and/or alternative 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, and rosuvastatin). In panels d–f, cumulative frequency of individuals having observed actionable genotypes based on the five currently implemented DGIs (open circles), cumulative frequency of individuals with actionable genotypes exposed to associated medications (filled circles), and predicted cumulative frequency of actionable genotypes based on a total of 12 pharmacogenes (“x”) are shown for (d) all genotyped patients, (e) patients of EA descent, and (f) patients of AA descent.
among the five DGIs implemented to date, highlighting the usefulness and potential benefit of panel-based genotyping for pharmacogenomic testing. Although drug-dosing regimens are tested and approved on the basis of population data, significant variation in drug response exists, much of which can be attributed to common genetic variation in genes associated with drug metabolism and response. Although testing a large number of pharmacogenes may be expected to identify clinically important variants in many patients, the degree of impact may be underestimated, as illustrated by our finding that more than 9 out of 10 patients tested have at least one actionable variant among the small range of DGIs tested, even while using a conservative definition for “actionable.” Importantly, the impact in AA patients is even greater, with nearly all individuals having at least one actionable genotype. Some of this higher estimate is driven by the designation of the ancestral CYP3A5*1 allele as actionable, further emphasizing the need to include diverse ancestries in large genome analyses.

Comparing genotypes from the PREDICT cohort with those reported in previously published cohorts demonstrates that the proportions are similar to predicted minor allele frequencies. This validates the performance of the clinical test but, more importantly, suggests that for designing such clinical tests and determining cost and benefit, published minor allele frequencies can be relied on for modeling the number of clinically significant findings that will be identified through testing. Our estimate of the addition of variants in six additional genes to the PREDICT program shows that the impact of these additional genotypes on the frequency of having at least one actionable genotype is minimal, but the frequency of having multiple actionable genotypes increases more substantially.

Critical to the success of a pharmacogenomic testing program is the development of a framework for provider notification and follow-up of actionable genotypes. To improve patient outcomes, identification of risk based on a DGI must be followed by risk modification through dosage adjustment, medication change, or changes in therapeutic monitoring. Currently, ideal methods have not yet been established for communicating pharmacogenetic test results and their interpretations to the spectrum of providers involved in a patient’s care. In developing such methods, accurate prediction of the number of patients with actionable findings will help determine the requisite resources to optimize patient safety.

Defining the genotypes that are of clinical value has significant impact on the frequency of patients with “valuable” genotypes. The “actionable” genotype definition used here is conservative, requiring the genotype result to trigger a recommendation for

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**Figure 3** Medication exposures among genotyped individuals. (a) Medication exposure among all (open circles) and PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) preemptive model target population (filled circles) individuals for each medication currently implemented in the PREDICT program. (b) Cumulative number of drug exposures to medications implemented in the PREDICT program, in order of implementation. Drug 1: clopidogrel and/or prasugrel; 2: statins; 3: warfarin; 4: thiopurines; and 5: tacrolimus. The solid horizontal line indicates the total number of panel tests completed in the entire cohort, and the dotted line indicates the number of panel tests completed in the target population.
change in standard therapy. In practice, all genotypes can be clinically useful; for example, in a patient needing antplatelet therapy, the CYP2C19*1/*1 genotype (homozygous wild type) reassures the provider that clopidogrel is probably efficacious. Using the more stringent criteria of “high-risk genotypes,” 5% of patients were identified as being at risk. In the panel-based model, these rarer, high-risk genotypes are provided along with more common actionable genotypes.

As expected on the basis of published minor allele frequencies, the frequencies of actionable genotypes for specific DGIs are different between the EA and AA populations. EAs had a higher frequency of actionable genotypes related to simvastatin than did AAs, and participants in pharmacogenomic research studies identifying the SLCO1B1 risk variant have been predominantly of European–American descent. However, individuals of African descent are at higher risk for statin-induced myopathy; different SNPs may be present and confer risk for inefficacy or toxicity among AAs, as well as Asians, Hispanics, or other populations. These variants may be incorporated into future clinical tests. Furthermore, resequencing of large populations is identifying rare variants in pharmacogenes. As these are functionally characterized and incorporated into preemptive testing models, the portion of subjects with no actionable variants will fall further. In this study, AAs have a high frequency of actionable genotypes related to tacrolimus. Although clinicians have long been aware of ancestry-based differences in drug response for this medication, the heterogeneity of actionable alleles within each group (e.g., 10% of AA patients are homozygous for CYP3A5*3) suggests that genotyping will provide a more accurate prediction of drug response than race/ethnicity. Using the metric of “actionable genotypes” to determine the value of pharmacogenomic testing, the PREDICT test demonstrates the greatest value for AA patients, in whom actionable genotypes were identified in 96% of patients. In general, despite a paucity of pharmacogenomic research in minority populations, clinical pharmacogenomic programs such as PREDICT have the potential to improve medication outcomes for non-EA patients by personalizing therapeutic doses and medication choices, just as incorporation of genetic ancestry has been shown to increase precision in evaluating pulmonary function.

In contrast to indication-based testing, in which pharmacogenomic testing is pursued for specific genes as indicated on the basis of medication exposure, the panel-based PREDICT approach tests genotypes for all potential DGIs; this will result in “unnecessary” genetic testing in patients with no exposure to the associated medication. Pharmacogenotypes are most valuable in cases in which a patient has an actionable genotype and is exposed to the associated medication. Given the relatively recent initiation of the PREDICT program and the serial implementation of DGIs, there are not sufficient accumulated data to specifically quantify drug exposures occurring after genotype and CDS data are entered into the EMR. However, using lifetime exposures (to date) to the associated medications as an approximation, the majority of patients genotyped were prescribed one of the medications, and, more importantly, among those with actionable genotypes, more than 40% had evidence of exposure to the specific medication associated with that genotype. Moving forward, each of these cases represents an opportunity to improve therapeutic outcomes.

Our comparison of preemptive panel-based testing with a reactive testing strategy demonstrates that preemptive testing results in far fewer tests being performed. A formal pharmacoeconomic evaluation is under way, but given that the panel-based test is comparable in cost to single-gene assays, it is reasonable to expect that the panel-based test will prove to be more cost effective than individual assays. Preemptive panel-based testing has the added benefit of timeliness. If the panel is completed before medication exposure or at the point of first medication prescription, genotypes are available at the time of medication order/prescription for all subsequent medications. Our previous work has demonstrated that the opportunities to use genetic test results to guide care are common, with 65% of regular clinic patients receiving a medication with pharmacogenetic indications. Additional genotypes present on the panel or new DGIs for existing genotypes may also prove clinically useful in the future, increasing utility without additional testing costs.

The retrospective nature of this study and the selection process for inclusion of patients in the PREDICT program, either by indication, identification via predictive modeling, patient request, or physician preference, may limit the applicability of these findings to other cohorts. However, the finding that this selected patient population closely mirrors expected results based on population data is encouraging in that accurate predictions can be made for other clinical settings. Provided there are reported genotype frequency data for appropriate races/ethnicities in a population, accurate predictions can be made for other clinical settings.

Taken together, these data highlight the potential of panel-based pharmacogenotyping to identify actionable variants. The frequency with which patients harboring actionable variants are exposed to the medications of interest, the degree to which providers make use of genotype-guided CDS, and the extent to which adverse therapeutic outcomes will be reduced remain to be determined.

METHODS
Institutional pharmacogenotyping program. At Vanderbilt, the PREDICT program began pharmacogenomic testing in September 2010. This program is unique in its approach to preprescription genotyping, leveraging both a predictive model to identify patients at risk for future exposure to target medications and indication-triggered testing to obtain a multiplexed genotype test. This preemptive approach enables genotype-guided CDS for providers at the time of medication initiation by prescription or order. Genotyping is completed using a panel-based test, currently with the VeraCode ADME Core panel (Illumina, San Diego, CA), through which genotypes for 184 variants in 34 genes are determined. Testing is performed in a Clinical Laboratory Improvement Amendments–certified laboratory that participates in the College of American Pathologists biannual pharmacogenetics proficiency exchange. Before reporting clinical results for the initial gene, CYP2C19, the genotypes of 56 commercially purchased control samples were tested, and 100% concordance for CYP2C19 was obtained. Subsequent clinically actionable SNPs were monitored for accuracy before reporting into patient medical records by measuring concordance. Although 100% concordance rates would be ideal, for most, concordance rates of >99% were achieved. After the launching of an actionable SNP, the performance of each is monitored monthly and
documented as part of laboratory quality control. Specific genotype results are released into the EMR after review of the relevant evidence, development of genotype-specific CDS, and approval by institutional oversight.

In September 2010, PREDICT testing was initiated for patients undergoing cardiac catheterization because ~40% of these patients receive clopidogrel. CDS for clopidogrel prescription based on patient genotypes for CYP2C19 represented the first targeted patient genotyping and clinically implemented DGI at Vanderbilt. Since then, the program has expanded to provide genotyping to patients presenting for both inpatient and outpatient care, with accompanying prompts to providers to consider testing in patients presenting for cardiac catheterization or treatment of acute lymphocytic leukemia (due to exposure to thiopurine therapy), and for those with 40% or higher likelihood of exposure to clopidogrel, warfarin, or a statin in the next 3 years by the PREDICT statistical model. Portions of this study were supported by the Vanderbilt Institute for Clinical and Translational Research under National Center for Advancing Translational Sciences/National Institutes of Health (NIH) grant UL1 TR000445; and NIH/National Institute of General Medical Science Clinical Pharmacology Training Program ST32 GM007569-33 (supporting S.L.V.D.).

AUTHOR CONTRIBUTIONS
S.L.V.D., Y.S., E.A.B., J.S.S., J.F.P., J.C.D., and D.M.R. wrote the manuscript. S.L.V.D., Y.S., E.A.B., J.S.S., J.F.P., and D.M.R. designed the research. S.L.V.D., E.A.B., J.C.D., and D.M.R. performed the research. Y.S. and J.S.S. analyzed the data.

CONFLICT OF INTEREST
The authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Genotype-guided pharmacotherapy has been clinically implemented in limited settings. At Vanderbilt, the PREDICT program has preemptively tested pharmacogenomic variants for the clinical care of more than 10,000 patients to date.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We determined the frequencies of actionable genotypes and medication exposures for five DGIs used in PREDICT and compared the number of tests obtained under panel-based preemptive testing vs. indication-based testing.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ One or more actionable variants were identified in 91% of patients. Most genotyped patients had at least one drug exposure, and those with one drug exposure were likely to be exposed to a second target drug. Fewer genetic tests are performed with preemptive genotyping than while using a reactive strategy.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ These data inform potential implementation of pharmacogenomic programs and may lead to increased adoption of clinical pharmacogenomic programs.

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