Title: "The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenetic Implementations Across Diverse Healthcare Systems"

Authors: [1,2]Jasmine A. Luzum, [3]Ruth E. Pakyz, [4]Amanda R. Elsey, [5]Cyrine E. Haidar, [6,7]Josh F. Peterson, [11]Michelle Whirl-Carrillo, [2]Samuel K. Handelman, [3]Kathleen Palmer, [8]Jill M. Pulley, [9]Marc Beller, [10]Jonathan S. Schildcrout, [8]Julie R. Field, [4]Kristin W. Weitzel, [4]Rhonda M. Cooper-DeHoff, [4]Larisa H. Cavallari, [12]Peter H. O'Donnell, [11]Russ B. Altman, [13]Naveen Pereira, [12]Mark J. Ratain, [6]Dan M. Roden, [14]Peter J. Embi, [2,15]Wolfgang Sadee, [11]Teri E. Klein, [4]Julie A. Johnson, [5]Mary V. Relling, [16]Liewei Wang, [16]Richard M. Weinshilboum, [3]Alan R. Shuldiner, [17]Robert R. Freimuth, for the Pharmacogenomics Research Network Translational Pharmacogenetics Program

Affiliations:

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

[2]Center for Pharmacogenomics, College of Medicine, Ohio State University, Columbus, OH, USA

[3]Program for Personalized and Genomic Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA

[4]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, Gainesville, FL, USA

[5]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[6]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[7]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[8]Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[9]Office of Research Informatics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version record. Please cite this article as doi:10.1002/cpt.630.

[10]Department of Statistics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[11]Stanford University School of Medicine, Palo Alto, California, USA

[12]Center for Personalized Therapeutics, University of Chicago, Chicago, IL, USA

[13]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

[14]Department of Biomedical Informatics, Ohio State University, Columbus, OH, USA

[15]Department of Cancer Biology and Genetics, College of Medicine, Ohio State University, Columbus, OH, USA

[16]Department of Molecular Pharmacology & Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA

[17]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

Author for correspondence: Robert R. Freimuth, PhD, Address: 200 First Street SW, Rochester, MN 55905, Phone: 507-284-0753, Fax: 507-284-1516, Email: Freimuth.Robert@mayo.edu

Words (4,000 maximum excluding abstract, references, tables, and figures): 3983

References (50 maximum): 45

Tables & Figures (7 maximum): 3

Online Supplementary Materials: 3 Excel files and 1 PDF file

Key words: pharmacogenetics; implementation; healthcare system; metrics; outcomes

Abstract (150 words maximum)

Numerous pharmacogenetic clinical guidelines and recommendations have been published, but barriers have hindered the clinical implementation of pharmacogenetics. The Translational Pharmacogenetics Program (**TPP**) of the NIH Pharmacogenomics Research Network was established in 2011 to catalog and contribute to the development of pharmacogenetic implementations at eight US healthcare systems, with the goal to disseminate real-world solutions for the barriers to clinical pharmacogenetic implementation. The TPP collected and normalized pharmacogenetic implementation metrics through June 2015, including gene-drug pairs implemented, interpretations of alleles and diplotypes, numbers of tests performed and actionable results, and workflow diagrams. TPP participant institutions developed diverse solutions to overcome many barriers, but the use of Clinical Pharmacogenetics Implementation Consortium (**CPIC**) guidelines provided some consistency among the institutions. The TPP also collected some pharmacogenetic implementation outcomes (scientific, educational, financial, and informatics), which may inform healthcare systems seeking to implement their own pharmacogenetic testing programs.

Introduction

Patients' risk for adverse drug effects or therapeutic failure might be decreased by personalizing pharmacotherapy for select drugs to each individual's genetics. Indeed, the United States Food & Drug Administration (**US FDA**) lists over 160 drugs with "Pharmacogenomic Biomarkers in Drug Labeling,"(1) in which many drugs include recommendations for adjustment of therapy based on patients' genetics. Moreover, the Clinical Pharmacogenetics Implementation Consortium (**CPIC**) has published pharmacogenetic guidelines for 33 drugs as of mid-2016.(2) Despite the growing body of knowledge of gene–drug interactions and their clinical significance, the clinical implementation of pharmacogenetics has been slow. A recent nationwide survey found that only 10% of physicians felt adequately informed about pharmacogenetic testing, and only 13% had ordered a pharmacogenetic test within the past 6 months.(3) The slow clinical implementation of pharmacogenetics is due to several recognized barriers,(4, 5) including (i) logistics of performing accurate and rapid turnaround genotyping in a Clinical Laboratory Improvement Amendments (**CLIA**)-approved laboratory setting; (ii) lack of infrastructure or a standardized format for the return of pharmacogenetic test results in the electronic health record (**EHR**); (iii) lack of infrastructure or standardized format for pharmacogenetic clinical decision support (**CDS**) in the EHR; (iv) lack of prospective genotype-directed randomized clinical trials validating pharmacogenetic-guided approaches; (v) inexperience of clinicians in interpreting and acting on pharmacogenetic information; (vi) paucity of clear and consistent recommendations for pharmacogenetic testing by professional associations; and (vii) cost and reimbursement considerations related to pharmacogenetic testing.

The Translational Pharmacogenetics Program (**TPP**) of the NIH Pharmacogenomics Research Network (**PGRN**) was established in 2011 as an implementation science project to study and contribute to the development of pharmacogenetic implementations at eight US healthcare systems. The overall goals of the TPP were to harness the multidisciplinary expertise and extensive institutional investments

at each participating site, implement routine pharmacogenetic-based dosing and drug selection within diverse healthcare systems, identify common approaches to implementation, identify and propose solutions to logistic barriers to implementation, and disseminate 'best-practice' guidelines for overcoming those barriers.(4) The TPP included eight healthcare systems affiliated with the following institutions: Harvard University, Mayo Clinic, Ohio State University, St. Jude Children's Research Hospital, University of Chicago, University of Florida, University of Maryland, and Vanderbilt University. In this manuscript, we report the experience from seven TPP sites through June 2015 on pharmacogenetic implementation metrics, areas of diversity in pharmacogenetic implementations, and areas of similarity in pharmacogenetic implementations. (Harvard University chose to explore next generation sequencing approaches and had not yet implemented pharmacogenetic testing at the time of data collection). We also report on selective scientific, educational, financial, and informatics outcomes at some of the TPP sites. We believe that the metrics and outcomes of these initial pharmacogenetic implementations across the TPP demonstrate the first steps and approaches for overcoming the aforementioned barriers to pharmacogenetic clinical implementation, which will be useful for other health care systems considering clinical implementation of pharmacogenetics.

Results

Implementation metrics

A major coordinated task of the TPP was to summarize metrics that described each of the pharmacogenetic implementations across seven TPP sites. A summary of the major metrics of the pharmacogenetic implementations through June 2015 is presented in Table 1 (n = 20,258 total patients tested), and areas of similarity and diversity are discussed in the following sections. The numbers of distinct test results, total numbers of results reported to EHRs, and the numbers of actionable genotypes for select gene-drug pairs implemented through June 2015 are displayed in Table 2.

Actionable results were defined by CPIC guidelines for all gene-drug pairs, except for *CYP2C9/VKORC1* where actionable was defined by the FDA label when the expected warfarin dose did not include the standard 5mg starting dose, and the individual sites defined their own actionable *CYP2D6*-codeine results. While all of the results could inform decisions about drug therapy, nearly 1 out of 4 (23.6%) of the pharmacogenetic tests (n = 22,928 total) were classified as potentially actionable since the associated CPIC recommendation included a change of drug or dose.

For the three most commonly implemented gene-drug pairs (*CYP2C19*-clopidogrel, *TPMT*-thiopurines, and *SLCO1B1*-simvastatin; Table 3), additional detailed metrics from each TPP site were collected and normalized into tables that were made publicly accessible via the Pharmacogenomics Knowledgebase website (**PharmGKB®**)(6) (https://www.pharmgkb.org/page/tppTables) and also available online as supplementary material (online supplemental files 1, 2, and 3). These tables report the specific genotyping platforms used, haplotypes tested and their functional interpretations, diplotype and phenotype counts, modes of pre-test and post-test CDS, and clinical recommendations based on the test results. For the most commonly implemented gene-drug pair (*CYP2C19*-clopidogrel), workflow diagrams illustrating the clinical processes and flow of data related to the pharmacogenetic implementations were also created by some of the sites and made publicly available (https://www.pharmgkb.org/page/tppTables) and online as supplementary material (online supplemental file 4).

Areas of diversity

The pharmacogenetic implementation metrics revealed that the TPP sites were diverse in nearly every area of their pharmacogenetic implementations (Table 1). Two sites implemented pharmacogenetic testing as part of clinical research protocols, two sites implemented as part of clinical

practice, and three sites implemented pharmacogenetic testing via both clinical research protocols and clinical practice. The clinical research implementations performed pharmacogenetic testing for patients that were recruited and consented for IRB-approved clinical research studies, whereas the clinical practice implementations added pharmacogenetic testing in certain clinical settings to guide drug therapy decisions. A surprising area of diversity was the roles of those directly involved in the pharmacogenetic testing workflow for *CYP2C19*-clopidogrel (online supplemental file 4). For example, pharmacists had direct roles in the patient interface at the University of Florida(7) and St. Jude Children's Hospital(8), but pharmacists were selectively involved in specific drug-gene interactions at Vanderbilt University.(9) Pharmacists were not involved in the patient interface at Ohio State University(10) or the University of Maryland,(11) but they were involved in the pharmacogenetic implementation design and evaluation. Ohio State University was unique in that genetic counselors directly interacted with patients in the pharmacogenetic workflow.(12)

The use of reactive testing (*i.e.,* pharmacogenetic test only ordered in response to a specific trigger, such as a drug order) versus preemptive testing (*i.e.,* pharmacogenetic test ordered for all patients presenting to the healthcare system or a select clinical setting without a specific trigger) also varied between sites. At Vanderbilt University, the *CYP2C19*-clopidogrel test was ordered if the patient was scheduled for a left heart catheterization. At the University of Maryland, the *CYP2C19*-clopidogrel test was ordered if the patient consented to participate in a research study and was admitted to the cardiac catheterization laboratory for a left heart catheterization. The *CYP2C19*-clopidogrel test was reactively ordered at the University of Florida if the patient received percutaneous coronary intervention. Under their research protocol, St. Jude Children's Hospital preemptively tested all new consenting patients for *CYP2C19*, the University of Chicago preemptively tested adult patients receiving outpatient care in Department of Medicine clinics, and Vanderbilt University also preemptively tested adult outpatients in Primary Care, Cardiology, and Endocrinology. At Mayo Clinic, testing was not

recommended in response to an order for clopidogrel, but if the results for *CYP2C19* were already available (from a previous test/indication) they were used to guide clopidogrel therapy. At Ohio State University, the *CYP2C19*-clopidogrel test was ordered for any patient with hypertension or heart failure that consented to be part of a research study evaluating the impact of genomic counseling.(10)

Across the TPP, pharmacogenetic testing was implemented within numerous clinical settings (*e.g.,* inpatient and outpatient, general medicine and sub-specialties, etc.) and target patient populations (*e.g.,* adults and children, drug-specific, disease-specific, high-risk ethnic groups, etc.). Several different genotyping platforms were used across the TPP sites, which had high call rates (>99%) and a range of turn-around-times (*e.g.,* the median turn-around-time for reactive testing was 2.6 days with a range of 0.3 - 16 days).

Areas of similarity

Despite significant diversity of pharmacogenetic implementations, a common theme of successful implementation across sites was the leadership of clinician-champions, use of multidisciplinary teams, and strong institutional involvement, including the infrastructure and resources to execute. TPP programs were also similar in the clinical recommendations offered during prescribing. Much of this parity between programs can be attributed to the common use of CPIC guidelines. Other similarities included the specific pharmacogenetic tests (gene-drug pairs) implemented (Table 2) and the general process for result interpretation. The more detailed tables for *CYP2C19*-clopidogrel, *TPMT*-thiopurines, and *SLCO1B1*-simvastatin (available as online supplemental files 1, 2, and 3 or at https://www.pharmgkb.org/page/tppTables) showed general uniformity of the process for test result interpretation. Interpretation was consistent with the stepwise process advised by CPIC guidelines (patient diplotype is translated into a predicted phenotype, which is linked to a clinical recommendation), and the recommendations themselves were mostly consistent with those given in

CPIC guidelines. For example, in line with the strong recommendation for alternative therapy in *CYP2C19* poor metabolizers, six out of seven sites recommended or considered an alternative drug instead of clopidogrel. Only one site, Ohio State University, did not make specific drug treatment recommendations (instead, the report only included the diplotype, predicted phenotype, and several informative citations, without an explicit recommendation). In line with the moderate CPIC classification for recommending alternative therapy in *CYP2C19* intermediate metabolizers, five out of seven sites recommended an alternative drug to clopidogrel in *CYP2C19* intermediate metabolizers; however, the University of Maryland also recommended that the dose of clopidogrel could be increased, and Ohio State University (like in the case of poor metabolizers) did not give an explicit recommendation. In about half of cases, therapy was changed for patients with actionable genotypes (Table 1; median change rate = 48% and range = 36% - 100%). When an actionable genotype result was detected and the therapy was *not* changed, prescribers stated several justifications (*e.g.,* contraindication to the alternative therapy, increased cost of the alternative therapy, patient preference, and continuation of therapy managed by another prescriber).(13, 14)

Scientific outcomes

The TPP catalyzed a wealth of data and infrastructure to facilitate research. For example, at Ohio State University, the patients who participated in pharmacogenetic implementation studies(10, 12) also consented to participate in follow-up survey research and retrospective chart reviews using the data in their EHRs. Those opportunities spurred several ongoing "spin-off" research projects. The University of Chicago studies pharmacogenomic implementation and clinical decision support via the "1,200 Patients Project".(15-18) Three TPP sites, the University of Florida, University of Maryland, and Vanderbilt University, are funded as part of the NIH's "Implementing GeNomics In pracTicE" (IGNITE) Network,(19) which includes a pharmacogenetics interest group that is undertaking numerous multi-institution

projects. Mayo Clinic and Vanderbilt University are also funded as part of eMERGE,(20) which had a pharmacogenetics-focused project and other research efforts to learn from the pharmacogenetic implementations and the large population of genotyped patients. Several TPP groups, joined by several other institutions as part of the IGNITE Pharmacogenetics Interest Group, have conducted multi-institution analyses of cardiovascular outcomes following clinical implementation of *CYP2C19*-genotyped guided antiplatelet therapy. The data resulting from this collaborative effort will help to define the impact of pharmacogenetics on clinical outcomes in cardiovascular patients undergoing percutaneous coronary intervention. In addition, Mayo Clinic is leading the ongoing international, multi-center, randomized, prospective clinical trial TAILOR PCI to assess whether *CYP2C19*-genetically tailored anti-platelet therapy can improve clinical outcomes with clopidogrel after percutaneous coronary intervention with stent implantation (ClinicalTrials.gov identifier: NCT01742117).(21)

Educational outcomes

The TPP sites individually created and continue to update numerous pharmacogenetic educational materials for patients, clinicians, and researchers that are freely available online.(22-30) A collection of links to resources can be found on PharmGKB® at https://www.pharmgkb.org/page/pgxImplementationResources. These resources provide a wealth of pharmacogenetic information that includes pharmacogenetic publications, presentations, videos, competencies, residency programs, conferences, continuing education, and core laboratory services for genetic testing. Though not funded as part of TPP, the University of Florida publishes a newsletter geared toward personalized medicine, particularly pharmacogenetics, titled "SNP•its" (http://personalizedmedicine.ufhealth.org/tag/snpits/), which evaluates and summarizes journal articles that are most readily applicable and relevant to practicing clinicians. Information on this publication as well as educational and implementation materials are available on their website

(http://personalizedmedicine.ufhealth.org/).(26) The Mayo Clinic created a variety of educational materials for providers and patients to enhance pharmacogenetic implementation into practice. These include online resources linked to CDS to be used by providers at the point-of-care ("AskMayoExpert" enterprise knowledge content management), grand rounds presentations, online modules and videos, and brochures, as well as links to pharmacogenetic results in the patient portal (http://mayoresearch.mayo.edu/center-for-individualized-medicine/drug-gene-testing.asp). St. Jude Children's Research Hospital has created a website (www.stjude.org/pg4kds/implement) to track which genes/drugs it has implemented and contains implementation specific publications, presentations, as well as gene-specific clinician pharmacogenetic competencies. Vanderbilt University developed "My Drug Genome," (www.mydruggenome.org)(22) which is a resource to learn about how genetics can affect the way medications work and how genetic results can be incorporated into personalized patient care. Additionally, Vanderbilt has led the creation of a site to organize clinical decision support information across multiple sites.(28) Vanderbilt also supported the development of a Coursera MOOC (Massive Open Online Course) in personalized medicine that includes multiple pharmacogenetic modules.(29)

St Jude Children's Research Hospital and University of Florida established the first two American Society for Health System Pharmacists-accredited post-graduate year 2 pharmacy residencies in clinical pharmacogenomics. The University of Chicago,(16) Ohio State University,(31) Mayo Clinic, and Vanderbilt University offer post-doctoral fellowship programs that are accredited by the American Board of Clinical Pharmacology and offer training in pharmacogenomics. Additionally, students enrolled in the pharmacy and medical schools at the University of Florida and University of Maryland, respectively, received their personal pharmacogenetic genotype test results as part of their curriculum.(32, 33) TPP members continue to present at grand rounds, in-services, and high profile domestic and international

symposia, which have been shown to significantly improve attitudes toward pharmacogenetic testing(34) and pharmacogenetic testing rates.(7)

Financial outcomes

Cost and reimbursement for pharmacogenetic testing remained a highly complex issue. Methods for estimating cost and payment methods for pharmacogenetic testing differed between, and even within, the TPP sites. Therefore direct comparisons of costs between TPP sites were not possible. Payment for clinical pharmacogenetic testing after submission to third party payers was sometimes sent to the patient themselves or covered by the institution. The processes used for billing and the payer varied based on a patient's inpatient or outpatient status at the time of the test. Payment for research protocol pharmacogenetic testing was typically covered by research grants. To further complicate this issue, the costs of genetic testing and reimbursement policies by third party payers are rapidly changing; the TPP provided a snapshot in time on these financial issues. In the University of Florida's pharmacogenetic testing program, seven different third party payers (including Medicare) reimbursed for the *CYP2C19*-clopidogrel test, with an 85% reimbursement rate during the first month of billing.(14) Additionally, the hospital at the University of Florida agreed to cover the costs of the test for inpatients as part of the diagnosis-related group based payment. A cost-effectiveness study by investigators at the University of Maryland found that *CYP2C19* genotype-guided antiplatelet therapy selection may be more cost-effective and may provide more clinical value due to fewer adverse outcomes,(35) and additional cost-effectiveness data on *CYP2C19* genotype-guided antiplatelet therapy are expected from the IGNITE Pharmacogenetics Interest Group.

Informatics outcomes

The TPP sites developed infrastructure to support the ordering of pharmacogenetic tests and the return of test results, which was designed to fit into each site's workflow. In general, the existing test order/result process within each EHR system could be leveraged, but several types of customization were necessary to enable the pharmacogenetic data to be used for CDS. For example, currently there are no standards for representing genomic test results within EHR systems. Those results can include collections of sequence data, genotypes, named alleles (e.g., star nomenclature), and phenotypic interpretations (e.g., metabolizer status), and each TPP site individually determined how those data would be represented and stored. The storage location of pharmacogenetic results to be displayed in clinical systems also varied among sites. In some cases pharmacogenetic data were stored directly within the EHR as a traditional lab test, in others the genomic data were stored in an ancillary system linked to the EHR, and in some it was a combination of both approaches. In all cases, some level of customization was needed in order to store and present the information. While some common challenges were identified, heterogeneity in data representation and storage location complicated the comparison of implementations among sites and, along with differences in clinical workflow, limited the portability of CDS rule algorithms.

Discussion

Many barriers to the clinical implementation of pharmacogenetics have been recognized,(4, 5) but the PGRN TPP, which collected metrics and outcomes from pharmacogenetic implementations at diverse US healthcare systems, demonstrated that some of those barriers can be overcome. While the NIH PGRN TPP provided seed-funding for the programs described herein, some programs were active at the time TPP was initiated. In all cases, significant institutional resources were required to develop the programs that have been described. Additionally, some of the groups have obtained significant additional extramural funding to advance their pharmacogenetic programs. However the lessons

learned and barriers overcome at these sites can facilitate more cost effective implementations at other sites, if they take advantage of the resources developed and knowledge shared from the various TPP sites. A variety of genotyping platforms were utilized in CLIA-approved laboratory settings (both on site and outsourced), demonstrating the availability of accurate genotyping methods in CLIA-approved laboratories. A variety of methods for ordering and returning pharmacogenetic test results and for CDS were utilized in EHRs, demonstrating the diversity of approaches to establishing the information infrastructure needed to provide CDS for pharmacogenetics. CPIC guidelines were widely used as the framework for pharmacogenetic test interpretation and clinical recommendations, demonstrating the importance of evidence-based, clinical pharmacogenetic guidelines in the implementation of clinical pharmacogenetic programs.

Despite these successes in overcoming several barriers encountered by the TPP, some barriers still remain. For example, CPIC recently standardized the terms for phenotypes and for allele function used within CPIC guidelines to represent the interpretation of pharmacogenetic tests (e.g., metabolizer status)(36) and registered those terms within the Logical Observation Identifiers Names and Codes (**LOINC**) terminology (http://loinc.org/). However lack of accepted, standards-based methods for representing many elements of pharmacogenetic (and all genetic) test results persists. Specifically, genomic data can be reported and stored in a variety of formats (e.g., diplotypes, variant call format [**VCF**], Human Genome Variation Society [**HGVS**] or star allele nomenclatures, positive/negative carrier status) that may be stored in the EHR as discrete data elements or as part of narrative text. This heterogeneity in data representation can be a significant barrier to the retrieval and exchange of pharmacogenetic data. Moreover, data on cost/reimbursement of pharmacogenetic testing and prescriber adherence to therapy recommendations were not able to be consistently collected and compared across TPP sites.

The pharmacogenetic implementation metrics of the TPP revealed promising potential for clinical relevance. The TPP demonstrated that it is possible to implement pharmacogenetic testing for several drugs, and many sites are implementing additional tests. Based on the large numbers of functionally annotated haplotypes in genes known to affect drug metabolism or transport, we expected to see a large amount of genetic variability in the patient populations, and the metrics of the TPP confirmed that expectation. Indeed, 354 distinct test results were observed when only 8 different gene-drug pairs were considered. The TPP also demonstrated the potential for widespread pharmacogenetic implementation. Nearly 100,000 pharmacogenetic test results were posted in the respective EHRs at seven TPP healthcare systems thus far. The potential feasibility for widespread application was also demonstrated by the variety of patient populations and clinical settings in which pharmacogenetic testing was implemented. And finally, nearly 1 out of 4 pharmacogenetic tests had a potentially actionable result, which demonstrated the numerous potential opportunities to personalize patients' pharmacotherapy to their genetics.

The institutions that comprise the TPP have also provided valuable information for healthcare systems seeking to implement their own pharmacogenetic testing programs. This includes a variety of resources that are freely available online (e.g., publications, videos, continuing education, conferences, lookup tables, and workflow diagrams) (22-30) and the identification of areas of diversity and similarity among the TPP sites in this manuscript. Despite the diversity in methods of implementation, the clinical recommendations for drugs were largely the same across sites, showing that there are actionable recommendations for drugs that can be implemented with minimal ambiguity. Due to the diversity in clinical workflows across sites, it may be difficult to exactly replicate an implementation from one site directly to another, but this diversity provides the opportunity to study the strengths and limitations of each implementation from a process/workflow perspective. The diversity among the sites in the TPP indicated that healthcare systems can customize their pharmacogenetic implementations to their local

clinical workflows and specific needs (as with any clinical service), and the TPP demonstrated that multiple different pharmacogenetic implementation models can be achieved that are all based on the same clinical guideline. Moreover, CPIC maintains a list of institutions that have indicated they are implementing CPIC guidelines clinically that exemplify additional models of pharmacogenetic implementation (not just TPP sites).(37) The areas of similarity (the specific pharmacogenetic tests implemented, the general process for result interpretation, and the clinical recommendations) were facilitated by the utilization of the CPIC guidelines, and thus the CPIC guidelines represent a useful framework for other healthcare systems seeking to implement their own pharmacogenetic testing programs.

In conclusion, through implementation science, the collection and normalization of pharmacogenetic implementation metrics across seven TPP sites revealed a large amount of diversity among pharmacogenetic implementations related to clinical context and workflow. However a common theme of successful implementation across sites was the leadership of clinician-champions and multidisciplinary teams, as well as the need for institutional investment, including the infrastructure and resources to execute. Moreover, the use of CPIC guidelines provided a common thread across sites. The TPP demonstrated that some of the barriers to the clinical implementation of pharmacogenetics can be overcome, but some barriers still remain. The TPP directly and indirectly catalyzed many accomplishments in multiple areas, including scientific, educational, financial, and informatics, which beckons a call for more support of programs like the TPP. The TPP showed that these accomplishments are possible, but more work needs to be done in identifying solutions to overcoming the remaining barriers to the clinical implementation of pharmacogenetics more broadly across diverse healthcare settings and patient populations.

Methods

The design and goals of the TPP were previously described.(4) Briefly, each TPP site implemented one or more pharmacogenetic tests into clinical practice or clinical research protocols, and the sites have individually published their implementation profiles.(8, 10, 11, 14, 15, 38-44) TPP participants met in-person biannually and at least quarterly by teleconference. A Data Collection & Harmonization Working Group was created to facilitate the collection of normalized data, and the Working Group consisted of at least one representative from each TPP site that met via a weekly web/teleconference. Sites were surveyed on multiple planned metrics describing their individual implementations(4) and on the gene-drug pairs that either were implemented or planned to be implemented by 2015. Due to the small sample size (n = 7 TPP sites contributed metric data), only descriptive statistics were calculated using Microsoft Excel. The most commonly implemented gene-drug pairs were chosen for additional types of data collection using standardized templates created in Microsoft Excel or PowerPoint. For the three most commonly implemented gene-drug pairs (*CYP2C19*-clopidogrel, *TPMT*-thiopurines, and *SLCO1B1*-simvastatin), standardized tables reporting the specific genotyping platforms used, haplotypes tested and their functional interpretations, diplotype and phenotype counts, modes of pre-test and post-test CDS, and clinical recommendations based on test results were created in Microsoft Excel. For the most commonly implemented gene-drug pair (*CYP2C19*-clopidogrel), workflow diagrams illustrating the clinical processes and flow of data related to the pharmacogenetic implementations were also created by some institutions. Some of the workflow diagrams utilized a common “swim lane” format that allowed for more direct comparison of workflows across TPP sites. Each “swim lane” represented a generalized role of an actor within the overall workflow (e.g., the patient, clinical team, clinical information systems, labs, pharmacist, genetic counselor, and research coordinator).

Study Highlights (must be <150 words not including the questions [questions are 30 words] – currently 149 words)

What is the current knowledge on the topic?

Numerous pharmacogenetic clinical guidelines have been published, but the clinical implementation of pharmacogenetics has been hindered by many barriers. The Translational Pharmacogenetics Program (**TPP**) of the NIH Pharmacogenomics Research Network facilitated the implementation of pharmacogenetic testing in diverse health care settings and examined commonalities and differences in institutionally supported pharmacogenetic implementations.

What question did this study address?

What lessons can be learned from early pharmacogenetic implementations, and how can they aid other institutions?

What does this study add to our knowledge?

The TPP collected and normalized numerous pharmacogenetic implementation metrics across seven healthcare systems. The pharmacogenetic implementations developed diverse solutions to overcoming many barriers. The Clinical Pharmacogenetics Implementation Consortium guidelines created uniformity among sites. The TPP also contributed to the establishment of research and informatics infrastructure, evaluation of financial issues, and the dissemination of pharmacogenetic education.

How this might change clinical pharmacology and therapeutics?

The TPP demonstrated that pharmacogenetics can be implemented across a variety of clinical settings, which may facilitate more widespread implementation with the potential to improve clinical outcomes.

Acknowledgements

This work was supported by National Institutes of Health (NIH) grants U01 HL105198 (A.R.S.), U01 GM92666 and R24 GM115264 (M.V.R. and C.E.H.), U01 HL105198 (M.V.R.), GM61374 (T.E.K., R.B.A. and M.W.C.), U01 GM92655 (W.S.), U19 HL065962 (D.M.R.), RO1 GM28157 and U19 GM61388 (R.M.W., L.W.), KL2 RR024151 (N.L.P.), U01 GM074492 and U01 HG007269, UL1 TR 000064, UL1 TR001427 (J.A.J.), and U19 GM61388 (R.R.F.), NIH/National Cancer Institute grants CA 36401 and CA 21765 (M.V.R.), and by American Lebanese Syrian Associated Charities (M.V.R.). J.A.L. was supported by a Post-Doctoral Fellowship from the American Heart Association (14POST20100054) and the NIH student loan repayment program (L30 HL110279). Full list of authors in the Translational Pharmacogenetics Program Group: Pharmacogenomics of Anti-Platelet Intervention (PAPI) Study: University of Maryland School of Medicine, Baltimore, Maryland, USA: Alan R. Shuldiner, Mark Vesely, Shawn W. Robinson, Nicholas Ambulos Jr., Sanford A. Stass, Mark D. Kelemen, Lawrence A. Brown, Toni I. Pollin, Amber L. Beitelshees, Richard Y. Zhao, Ruth E. Pakyz, Kathleen Palmer, Tameka Alestock, Courtney O'Neill, Kristin Maloney, Amie Branham, Danielle Sewell, and Linda Jo Bone Jeng; Pharmacogenetics of Anticancer Agents Research in Children (PAAR4Kids): PG4KDS Protocol: Clinical Implementation of pharmacogenetics, St. Jude Children's Research Hospital, Memphis, Tennessee, USA: Mary V. Relling, Kristine Crews, James Hoffman, Cyrine Haidar, Donald Baker, Fran Greeson, Aditya Gaur, Ulrike Reiss, Alicia Huettel, Cheng Cheng, Amar Gajjar, Alberto Pappo, Melissa Hudson, Ching-Hon Pui, Sima Jeha, and William E. Evans; Medical College of Wisconsin: Ulrich Broeckel; The Pharmacogenomics Knowledgebase (PharmGKB), Stanford University, Stanford, California, USA: Russ B. Altman, Li Gong, Michelle Whirl-Carrillo, and Teri E. Klein; Expression Genetics in Drug Therapy (XGEN), The Ohio State University, Columbus, Ohio, USA: Wolfgang Sadee, Kandamurugu Manickam, Kevin M. Sweet, Peter J. Embi, Jeremy Harper, Samuel Handelman, and Jasmine A. Luzum; Pharmacogenomics of Arrhythmia Therapy (PAT), Vanderbilt University School of Medicine, Nashville, Tennessee, USA: Dan Roden, Josh Peterson, Josh Denny,

Jonathan Schildcrout, Erica Bowton, Jill Pulley, Marc Beller, Jennifer Mitchell, Ioana Danciu, Julie Field, and Lisa Price; Pharmacogenetics of Phase II Drug Metabolizing Enzymes (PPII), Mayo Clinic, Rochester, Minnesota, USA: Naveen L. Pereira, Richard Weinshilboum, and Liewei Wang; Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR), University of Florida, Gainesville, Florida, USA: Julie A. Johnson, David Nelson, Michael Clare-Salzler, Amanda Elsey, Benjamin Burkley, Taimour Langaee, Felix Liu, David Nessl, Hui-Jia Dong, Larry Lesko, Jenny Ashton, and Ben Staley; Pharmacogenomics Ontology (PHONT), Mayo Clinic, Rochester, Minnesota, USA: Robert R. Freimuth and Christopher G. Chute.

Conflict of Interest/Disclosure

J.A.L. is a consultant for Gnome Diagnostics, LLC. M.W.C and T.E.K. are scientific advisors for Rxight pharmacogenetics. R.B.A. is a founder, stockholder and a scientific consultant for Personalis Inc and a paid advisor for Pfizer and Karius. P.H.O. and M.J.R. are named as co-inventors on a pending patent for a Genomic Prescribing System and are co-founders of PrescriptIQ, Inc. M.J.R. is a co-inventor holding patents related to pharmacogenetic diagnostics and receives royalties related to *UGT1A1* genotyping. No royalties were received from the genotyping performed in this study. Dr. Shuldiner is a full-time employee of Regeneron Pharmaceuticals, Inc. R.M.W and L.W. are founders and stockholders in OneOme, LLC. All other authors do not have any conflicts of interest to disclose.

Author Contributions

R.R.F., J.A.L., R.E.P., A.R.E., C.E.H., J.F.P., M.W-C., S.K.H., K.P., K.W.W., L.H.C., P.H.O., N.L.P., M.J.R., D.R., P.J.E., W.S., T.E.K., J.A.J., M.V.R., L.W., R.W., and A.R.S. wrote the manuscript; R.R.F., C.E.H., J.F.P., R.M.C-D., P.H.O., R.B.A., M.J.R., D.R., P.J.E., W.S., J.A.J., M.V.R., L.W., R.W., and A.R.S. designed the research; R.R.F., R.E.P., A.R.E., C.E.H., J.F.P., M.W-C., K.P., J.P., M.B., J.S.S., J.R.F., K.W.W., R.M.C-D., L.H.C., P.H.O., M.J.R., D.R., P.J.E., W.S., T.E.K., J.A.J., M.V.R., L.W., R.W., and A.R.S. performed the research; R.R.F., J.A.L., R.E.P., A.R.E., C.E.H., J.F.P., M.W-C., S.K.H., J.P., M.B., J.S.S., J.R.F., K.W.W., L.H.C., P.H.O., M.J.R., D.R., P.J.E., W.S., T.E.K., J.A.J., M.V.R., and A.R.S. analyzed the data.

References

1. United States Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling. Available from: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.
2. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2011 Mar;89(3):464-7.
3. Stanek EJ, Sanders CL, Taber KA, Khalid M, Patel A, Verbrugge RR, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clin Pharmacol Ther. 2012 Mar;91(3):450-8.
4. Shuldiner AR, Relling MV, Peterson JF, Hicks JK, Freimuth RR, Sadee W, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2013 Aug;94(2):207-10.
5. Manolio TA, Chisholm RL, Ozenberger B, Roden DM, Williams MS, Wilson R, et al. Implementing genomic medicine in the clinic: the future is here. Genet Med. [Review]. 2013 Apr;15(4):258-67.
6. Hewett M, Oliver DE, Rubin DL, Easton KL, Stuart JM, Altman RB, et al. PharmGKB: the Pharmacogenetics Knowledge Base. Nucleic Acids Res. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. 2002 Jan 01;30(1):163-5.
7. Owusu-Obeng A, Weitzel KW, Hatton RC, Staley BJ, Ashton J, Cooper-Dehoff RM, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacotherapy. [Research Support, N.I.H., Extramural

Review]. 2014 Oct;34(10):1102-12.
8. Hoffman JM, Haidar CE, Wilkinson MR, Crews KR, Baker DK, Kornegay NM, et al. PG4KDS: a model for the clinical implementation of pre-emptive pharmacogenetics. Am J Med Genet C Semin Med Genet. 2014 Mar;166C(1):45-55.
9. Khan NA, Peterson JF. A surveillance tool to support quality assurance and research in personalized medicine. AMIA Annual Symposium proceedings AMIA Symposium. [Research Support, N.I.H., Extramural]. 2011;2011:701-8.
10. Sweet K, Gordon ES, Sturm AC, Schmidlen TJ, Manickam K, Toland AE, et al. Design and implementation of a randomized controlled trial of genomic counseling for patients with chronic disease. J Pers Med. 2014 Jan 08;4(1):1-19.
11. Shuldiner AR, Palmer K, Pakyz RE, Alestock TD, Maloney KA, O'Neill C, et al. Implementation of pharmacogenetics: the University of Maryland Personalized Anti-platelet Pharmacogenetics Program. Am J Med Genet C Semin Med Genet. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2014 Mar;166C(1):76-84.
12. Sturm AC, Sweet K, Manickam K. Implementation of a clinical research pharmacogenomics program at an academic medical center: role of the genetics healthcare professional. Pharmacogenomics. [Editorial

Research Support, N.I.H., Extramural]. 2013 May;14(7):703-6.
13. Peterson JF, Field JR, Unertl KM, Schildcrout JS, Johnson DC, Shi Y, et al. Physician response to implementation of genotype-tailored antiplatelet therapy. Clin Pharmacol Ther. 2016 Jul;100(1):67-74.
14. Weitzel KW, Elsey AR, Langaee TY, Burkley B, Nessl DR, Obeng AO, et al. Clinical pharmacogenetics implementation: approaches, successes, and challenges. Am J Med Genet C Semin Med Genet. [Research Support, N.I.H., Extramural]. 2014 Mar;166C(1):56-67.
15. O'Donnell PH, Danahey K, Jacobs M, Wadhwa NR, Yuen S, Bush A, et al. Adoption of a clinical pharmacogenomics implementation program during outpatient care--initial results of the University of Chicago "1,200 Patients Project". Am J Med Genet C Semin Med Genet. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2014 Mar;166C(1):68-75.
16. Dolan ME, Maitland ML, O'Donnell PH, Nakamura Y, Cox NJ, Ratain MJ. Institutional Profile: University of Chicago Center for Personalized Therapeutics: research, education and implementation science. Pharmacogenomics. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2013 Sep;14(12):1383-7.
17. Hussain S, Kenigsberg BB, Danahey K, Lee YM, Galecki PM, Ratain MJ, et al. Disease-drug database for pharmacogenomic-based prescribing. Clin Pharmacol Ther. 2016 Aug;100(2):179-90.
18. O'Donnell PH, Danahey K, Ratain MJ. The Outlier in All of Us: Why Implementing Pharmacogenomics Could Matter for Everyone. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. 2016 Apr;99(4):401-4.
19. Weitzel KW, Alexander M, Bernhardt BA, Calman N, Carey DJ, Cavallari LH, et al. The IGNITE network: a model for genomic medicine implementation and research. BMC Med Genomics. [Research Support, N.I.H., Extramural]. 2016 Jan 05;9:1.
20. Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, Manolio TA, et al. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. Genet Med. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. 2013 Oct;15(10):761-71.
21. Pereira NL, Sargent DJ, Farkouh ME, Rihal CS. Genotype-based clinical trials in cardiovascular disease. Nat Rev Cardiol. [Research Support, N.I.H., Extramural

Review]. 2015 Aug;12(8):475-87.
22. Vanderbilt University. My Drug Genome. Available from: mydruggenome.com.
23. Mayo Clinic Center for Individualized Medicine. Pharmacogenomics Program. Available from: http://mayoresearch.mayo.edu/center-for-individualized-medicine/pharmacogenomics.asp.
24. St. Jude Children's Research Hospital. PG4KDS: Clinical Implementation of Pharmacogenetics. Available from: www.stjude.org/pg4kds.
25. Vanderbilt University. Vanderbilt Pharmacogenomics. Available from: http://www.pharmacogenomics.mc.vanderbilt.edu/.
26. University of Florida Health Personalized Medicine Program. Available from: http://personalizedmedicine.ufhealth.org/.

27. University of Chicago Center for Personalized Therapeutics. Available from: https://cpt.uchicago.edu/page/what-pharmacogenomics-0.
28. EMERGE & IGNITE Networks. CDS_KB: Clinical Decision Support Knowledgebase. Available from: https://cdskb.org/.
29. Vanderbilt University. Case Studies in Personalized Medicine. Available from: https://www.coursera.org/learn/personalizedmed.
30. Ohio State University Center for Pharmacogenomics. How to Teach Pharmacogenomics. Available from: https://fd4me.osu.edu/.
31. Kitzmiller JP, Phelps MA, Neidecker MV, Apseloff G. Establishing a clinical pharmacology fellowship program for physicians, pharmacists, and pharmacologists: a newly accredited interdisciplinary training program at the Ohio State University. Adv Med Educ Pract. 2014;5:191-6.
32. Perry CG, Maloney KA, Beitelshees AL, Jeng L, Ambulos NP, Jr., Shuldiner AR, et al. Educational innovations in clinical pharmacogenomics. Clin Pharmacol Ther. 2016 Jun;99(6):582-4.
33. Weitzel KW, McDonough CW, Elsey AR, Burkley B, Cavallari LH, Johnson JA. Effects of Using Personal Genotype Data on Student Learning and Attitudes in a Pharmacogenomics Course. Am J Pharm Educ. 2016 Sep 25;80(7):122.
34. Luzum JA, Luzum MJ. Physicians' attitudes toward pharmacogenetic testing before and after pharmacogenetic education. Pers Med. 2016 Mar;13(2):119-27.
35. Reese ES, Daniel Mullins C, Beitelshees AL, Onukwugha E. Cost-effectiveness of cytochrome P450 2C19 genotype screening for selection of antiplatelet therapy with clopidogrel or prasugrel. Pharmacotherapy. [Research Support, N.I.H., Extramural]. 2012 Apr;32(4):323-32.
36. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2016 Jul 21.
37. Clinical Pharmacogenetics Implementation Consortium (CPIC). Implementation. Available from: https://cpicpgx.org/implementation/.
38. Farrugia G, Weinshilboum RM. Challenges in implementing genomic medicine: the Mayo Clinic Center for Individualized Medicine. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2013 Aug;94(2):204-6.
39. Bielinski SJ, Olson JE, Pathak J, Weinshilboum RM, Wang L, Lyke KJ, et al. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. Mayo Clinic proceedings. [Evaluation Studies

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2014 Jan;89(1):25-33.
40. Schildcrout JS, Shi Y, Danciu I, Bowton E, Field JR, Pulley JM, et al. A prognostic model based on readily available clinical data enriched a pre-emptive pharmacogenetic testing program. J Clin Epidemiol. [Research Support, N.I.H., Extramural

Research Support, U.S. Gov't, P.H.S.]. 2016 Apr;72:107-15.
41. Schildcrout JS, Denny JC, Bowton E, Gregg W, Pulley JM, Basford MA, et al. Optimizing drug outcomes through pharmacogenetics: a case for preemptive genotyping. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural]. 2012 Aug;92(2):235-42.
42. Peterson JF, Bowton E, Field JR, Beller M, Mitchell J, Schildcrout J, et al. Electronic health record design and implementation for pharmacogenomics: a local perspective. Genet Med. [Research Support, N.I.H., Extramural]. 2013 Oct;15(10):833-41.

43. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, et al. Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural]. 2012 Jul;92(1):87-95.
44. O'Donnell PH, Bush A, Spitz J, Danahey K, Saner D, Das S, et al. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. Clin Pharmacol Ther. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. 2012 Oct;92(4):446-9.

Table 1. Summary of pharmacogenetic implementation metrics across seven TPP sites from 2011 to June 2015.

Metrics	Findings
Types of Pharmacogenetic Implementations	• Clinical only (n = 2 sites) • Research only (n = 3 sites) • Clinical and research (n = 2 sites)
Triggers Prompting Pharmacogenetic Test Orders*	• Reactive in select patients (*e.g.,* a relevant drug or procedure is ordered for the patient) • Preemptive in select patients (*e.g*., ordered for all patients presenting to a select clinical setting regardless of relevant drug use) • Preemptive in all patients (*e.g*., ordered for all patients presenting to the healthcare system regardless of relevant drug use) • Neither reactive nor preemptive (*e.g*., if test results were already available from a previous test, then they were used to guide therapy)
Target Patient Populations	• Numerous (*e.g.,* all patients [adults and children], drug-specific, disease-specific, high-risk ethnic groups [patients of Asian ancestry with an order for carbamazepine], etc.)
Clinical Settings	• Numerous (*e.g.,* inpatient and outpatient, cardiac catheterization lab, primary care, family medicine, internal medicine, cardiology, endocrinology, pediatric and adult gastroenterology, pediatric oncology, pediatric HIV, pediatric hematology, neurology, rheumatology, psychiatry, etc.)
Modes of Pharmacogenetic Test Order Entry	• Electronic (CPOE; n = 6 sites) • Paper (n = 1 site)
Roles of Ordering Providers	• Physician only (n = 1 site) • Research study physician only (n = 2 sites) • Physician or nurse practitioner (n = 2 sites) • Physician, nurse practitioner, physician assistant, or pharmacist (n = 1 site) • Any provider with ordering authority (n = 1 site)
Options for Ordering Pharmacogenetic Test Prior to Drug Order*	• Required • Recommended
Types of Alerts Prompting Pharmacogenetic Test Order or Notification of Pharmacogenetic Test Results*	• Active (*i.e.,* alert and/or specific message sent) • Passive (*i.e.,* no alert or specific message sent; the test order or test result was available on demand) • Active + passive
Persons Receiving Results*	• Provider only • Provider + patient
Total Number of Patients Tested	• 20,258 total across all seven sites (range = 208 - 14,752 by individual sites)
Percentage of Therapy Changes in Response to an Actionable Result†	• Median = 48% (range = 36% - 100%)

Genotyping Platforms	• Numerous (*e.g.,* Affymetrix DMET™ Plus, Illumina VeraCode® ADME Core Panel, Sequenom iPLEX® ADME pharmacogenetic Panel, Life Technologies QuantStudio™ 12K Flex, GenMark Dx®, Life Technologies ViiA™ 7, polymerase chain reaction with allele-specific primer extension, customized arrays, etc.)
Genotyping Location*	• On site • Outsourced
Genotype Call Rates	• All sites > 99%
Estimated Turn-Around-Time‡	• Reactive testing: median = 2.6 days (range = 0.3 - 16 days) • Preemptive testing: median = 14 days (range = 1 - 249 days)

*Number of sites was not included because the counts are specific to each gene-drug pair, which may vary within a given site

†Based on data that was available for *CYP2C19*-clopidogrel and *TPMT*-thiopurines from three sites

‡Time between when pharmacogenetic test was ordered and when the pharmacogenetic test results were reported

CPIC = Clinical Pharmacogenetics Implementation Consortium; CPOE = computerized physician order entry; TPP = Translational Pharmacogenetics Program

Table 2. Numbers of select pharmacogenetic genes tested for by the TPP sites, along with examples of drugs for which actions were taken at some sites, total numbers of pharmacogenetic tests reported to EHRs, numbers of actionable genotypes for a select group of commonly implemented gene-drug pairs, whether a CPIC guideline is available, and whether there is pharmacogenetic information in the FDA label.

Gene-drug pair	Number of TPP sites reporting this data	Numbers of distinct test results*	Numbers of test results reported in the EHR†	Numbers (%) of actionable results‡	CPIC Guideline	FDA Label
CYP2C19-clopidogrel	7	57	24,924	7,221 (29.0%)	✓	✓
TPMT-thiopurines	6	26	20,170	1,987 (9.4%)	✓	✓
SLCO1B1-simvastatin	5	30	14,508	3,513 (24.2%)	✓	
CYP2C9/VKORC1-warfarin	3	30	15,545	5,054 (32.5%)	✓	✓
CYP2D6-codeine	2	193	2,533	275 (10.8%)	✓	✓
IFNL3- ribavirin, peginterferon	2	3	6,453	4,437 (68.8%)	✓	
DPYD- fluorouracil, capecitabine	1	13	2,371	9 (0.4%)	✓	✓
HLAB-abacavir	1	2	10,816	432 (4.0%)	✓	✓
	Total	**354**	**97,320**	**22,928 (23.6%)**	**8 (100%)**	**6 (75%)**

*Result formats were gene-specific (*e.g., IFNL3* was reported as the genotype for a single variant [rs12979860], *HLAB* was reported as either positive or negative for *57:01, *CYP2C9/VKORC1* was reported as the compound diplotype, and the results for all other genes were reported as the diplotype for the single gene based on multiple genotyped variants)
†Includes 1,286 no calls and ambiguous calls (1.4%)
‡Actionable was defined by CPIC guidelines for all gene-drug pairs, except for *CYP2C9/VKORC1* where actionable was defined by the FDA label when the expected dose did not include the standard 5mg starting dose, and the individual sites defined their own actionable *CYP2D6*-codeine results

CPIC = Clinical Pharmacogenetics Implementation Consortium; *CYP2C19* = gene for cytochrome P450 family 2 subfamily C member 19; *CYP2C9* = gene for cytochrome P450 family 2 subfamily C member 9; *DPYD* = gene for dihydropyrimidine dehydrogenase; EHR = EHR; FDA = United States Food & Drug Administration; *HLA-B* = gene for major histocompatibility complex, class I, B; *IFNL3* = gene for interferon, lambda 3, also known as interleukin 28B; *SLCO1B1* = gene for solute carrier organic anion transporter family member 1B1; *TPMT* = gene for thiopurine S-methyltransferase; *VKORC1* = gene for vitamin K epoxide reductase complex subunit 1.

Table 3. Pharmacogenomic guidelines and implementations at TPP sites.

Gene-Drug Interaction	Number of Implementing Sites
CYP2C19-clopidogrel	7
TPMT-thiopurines	6
CYP2C9/VKORC1-warfarin	4
SLCO1B1-simvastatin	5
CYP2D6/CYP2C19-TCAs	2
CYP2D6-codeine	2
HLA-B-abacavir	2
CYP2D6-SSRIs	1
CYP3A5-tacrolimus	1
IFNL3-ribavirin/interferon	1
ITPA-ribavirin	1
GLCC1-budesonide,fluticasone, triamcinolone	1
CYP3A4-amlodipine, atorvastatin, simvastatin, and lovastatin	1
HLA-B-allopurinol	0
HLA-B-carbamazepine	1
DPYD-5FU/capecitabine	1
IL28B-pegInteron	2
HLA-B-phenytoin, fosphenytoin therapy	1
G6PD-rasburicase, Septra	1
CFTR-Ivacaftor	0
UGT1A1-irinotecan	2

CYP2D6 - tamoxifen	1
5-HTT-SSRIs	1
DRD4-methylphenidate	1
HTR 2A/2C-clozapine, aripiprazole	1
NAT2-Isoniazid	1
OPRM1-Naltrexone	1

Text in bold indicates that CPIC guidelines have been published for the gene-drug(s) interaction. TCAs – tricyclic antidepressants. SSRIs - selective serotonin re-uptake inhibitors.