Design and Anticipated Outcomes of the eMERGE-PGx Project: A Multi-Center Pilot for Pre-Emptive Pharmacogenomics in Electronic Health Record Systems

A full list of authors and affiliations appears at the end of the article.

Abstract

We describe here the design and initial implementation of the eMERGE-PGx project. eMERGE-PGX, a partnership of the eMERGE and PGRN consortia, has three objectives: 1) Deploy PGRNseq, a next-generation sequencing platform assessing sequence variation in 84 proposed pharmacogenes, in nearly 9,000 patients likely to be prescribed drugs of interest in a 1–3 year timeframe across several clinical sites; 2) Integrate well-established clinically-validated pharmacogenetic genotypes into the electronic health record with associated clinical decision support and assess process and clinical outcomes of implementation; and 3) Develop a repository of pharmacogenetic variants of unknown significance linked to a repository of EHR-based clinical phenotype data for ongoing pharmacogenomics discovery. We describe site-specific project implementation and anticipated products, including genetic variant and phenotype data repositories, novel variant association studies, clinical decision support modules, clinical and process outcomes, approaches to manage incidental findings, and patient and clinician education methods.

Conflict of Interest

A.A.V.--Intellectual Property/Royalty Income: Cincinnati Children’s Hospital and Medical Center holds a license agreement on a pharmacogenetics interpretation algorithm. I am an inventor, and I have received royalties from the company to which this has been licensed; E.B.--Intellectual Property/Shareholder: I am a co-inventor of web-enabled technology for collecting and utilizing healthcare data, and I hold shares in a company that is licensing this technology from Mount Sinai School of Medicine; E.B.L. I receive royalties from UpToDate from authoring several sections.

Author Contributions

L.J.R.-T., S.C.S., A.S.G., D.M.R. and J.C.D wrote the manuscript
L.J.R.-T., S.C.S., A.S.G., B.A., M.A.B., S.J.B., A.B., M.H.B., D.S.C., J.J.C., D.R.C., K.F.D., C.J.G., O.G., D.S.K., K.A.L., S.L., S.M., A.R.M., J.A.P., V.P., J.P., C.L.P., J.F.P., C.A.P., J.R., L.V.R., M.D.R., S.S., S.A.S., M.S., A.V., A.A.V., W.A.W., E.B., R.L.C., C.G.C., J.L.H., J.B., B.K., I.A.H., I.J.K., G.P.J., E.B.L., C.A.M., and M.S.W., T.M., R.L., and S.V., D.A.N and S.E.S., D.M.R. and J.C.D. designed the research.
L.J.R.-T. and S.C.S. analyzed the data
A.S.G., D.A.N and S.E.S., contributed New Reagents / Analytic Tools

Author Manuscript

Clin Pharmacol Ther. 2014 October ; 96(4): 482–489. doi:10.1038/clpt.2014.137.
Keywords
pharmacogenetics; pharmacogenomics; next generation sequencing; study design; pre-emptive genotyping

Introduction
A widely-held vision arising from the Human Genome Project is to use information on genomic variation to guide preventive and therapeutic decision-making for individual patient treatment. An area thought to be ready for evaluating the implementation of genomics-guided clinical decision-making is pharmacogenomics – the analysis of the genetic component of drug therapy response variability. As is the case in many areas of genetic association research, there are few formal investigations into the real-world health practice, implementation, and clinical outcomes of genetically-tailored drug prescribing. Such investigations are particularly difficult due to logistic barriers in delivering variant information, along with genotype-specific clinical decision support (CDS), to prescribers.

Discovery efforts to identify novel pharmacogenetic variants have typically focused on a limited number of common variants in specific target “pharmacogenes”. Recent advances in DNA sequencing are permitting deep-coverage sequencing on large numbers of samples, resulting in the identification of large numbers of rare variants across the genome. Some of these pharmacogenetic rare variants will contribute to variable drug responses, but their detection and clinical effect assessment will be difficult both in the small cohorts that have adverse event data or more traditional larger cohorts, which typically have limited clinical outcome data.

The eMERGE-PGx project, described here, is a multi-center pilot of pharmacogenetic sequencing in clinical practice designed to address these issues and initiated through a collaboration between the Electronic Medical Records and Genomics (eMERGE) Network and the Pharmacogenomics Research Network (PGRN). Work in eMERGE-PGx will sequence 84 key pharmacogenes and examine the process for implementing preemptive genotyping for known pharmacogenetic drug-gene pairs at the 10 academic medical centers and health systems in the eMERGE-II Network through three specific aims: 1) Deploy PGRNseq, a next-generation sequencing platform assessing sequence variation in the target pharmacogenes, in a patient population likely to be prescribed drugs of interest in a 1–3 year timeframe; 2) Integrate well-established CLIA-validated pharmacogenetic genotypes into the electronic health record (EHR) with associated clinical decision support (CDS) and assess process and clinical outcomes of this implementation; and 3) Develop a repository of pharmacogenetic variants of unknown significance linked to a repository of an EHR-based clinical phenotype data for ongoing pharmacogenomics discovery.

The eMERGE-PGx project is possible due to the unique and complementary strengths of the eMERGE Network and the Pharmacogenomics Research Network (PGRN). The 14 PGRN sites each advance a set of aims in a specific pharmacogenomics area and PGRN includes a set of network-wide resources that enable sites’ specific aims. These resources include the PGRNseq platform, described below, to sequence 84 genes identified by PGRN.
investigators as likely important modulators of drug action. Another key activity of PGRN is the creation of multi-institutional consortia to study drug response across PGRN and other collaborating sites coordinated by PGRN and the Pharmacogenomics Knowledge Base (PharmGKB): examples include the international warfarin 9, 10, clopidogrel, and drug transporter consortia, and the Translational Pharmacogenetics Program, “real-world” pharmacogenetics implementation project11. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is another PGRN-based effort that provides specific peer-reviewed guidelines on possible actions a clinician should consider when a drug is prescribed to a patient with relevant pharmacogenomic testing results12.

eMERGE is a multi-center network of health systems with biorepositories linked to EHRs 7, 13. The goals of research within the eMERGE Network are to identify novel genetic associations with disease using EHR data and to explore methods for integrating genotyping and sequencing results clinical practice. eMERGE provides expertise in defining and extracting clinical phenotypes from diverse EHRs 14–27, integrating complex genomic data generated across sites into unified datasets 28, incorporating large-scale genomics data into the EHR and pairing these data with relevant linked CDS 29, 30, and engaging with and educating patients and prescribers around issues associated with incorporating genetics into clinical care 31, 32.

Figure 1 provides an overview of the design of the eMERGE-PGx study, driven by the three aims of the project detailed above. Where appropriate, we have indicated which methods and results sub-sections pertain to aim 1, aim 2, or aim 3. In the discussion section, we include anticipated lessons to be learned during this complex project. The implementation of eMERGE-PGx and the measureable outcomes vary, by necessity, across participating sites based on available patient populations, EHR systems, patient and prescriber preferences, and institutional policies. This variation allows for the critical evaluation of a real-world implementation of pharmacogenomics into clinical care. In this manuscript we seek to highlight the commonalities of the eMERGE-PGx project across sites, as well as site-specific differences that may influence outcomes.

Results--Anticipated Outcomes of the PGx Project

Generation of pharmacogene sequence data and validated pharmacogenetic genotypes for 9000 participants (Project Aims 1 and 2)

The 10 eMERGE-PGx sites will together recruit nearly 9000 individuals for this project. Individuals will have sequence data generated for 84 pharmacogenes using a novel platform (PGRNSeq). Participants will also have selected Clinical Laboratory Improvement Amendments (CLIA)-grade genotypes generated for deposit in EHR. Genotypes in the EHR will have associated CDS, helping providers to act on this genetic information. Details about sequencing, validation genotyping, sample and gene/drug pair selection, and genotype EHR integration with CDS are presented in the methods section of this manuscript.

Process and Clinical Outcomes (Project Aim 2)

eMERGE-PGx sites are collaborating to describe descriptive meta-data and define quantitative and qualitative outcomes across seven domains: recruitment, sequencing,
Searchable Genomic Repositories (Project Aim 3)

A major contribution of recent sequencing efforts has been the creation of variant repositories, such as the Exome Variant Server. We will create such a resource for eMERGE-PGx, called SPHINX (Sequence, Phenotype, and Pharmacogenomics INtegration eXchange, http://emergesphinx.org). SPHINX will contain a secure, de-identified, web-accessible repository of genomic variants. Sequence variants determined from PGRNseq on all enrolled eMERGE-PGx participants will be available to the public via SPHINX in aggregate forms. eMERGE members will also have the ability to search a subset of clinical data important for clinical phenotyping for these participants including demographics, international classification of diseases diagnosis codes, current procedural technology codes, and medications mapped to RxNorm identifiers (http://www.nlm.nih.gov/research/umls/rxnorm/). We plan to map drug data from combinations of free text and electronic prescribing tools to structured vocabularies representing common drug ingredients using natural language processing tools such as the Medication Extraction (MedEx) and clinical Text Analysis and Knowledge Extraction System (cTAKES) systems. These clinical data will not adequately describe phenotypes for study, but will allow rapid hypothesis exploration. Once a potentially interesting population of individuals with an interesting set of variants is identified, each eMERGE site will have the potential – subject to local Institutional Review Board (IRB) approval – to access patients’ EHR for more extensive review of selected clinical records manually or via more rigorously defined phenotype algorithms.

Due to the risk of possible patient re-identification using demographic and clinical data, SPHINX will include important privacy safeguards. Genetic variation data will be presented in aggregate for the public interface, and cohort numbers on the public and private sides of SPHINX will be purposely obscured to protect individuals from re-identification.

Novel Pharmacogenetic Variant Gene Associations with Drug-Related Phenotypes (Project Aim 3)

The genotype-targeted preemptive programs implemented to date confine testing to a handful of common variants of known significance in a small number of candidate
pharmacogenes. By contrast, eMERGE-PGx may also identify novel variants in a larger set of 84 pharmacogenes and therefore provides a valuable discovery dataset. eMERGE, PGRN, and outside investigators will use data from the SPHINX repository described above, and, in some cases, with the cooperation of individual eMERGE-PGx sites, automated- or manually-abstracted data from EHR, to investigate phenotypic associations with novel variation uncovered by the PGRNseq platform.

Discussion

Lessons to be Learned from Consent and Education Procedures

The Consent, Education, Regulation and Consultation (CERC) working group has collaborated on a number of aspects of the eMERGE-PGx project, including engaging stakeholders about implementation, developing model patient consent forms, and creating patient and physician/prescriber educational materials including a patient website. Initial focus on consent development for enrolling participants into the eMERGE-PGx study at the various sites has included determining the critical elements of consent, developing shortened consent forms, and monitoring and addressing individual site IRB responses to the study. A manuscript describing the development of consents for the eMERGE-PGx study and IRB responses at the various sites is in process. The workgroup has also helped with the development of a patient website (http://myresults.org) that contains patient educational materials and videos about the eMERGE-PGx study, as well as the eMERGE Network in general. Each site is populating the website with information about their eMERGE-PGx projects and specifically about the results patients will receive. The website is available to the public and will provide easy access to information. Additionally, through collaboration with the eMERGE Electronic Health Record Integration (EHRI) working group, CERC Work Group members are evaluating and developing content to support CDS tools for physicians.

Lessons to be Learned from Next-Generation Sequencing Cross-Site Data Analysis and QC Pipelines

A significant lesson learned in genome-wide association studies (GWAS) that extends into next-generation sequencing (NGS) experiments is the importance of quality control (QC) pipelines and consideration of batch effects in sequencing results analysis. It has been observed that sequencing results can vary by capture reagent, sequencing platform, and bioinformatics filters, among other criteria. To ensure that eMERGE sites can combine the NGS data from this project, we have developed an NGS pipeline and quality control plan. First, all sites will be sequencing the identical set of Coriell Institute for Medical Research control samples, such that cross-site comparisons can be made in terms of concordance. [The Coriell Institute has a set of lymphoblastoid cell lines that are commonly used as controls for genotyping and sequencing experiments (http://www.coriell.org/)]. Second, the eMERGE Coordinating Center (eMERGE-CC) has developed a variant calling pipeline that will be used to process all of the NGS data. Sites will send variant call file (VCF) and BAM files (which are binary versions of sequence alignment files) to the eMERGE-CC, and the BAM files will be combined across all sites. In an effort to reduce batch effects, multi-
sample calling using the Genome Analysis Toolkit (GATK) will be performed for all samples.

Two commercial sequencing platforms are being used; one site is sequencing on an Ion Torrent platform, while other sites are using Illumina platforms. We will be performing analyses based on the Coriell control samples to determine how these datasets can best be combined.

Lessons to be Learned from Approaches to Incidental Findings

The PGRNseq platform includes several genes associated with highly penetrant actionable disorders. These include genes suggested by the American College of Medical Genetics (ACMG) for return of incidental pathogenic variants (with, in some cases, consideration of returning mutations that are ‘expected’ to be pathogenic) found in clinical genomic testing: Long QT syndrome genes KCNH2 and SCN5A, malignant hyperthermia genes RYR1 and CACNA1S, a catecholaminergic polymorphic ventricular tachycardia gene RYR2, and a familial hypercholesterolemia gene LDLR. Sequencing these genes in eMERGE-PGx offers an opportunity to explore the phenotypes of enrolled patients carrying their variants, with potential for offering additional clinical follow-up for these incidental findings. Since eMERGE was developed as a genetic discovery network, the issue of returning genomic results is nonstandard across sites. Some sites have indicated that they are working with their IRBs to identify a process to return these incidental findings. We anticipate the publication of manuscripts summarizing approaches to return of incidental findings across the eMERGE-PGx network.

In conclusion, The eMERGE-PGx project will obtain sequence from 84 pharmacogenes using the PGRNseq platform in 9,000 individuals likely to be prescribed drugs of interest in a 1–3 year timeframe, will integrate a number of well-established CLIA-validated pharmacogenetic genotypes into the EHR with associated CDS in these same individuals, and will develop a repository of pharmacogenetic variants of unknown significance linked to a repository of clinical phenotypes for future pharmacogenetic discovery. Anticipated products include process outcomes of implementation, searchable genomic and repositories, novel pharmacogenetic variant disease associations, and lessons learned from cross-site sequencing, community engagement and consent activities, and return of incidental findings. The activities pursued as part of eMERGE-PGx will both further the implementation of pharmacogenetics into clinical care and provide an important tool for the discovery of new pharmacogenetic variants.

Methods—Design of eMERGE-PGx

Implementation of the PGRNseq platform (Project Aim 1)

Relevant portions of DNA from all participants in the eMERGE-PGx project will be sequenced using the PGRNseq custom capture reagent. An in-depth description of the development, implementation, and validation of the capture reagent is in preparation and thus a brief description is presented here. PGRNseq is a low-cost, high-throughput, next generation sequencing platform focused on the custom capture of 84 genes, selected collaboratively by the PGRN community, with associations to, or under investigation for, a

Clin Pharmacol Ther. Author manuscript; available in PMC 2015 October 01.
wide variety of drug phenotypes. Supplementary Table 1 presents a list of genes targeted by
the PGRNseq capture reagent. Sequence captured from each gene includes the complete
coding regions plus 2 kilobases (kb) up- and 1 kb down-stream to assess variation within
nearby regulatory regions – nearly 1 megabase of total DNA sequence. PGRNseq’s design
also includes known variants present on other commercially available pharmacogenetic
panel genotyping platforms, such as Affymetrix’s (Santa Clara, CA) DMET Plus panel and
Illumina’s (San Diego, CA) VeraCode ADME panel, to facilitate meta-analyses with
existing large datasets. PGRNseq was designed for multiplexed processing while still
retaining the high coverage and sensitivity needed for effective novel genetic variation
discovery and accurate genotyping of known variants. Batches of 24 or 48 samples are
processed per flowcell lane, allowing for rapid throughput of many samples. (Flowcells, the
site of the Illumina sequencing process, consist of 8 lanes). Preliminary testing of this
platform using 24 samples / lane on cell lines derived from 32 diverse HapMap trios (two
parent + 1 child trios with DNA extensively analyzed by the International HapMap Project
http://hapmap.ncbi.nlm.nih.gov/) produced an average depth of coverage per sample of
496x, and genotypes derived from this PGRNseq data were 99.9% concordant with existing
single nucleotide variant data on these samples from the 1000 Genomes project. Thus,
overall, PGRNseq is a robust sequencing platform for the discovery and analysis of
pharmacogenetic variation, both common and rare.

Individual eMERGE-PGx sites have varying sequencing protocols. Supplementary Table 2
details the locations and platforms used for PGRNseq sequencing for eMERGE-PGx. This
design will permit comparison of sequencing quality control metrics across sequencing
locations and recruitment sites. It will also inform the processes institutions may need to
adopt to efficiently receive and process large amounts of sequence data from different
sources.

**Validation Genotyping (Project Aim 2)**

In order to accomplish the second eMERGE-PGx objective of integrating a number of well-
established, pharmacogenetic genotypes into the EHR with associated CDS, it will be
necessary to generate CLIA-certified genotype results. Next generation sequencing assays
are becoming more common in clinical genetics laboratories; however, the investment in test
validation is significant, as are the ongoing needs for operational expertise 41. In eMERGE-
PGx, two of the sites (Mount Sinai and Mayo Clinic42) are deploying selected portions of
PGRNseq as a clinical test in their CLIA and CAP certified genetics/genomics laboratories,
while using orthogonal platforms for other variants. Other sites are returning clinical
genotype results only from orthogonal platforms (e.g. custom MASSARRAY (Sequenom),
existing drug metabolism arrays, and Sanger sequencing) run in CLIA-certified laboratories
on- and off-site. Generation of genotype data from CLIA-certified laboratories is further
summarized in Supplementary Table 2.

**Study Participants (Project Aim 1)**

The eMERGE-PGx project involves a large (nearly 9000 subjects) cohort consented for
returning genetic information to their EHR for the purpose of clinical care decision-making.
The project was approved by the IRBs at each of the eMERGE-PGx sites. Institutions and
potential study populations vary, and Table 1 provides comparative recruitment and enrollment information for the different eMERGE sites. An expanded version of Table 1 which includes more information about the characteristics of the recruiting sites, additional details about inclusion criteria, and the specific methods used to recruit patients at each site, is provided in Supplementary Table 3. Each site is recruiting subjects based on their likelihood of being prescribed given target drugs in the near-term (a 1–3 year timeframe). Recruitment is in progress at all sites and full enrollment is projected by September 2015.

Several sites chose to identify the study population using a predictive algorithm incorporating site-specific data, such as that implemented in the Vanderbilt PREDICT program\textsuperscript{42,43}. Using historical EHR data, these sites identified demographic and clinical factors that predicted which patients were prescribed relevant drugs in the years preceding the eMERGE-PGx project. Then, using the most recently available data from EHR records and multivariable regression models, the investigators identified individuals in their clinical population most likely to be prescribed the relevant drugs as potential participants for the eMERGE-PGx study. Other sites used a similar, but simplified, approach of targeting patients they believed to be at high risk of being prescribed certain drugs based on demographic predictors such as diagnosis, age, and sex. At some sites these targeted approaches were implemented only among members of their biobank population (Geisinger Health System, Group Health Cooperative with University of Washington, and Mayo Clinic), while other sites implemented the approach in clinic populations. Other sites chose to use indication-based recruitment and recruited individuals assumed to be at high-risk for being prescribed certain drugs based on scheduled procedures (such as anticipated need for opioid pain medication after surgery).

In addition to patients, several sites are also enrolling prescribers into the eMERGE-PGx study to systematically capture their experiences with the implementation of pharmacogenetic variants into the EHR. Methods used to capture these experiences will include surveys, semi-structured interviews and focus groups.

Drug-Gene Pairs Implemented into Clinical Care (Project Aim 2)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) \textsuperscript{12} (http://www.pharmgkb.org/page/cpic), a shared project between PharmGKB and PGRN, publishes prescribing guidelines for using available genetic test results to make prescribing decisions. For eMERGE-PGx, each site engaged with local prescribers and institutional committees to choose a small number of drugs with CPIC guidelines for which pre-emptive pharmacogenetic genotyping could be obtained and results placed in the EHR with associated CDS to deploy at the time of drug order (hereafter referred to as drug-gene pairs). This study design addresses two primary barriers to the widespread implementation of pharmacogenetic genotyping in clinical practice, which are 1) lack of prescriber awareness or understanding of pharmacogenetics, and 2) time delay in receiving pharmacogenetic results at time of prescription \textsuperscript{30, 37–39, 44}. Table 2 lists the drugs with CPIC guidelines for which genotyping and associated CDS is being implemented at each of the eMERGE-PGx sites. The table also includes information about which prescribers at each site will see the CDS. Notably, six of the sites are implementing genotyping and CDS for the drug-gene
pairs of clopidogrel/CYP2C19, warfarin/CYP2C9/VKORC1, and simvastatin/SLC01B1. Some sites also chose to implement additional genotyping for drugs without current CPIC guidelines for this project (e.g., montelukast/SLC02B145 or tacrolimus/CYP3A546). The chosen target drugs were used for defining the study population at each site, as discussed previously.

**Pediatric Sites (Project Aims 1 and 2)**

eMERGE-PGx is recruiting a total of 2,575 patients from three pediatric sites. The pediatric focus presented additional design and implementation challenges. One challenge is that, to date, CPIC gene-drug guidelines focus primarily on medications typically prescribed in the adult population. One exception is the CYP2D6/codeine guideline. However, in February 2013, the FDA announced its intention to add a black box warning to the codeine label that strongly recommended avoiding codeine in all children following tonsillectomy. Two of the three pediatric sites are moving forward with pre-emptively integrating CYP2D6 genotypes into their EHR since, in addition to codeine, CYP2D6 metabolizes tramadol, hydrocodone and oxycodone, and the CPIC CYP2D6/codeine guideline also discusses these drugs. Another pediatric site will focus, in part, on the implementation of pre-emptive warfarin pharmacogenetics in children. This is an under-studied population for whom a validated dosing algorithm only recently became available47.

**EHR Implementation and Clinical Decision Support (CDS) (Project Aim 2)**

Each site is developing processes and workflow for genetic data integration into their institution’s EHR, and CDS is being developed locally based on the preferences of prescribers and the requirements of the EHR system in use. CDS required development of educational materials and automated systems to integrate validated genotype results into EHR. Many sites (CCHMC, CHOP, Geisinger, Group Health Cooperative / University of Washington, Marshfield, Mayo Clinic, Northwestern, and VUMC) are planning to place information for participants in electronic patient portals associated with the EHR. Table 2 includes information about which prescribers at each site will see the CDS. Supplementary Figure 1 shows examples of CDS alerts from several different eMERGE-PGx sites. Although the final design of decision support and educational materials vary by site, eMERGE-PGx sites are collaborating on educational materials and CDS design whenever possible.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Authors**

Laura J. Rasmussen-Torvik1, Sarah C. Stallings2, Adam S. Gordon3, Berta Almoguera4, Melissa A. Basford2, Suzette J. Bielinski5, Ariel Brautbar6, Murray Brilliant6, David S. Carrell7, John Connolly4, David R. Crosslin3, Kimberly F. Doheny8, Carlos J. Gallego9, Omri Gottesman10, Daniel Seung Kim3, Kathleen A. Leppig7, Rongling Li11, Simon Lin12, Shannon Manzi13, Ana R. Mejia10, Jennifer A.
Pacheco\textsuperscript{14}, Vivian Pan\textsuperscript{14}, Jyotishman Pathak\textsuperscript{15}, Cassandra L. Perry\textsuperscript{13}, Josh F. Peterson\textsuperscript{16}, Cynthia A. Prows\textsuperscript{17,23}, James Ralston\textsuperscript{7}, Luke V. Rasmussen\textsuperscript{1}, Marylyn D. Ritchie\textsuperscript{18}, Senthilkumar Sadhasivam\textsuperscript{19,23}, Stuart A. Scott\textsuperscript{20}, Maureen Smith\textsuperscript{14}, Aida Vega\textsuperscript{21}, Alexander A. Vinks\textsuperscript{22,23}, Simona Volpi\textsuperscript{11}, Wendy A. Wolf\textsuperscript{13,24}, Erwin Bottinger\textsuperscript{10}, Rex L. Chisholm\textsuperscript{14}, Christopher G. Chute\textsuperscript{25}, Jonathan L. Haines\textsuperscript{26}, John B. Harley\textsuperscript{23,27,28}, Brendan Keating\textsuperscript{4}, Ingrid A. Holm\textsuperscript{13,24,29}, Iftikhar J. Kullo\textsuperscript{30}, Gail P. Jarvik\textsuperscript{9}, Eric B. Larson\textsuperscript{7}, Teri Manolio\textsuperscript{11}, Catherine A. McCarty\textsuperscript{31}, Deborah A. Nickerson\textsuperscript{8}, Steven E. Scherer\textsuperscript{32}, Marc S. Williams\textsuperscript{33}, Dan M. Roden\textsuperscript{34}, and Joshua C. Denny\textsuperscript{16,35}

Affiliations

\textsuperscript{1}Department of Preventive Medicine, Northwestern University Feinberg School of Medicine
\textsuperscript{2}Vanderbilt Institute for Clinical and Translational Research
\textsuperscript{3}Department of Genome Sciences, University of Washington
\textsuperscript{4}Center for Applied Genomics, Children's Hospital of Philadelphia
\textsuperscript{5}Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic
\textsuperscript{6}Center for Human Genetics, Marshfield Clinic Research Foundation
\textsuperscript{7}Group Health Research Institute
\textsuperscript{8}Center for Inherited Disease Research, Institute of Genetic Medicine, Johns Hopkins University School of Medicine
\textsuperscript{9}Division of Medical Genetics, University of Washington
\textsuperscript{10}The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai
\textsuperscript{11}Division of Genomic Medicine, National Human Genome Research Institute
\textsuperscript{12}Biomedical Informatics Research Center, Marshfield Clinic Research Foundation
\textsuperscript{13}Division of Genetics and Genomics, Boston Children's Hospital
\textsuperscript{14}Center for Genetic Medicine, Northwestern University Feinberg School of Medicine
\textsuperscript{15}Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic
\textsuperscript{16}Department of Biomedical Informatics and Medicine, Vanderbilt University Medical Center
\textsuperscript{17}Division Human Genetics, Division Patient Services, Cincinnati Children’s Hospital Medical Center
\textsuperscript{18}Department of Biochemistry and Molecular Biology, The Pennsylvania State University

Clin Pharmacol Ther. Author manuscript; available in PMC 2015 October 01.
19 Department of Anesthesia, Cincinnati Children’s Hospital Medical Center
20 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai
21 Mount Sinai Faculty Practice Associates Primary Care Program, Icahn School of Medicine at Mount Sinai
22 Division of Clinical Pharmacology, Cincinnati Children’s Hospital Medical Center
23 Department of Pediatrics, College of Medicine, University of Cincinnati
24 Department of Pediatrics, Harvard Medical School
25 Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905
26 Center for Human Genetics Research, Vanderbilt University Medical Center
27 Cincinnati Children’s Hospital Medical Center, University of Cincinnati
28 US Department of Veterans Affairs Medical Center, Cincinnati, Ohio
29 The Manton Center for Orphan Disease Research, Boston Children’s Hospital
30 Division of Cardiovascular Diseases, Mayo Clinic
31 Essentia Institute of Rural Health, Duluth, MN
32 Human Genome Sequencing Center, Baylor College of Medicine
33 Genomic Medicine Institute, Geisinger Health System
34 Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine
35 Department of Medicine, Vanderbilt University School of Medicine

Acknowledgments

The eMERGE Network was funded through the following grants: U01HG006828 (Cincinnati Children’s Hospital Medical Center/Harvard); U01HG006830 (Children’s Hospital of Philadelphia); U01HG006389 (Essentia Institute of Rural Health); U01HG006382 (Geisinger Clinic); U01HG006375 (Group Health Cooperative and the University of Washington); U01HG006379 (Mayo Clinic); U01HG006380 (Icahn School of Medicine at Mount Sinai); U01HG006388 (Northwestern University); U01HG006378 (Vanderbilt University); and U01HG006385 (Vanderbilt serving as the Coordinating Center). The development of the PGRN-Seq platform was supported by the Deep Resequencing Resources of the Pharmacogenomic Research Network: U01 HL069757, U19 GM61388, and U01 GM097119. The activities being performed at Johns Hopkins Center for Inherited Disease Research (CIDR) and Johns Hopkins DNA Diagnostic Lab are funded by grant U01HG004438. This work is also supported by grant (HL069757). One list of actionable genes was generated with funding from the NHGRI, U01HG006507. At Mayo Clinic this work was also supported in part by Mayo Clinic Center for Individualized Medicine and National Institutes of Health grants U19 GM61388 (The Pharmacogenomics Research Network), R01 GM28157, U01 HG005137, R01 CA138461, and R01 AG034676 (The Rochester Epidemiology Project). At Vanderbilt University, the work was also supported by the Pharmacogenomics of Arrhythmia Therapy PGRN site grant from the National Institute of General Medical Sciences and the National Heart Lung and Blood Institute (U19 HL65262), which also supports the site’s participation in the TPP and CPIC.

Abbreviations

CDS Clinical Decision Support
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| Study Highlights |
|-----------------|
| **What is the current knowledge on the topic?** |
| There are very few formal investigations into the real-world implementation and clinical outcomes of genetically-tailored drug prescribing. Additionally, little is known about the importance of rare variants in pharmacogenes. |
| **What question does this study address?** |
| eMERGE-PGx examines associations of rare variants in pharmacogenes with EHR-derived phenotypes in a large (~9,000) study sample. eMERGE-PGx also examines what happens when you implement large-scale genetically-tailored drug prescription across several large medical centers. |
| **What will this study add to our knowledge?** |
| Results from eMERGE-PGx will both inform the critical question of HOW best to implement genetically-tailored prescription in medical practice and will provide multiple new genetic targets for pharmacogenetic investigation. |
| **How this might change clinical pharmacology and therapeutics?** |
| eMERGE-PGx represents a first step toward a vision of incorporating large scale sequence information into the flow of routine healthcare. |
Figure 1.
eMERGE PGx Project Design

Aim 1: Deploy PGRNseq, an NGS platform focusing on 84 known pharmacogenes
- Identify and recruit participants: Find people likely to be prescribed drugs with relevant pharmacogenes
- Implement PGRNseq platform at several study sites: Obtain targeted sequence on nearly 9,000 people

Aim 2: Preemptively implement pharmacogenetic genotypes on the EHR
- Obtain preemptive CLIA-validated genotyping
- Design result display and deposit genotypes in EHR
- Develop and deploy clinical decision support in EHR
- Assess process outcomes of performance and impact

Aim 3: Develop a repository for pharmacogenetic association studies [SPHINX http://emergesphinx.org]
- Populate SPHINX with variants in PGRNSeq genes
- Initiate functional and association studies

Clin Pharmacol Ther. Author manuscript; available in PMC 2015 October 01.
| Site                                                                 | Participant Pool                                                                 | Participant Selection Method                                                                 | Target Enrollment |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------|
| Boston Children’s Hospital (BCH)                                    | Patients (inpatient and clinic) followed by the anticoagulation service           | Participants 1 month of age or older who will potentially require warfarin                    | 250               |
| Children’s Hospital of Philadelphia (CHOP)                          | The entire hospital and outpatient clinics                                         | Participants taking more than 3 medications at once, EHR records for serious adverse event (SAE), SAE noted during hospitalization | 1650              |
| Cincinnati Children’s Hospital Medical Center (CCHMC)                | Pediatric general surgery, thoracic surgery, and orthopedic surgery clinics       | 6–21 year olds being evaluated for pectus excavatum or scoliosis                              | 375               |
|                                                                     | Past participants in tonsillectomy studies                                         | Participants 6–15 years old                                                                     | 300               |
| Geisinger Health System (GHS)                                       | MyCode™ biobank participants                                                      | All males over the age of 50 who were not on one of more of the target medications at the time of ascertainment | 1100              |
| Group Health/University of Washington                               | Northwest Institute of Genetic Medicine (NWIGM) biorepository participants         | Adults aged 50–65 years old at the time of entry to the repository indicating interest in return of clinically useful results. Preferential selection for individuals with certain diagnoses and medication history and all participants with Asian or African American descent. | 900               |
| Marshfield Clinic                                                   | Adults above the age of 50 with a primary care physician in the Marshfield Clinic. | Adults above the age of 50 with no prior use of simvastatin, warfarin or clopidogrel           | 750               |
| Mayo Clinic                                                        | Mayo Clinic Biobank participants who are adult primary care patients               | Predictive regression algorithm to estimate risk of receiving statin therapy                    | 1000              |
| Icahn School of Medicine at Mount Sinai                             | Patients with primary care providers at Mount Sinai Faculty Practice Associates—Primary Care Associates | Adults above the age of 50 with no prior use of simvastatin, warfarin, or clopidogrel          | 750               |
| Northwestern University                                            | Patients visiting the Northwestern Medical Group-General Internal Medicine Clinic  | Predictive regression algorithm to estimate risk of receiving simvastatin, clopidogrel, or warfarin | 750               |
| Vanderbilt University                                              | Vanderbilt internal medicine and cardiology clinics                               | Predictive regression algorithm to estimate risk of receiving simvastatin, clopidogrel, or warfarin | 1000              |
### Table 2
Implementation of well-established pharmacogenetic genotypes into the EHR, by eMERGE-PGx Site

| Site                                           | CPIC Gene/Drug Pairs* | Prescribers seeing CDS              | EHR vendor            |
|------------------------------------------------|-----------------------|-------------------------------------|-----------------------|
| Boston Children’s Hospital (BCH)               | *TPMT/thiopurines     | All prescribers including pharmacists | Cerner                |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
| Children’s Hospital of Philadelphia (CHOP)     | *CYP2D6/codeine       | All prescribing physicians           | Epic                  |
|                                                | *TPMT/thiopurines     |                                     |                       |
|                                                | *HLAB1502/carbamazepine |                                   |                       |
|                                                | Additional CPIC and Dutch Pharmacogenetics Working group recommendations | |                       |
| Cincinnati Children’s Hospital Medical Center (CCHMC) | *CYP2D6/codeine       | All prescribers                      | Epic                  |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *CYP2D6/tricyclic antidepressants |                   |                       |
|                                                | *CYP2C19/tricyclic antidepressants |                   |                       |
| Geisinger Health System (GHS)                 | *CYP2C19/clopodogrel  | All prescribing physicians           | Epic                  |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *SLCO1B1/simvastatin  |                                     |                       |
| Group Health/University of Washington          | *HLAB1502/carbamazepine |                       | All prescribing physicians | Epic |
| Marshfield Clinic                              | *CYP2C19/clopodogrel  | All prescribing physicians           | Internally Developed (Cattails) |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *SLCO1B1/simvastatin  |                                     |                       |
| Mayo Clinic                                    | *CYP2C19/clopodogrel  | All prescribing physicians           | General Electric Centricity (Rochester Campus) |
|                                                | *CYP2C9/warfarin      |                                     | Cerner (Arizona and Florida Campuses) |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *SLCO1B1/simvastatin  |                                     |                       |
|                                                | *CYP2D6/codeine       |                                     |                       |
|                                                | *CYP2D6/tramadol      |                                     |                       |
|                                                | *CYP2D6/tamoxifen     |                                     |                       |
| Icahn School of Medicine at Mount Sinai        | *CYP2C19/clopodogrel  | Primary care provider collaborators | Epic                  |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *SLCO1B1/simvastatin  |                                     |                       |
| Northwestern University                        | *CYP2C19/clopodogrel  | Primary care provider collaborators | Epic outpatient       |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *SLCO1B1/simvastatin  |                                     |                       |
| Vanderbilt University                          | *CYP2C19/clopodogrel  | All prescribing physicians           | Internally Developed (StarChart) |
|                                                | *CYP2C9/warfarin      |                                     |                       |
|                                                | *VKORC1/warfarin      |                                     |                       |
|                                                | *TPMT/thiopurines     |                                     |                       |

* Some of the eMERGE-PGx sites are also implementing gene/drug pairs that do not have CPIC guidelines. These include CHOP: SLC02B1 / montelukast, ABCB1 + CYP2C19 / ranitidine + omeprazole, CYP2D6 + ABCB1 + OPRM1 + COMT+ UGT2B7/ morphine, Marshfield: CYP4F2/ warfarin, Vanderbilt: CYP3A5/tacrolimus