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ORIGINAL ARTICLE

Preemptive Genotyping for Personalized Medicine: Design of the Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment Protocol

Suzette J. Bielinski, PhD, MEd; Janet E. Olson, PhD; Jyotishman Pathak, PhD; Richard M. Weinshilboum, MD; Liewei Wang, MD, PhD; Kelly J. Lyke; Euijung Ryu, PhD; Paul V. Targonski, MD, PhD; Michael D. Van Norstrand, MD, PhD; Matthew A. Hathcock, MS; Paul Y. Takahashi, MD; Jennifer B. McCormick, PhD, MPP; Kiley J. Johnson, MS, CGC; Karen J. Maschke, PhD; Carolyn R. Rohrer Vitek, MS; Marissa S. Ellingson, MS, CGC; Eric D. Wieben, PhD; Gianrico Farrugia, MD; Jody A. Morrisette, MBA; Keri J. Kruckeberg, BA; Jamie K. Bruflat, MS; Lisa M. Peterson, BS; Joseph H. Blommel, MS; Jennifer M. Skierka, BS; Matthew J. Ferber, PhD; John L. Black, MD; Linnea M. Baudhuin, PhD; Eric W. Klee, PhD; Jason L. Ross, MA; Tamra L. Veldhuizen, BS; Cloann G. Schultz, MS; Pedro J. Caraballo, MD; Robert R. Freimuth, PhD; Christopher G. Chute, MD, DrPH; and Iftikhar J. Kullo, MD

Abstract

Objective: To report the design and implementation of the Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment protocol that was developed to test the concept that prescribers can deliver genome-guided therapy at the point of care by using preemptive pharmacogenomics (PGx) data and clinical decision support (CDS) integrated into the electronic medical record (EMR).

Patients and Methods: We used a multivariate prediction model to identify patients with a high risk of initiating statin therapy within 3 years. The model was used to target a study cohort most likely to benefit from preemptive PGx testing among the Mayo Clinic Biobank participants, with a recruitment goal of 1000 patients. We used a Cox proportional hazards model with variables selected through the Lasso shrinkage method. An operational CDS model was adapted to implement PGx rules within the EMR.

Results: The prediction model included age, sex, race, and 6 chronic diseases categorized by the Clinical Classifications Software for *International Classification of Diseases, Ninth Revision* codes (dyslipidemia, diabetes, peripheral atherosclerosis, disease of the blood-forming organs, coronary atherosclerosis and other heart diseases, and hypertension). Of the 2000 Biobank participants invited, 1013 (51%) provided blood samples, 256 (13%) declined participation, 555 (28%) did not respond, and 176 (9%) consented but did not provide a blood sample within the recruitment window (October 4, 2012, through March 20, 2013). Preemptive PGx testing included *CYP2D6* genotyping and targeted sequencing of 84 PGx genes. Synchronous real-time CDS was integrated into the EMR and flagged potential patient-specific drug-gene interactions and provided therapeutic guidance.

Conclusion: This translational project provides an opportunity to begin to evaluate the impact of preemptive sequencing and EMR-driven genome-guided therapy. These interventions will improve understanding and implementation of genomic data in clinical practice.

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Pharmacogenomics (PGx) is the study of the role of genetic variation in drug response phenotypes.[1-4] An individual's drug response phenotype can range from serious, potentially life-threatening adverse drug reactions at one end of the spectrum to lack of therapeutic efficacy at the other. As a result, the clinical implementation of PGx at the bedside could make it possible to avoid adverse drug reactions, maximize drug efficacy, and select medications to optimize effect for specific indications on the basis of the genetic

From the Department of Health Sciences Research

Affiliations continued at the end of this article.

profile of individual patients. Over the past decade, numerous PGx variants with proven clinical utility have been identified and incorporated into drug labels by the US Food and Drug Administration (FDA).[5]

Widespread incorporation of PGx into clinical practice, despite its potential clinical implications that could, ultimately, affect virtually every patient, has proved to be challenging due to (1) delay in the initiation of therapy when traditional reactive ordering of PGx testing at the point of care is used, (2) lack of support for commercial electronic medical record (EMR) systems to integrate large-scale genomic data linked to automated clinical decision support (CDS), (3) lack of development of quality CDS, (4) prescriber uncertainty about benefits, both clinical and economical, for genome-guided therapy, and (5) ethical, legal, social, and financial concerns with regard to genomic medicine by patients and their families.[6] Changing the clinical paradigm to preemptively sequencing patients at high risk of needing specific medications and providing parallel CDS around results interpretation and actions could minimize some of these challenges by cost-effectively interrogating a large panel of PGx genes and integrating clinically actionable results into the patient's EMR that can be used by clinicians at the point of care. A distinct advantage to this approach is the ability to review the available sequence data and, based on new PGx discoveries, update the patient's record without the need for additional specimen collection and testing provided the variant was included in the PGx panel. Furthermore, CDS integrated into the EMR may increase awareness of drug-gene interactions, facilitate knowledge and acceptance of PGx testing, and guide the individualization of drug/dose selection.

Few aspects of genomic medicine have the potential to immediately impact the care of patients in a clinically meaningful fashion like PGx. Accordingly, the National Institutes of Health facilitated a collaboration between the Pharmacogenomics Research Network (PGRN)[7] (http://www.pgrn.org) and the Electronic Medical Records and Genomics (eMERGE) Network[8,9] (http://emerge.mc.vanderbilt.edu) to support pilot preemptive PGx DNA sequencing projects. The Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment protocol (RIGHT protocol) is an outcome of this collaboration in concert with the Mayo Clinic Center for Individualized Medicine.[6] The RIGHT protocol is tasked with extending PGx implementation beyond "reactive genotyping," which may in some instances have less than optimal turnaround times and cost, to include "preemptive sequencing," with integration of the clinically actionable PGx variants into the EMR to drive point-of-care CDS. Herein we report the design and implementation of the RIGHT protocol.

PATIENTS AND METHODS

Study Objectives

The goal of this project was to develop best practices for the implementation of genetic sequence data into clinical systems to improve patient outcomes. Specifically, the RIGHT protocol pilot has 3 main objectives. First, we sought to identify 1000 Mayo Clinic Biobank[10] participants who have a high likelihood that PGx information will be useful to their care within a 1- to 3-year window. This approach is justified given the relatively small sample size for this preemptive genotyping project and the need to optimize the number of "events" (ie, drug-gene pairing) during a limited follow-up period. Our second objective was to deploy a PGx panel test that includes the next-generation sequencing (NGS) reagent developed by the PGRN (PGRNseq)[11] that captures 84 pharmacogenes (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org) and *CYP2D6* genotyping in a Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) certified environment and integrate clinically actionable variants with existing clinical data in the patient EMR. Third, we aimed to develop and implement CDS at the point of care for clinically actionable PGx variants. Overarching these aims was the evaluation of objective specific metrics to begin to form a narrative for best practices of genomic medicine implementation.

Prediction Model Development

Given the limited sample size for this pilot project, a prediction model was developed to target a population of patients with a high likelihood of being prescribed a commonly used drug and