

Development of a Scalable Pharmacogenomic Clinical Decision Support Service

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Abstract: Advances in sequencing technology are making genomic data more accessible within the healthcare environment. Published pharmacogenetic guidelines attempt to provide a clinical context for specific genomic variants; however, the actual implementation to convert genomic data into a clinical report integrated within an electronic medical record system is a major challenge for any hospital. We created a two-part solution that integrates with the medical record system and converts genetic variant results into an interpreted clinical report based on published guidelines. We successfully developed a scalable infrastructure to support TPMT genetic testing and are currently testing approximately two individuals per week in our production version. We plan to release an online variant to clinical interpretation reporting system in order to facilitate translation of pharmacogenetic information into clinical practice.

Introduction: Through efforts spearheaded by the Clinical Pharmacogenomics Implementation Consortium (CPIC) and others, gene-based drug dosing guidelines have been developed for several well-characterized genes and drugs, including TPMT/thiopurines and VKORC1/CYP2C9/warfarin, and CYP2C19/clopidogrel, respectively. Although these guidelines nicely summarize phenotypes, genotypes, and dosing recommendations, there is a substantial translational barrier to implement these guidelines into a clinical decision support service offered within a hospital. We sought to develop a scalable pharmacogenomic clinical decision support service that: 1) analyzes genomic variant data, 2) incorporates CPIC guidelines, 3) produces customized clinical reports, and 4) integrates with electronic medical record systems. We created the Clinical Pharmacogenomics Service (CPS) at Boston Children's Hospital (BCH) to oversee incorporation of genomic information to make pediatric medication use safer. We decided to implement this service by standardizing thiopurine S-methyltransferase (TPMT) testing hospital-wide. TPMT is an enzyme that is responsible for the metabolism of thiopurine drugs such as azathiopurine, mercaptopurine, and thioguanine. Specific mutations in TPMT can cause individuals to have reduced activity, which can lead to several life-threatening adverse effects, including decreased bone marrow activity resulting in fewer red blood cells, white blood cells, and platelets.

Methods: The implementation was accomplished in two segments. First, we customized our medical record system, Cerner, to do the following: built text-based discern alerts for prescribers and pharmacists based on a problem list entry correlated with specific drugs, incorporated interpretation report and diplotype display in the lab hierarchy, built a specialty view to display pharmacogenomic results, built a consult note in the hierarchy, and created automated reports that run daily for pharmacogenetic tests in progress and any tests resulted in the past 24-hours. We are currently building pre-emptive alerts to fire when a target drug is ordered that would benefit from pharmacogenetic testing. Second, we built an online clinical reporting system that takes genetic variant data (currently SNPs) and generates a clinical report that we incorporate into the medical record. The reporting system automatically determines the appropriate gene star nomenclature (e.g., TPMT *1/*3A) based on sequenced variants and a haplotype table. From the gene star name the system formats, on the fly, the correct clinical report in an editable form for the lab directors to review. After the form is approved, the results are saved to a database and both HTML and PDF version of the report are available.

Results: In six months, we went from planning to production for TPMT testing hospital-wide. The service went live on August 1, 2012, and we are currently testing approximately two people per week. As of this submission, we analyzed a total of 26 individuals *1/*1 (n=22), *1/*3A (n=3), and *1/*3C (n=1), which appear to be following the expected population allele frequencies. Dosing changes were recommended in the four heterozygous cases. We anticipate releasing the clinical web application to further streamline the clinical interpretation and reporting process. Support for the pharmacogenomics service at BCH has been extremely positive from clinicians, pharmacists, and the genetic diagnostic laboratory.

Conclusions: We successfully demonstrated creating an end-to-end service for pharmacogenetic testing. We designed the system to be scalable knowing that additional pharmacogenetic variants will emerge and new reports will need to be created. Implementation required overcoming two major obstacles. First, modifying the current electronic record system to display the relevant pharmacogenetic information in real-time and second, mapping the genetic variant information (base pairs) into a clinical report. Building the informatics to process genetic data at the base-pair level gives us additional flexibility to transition to other types of genomic inputs such as exome, whole genome, or chip-based assays without modifying our reporting structure. We plan to continue expanding by offering additional pharmacogenetic services.