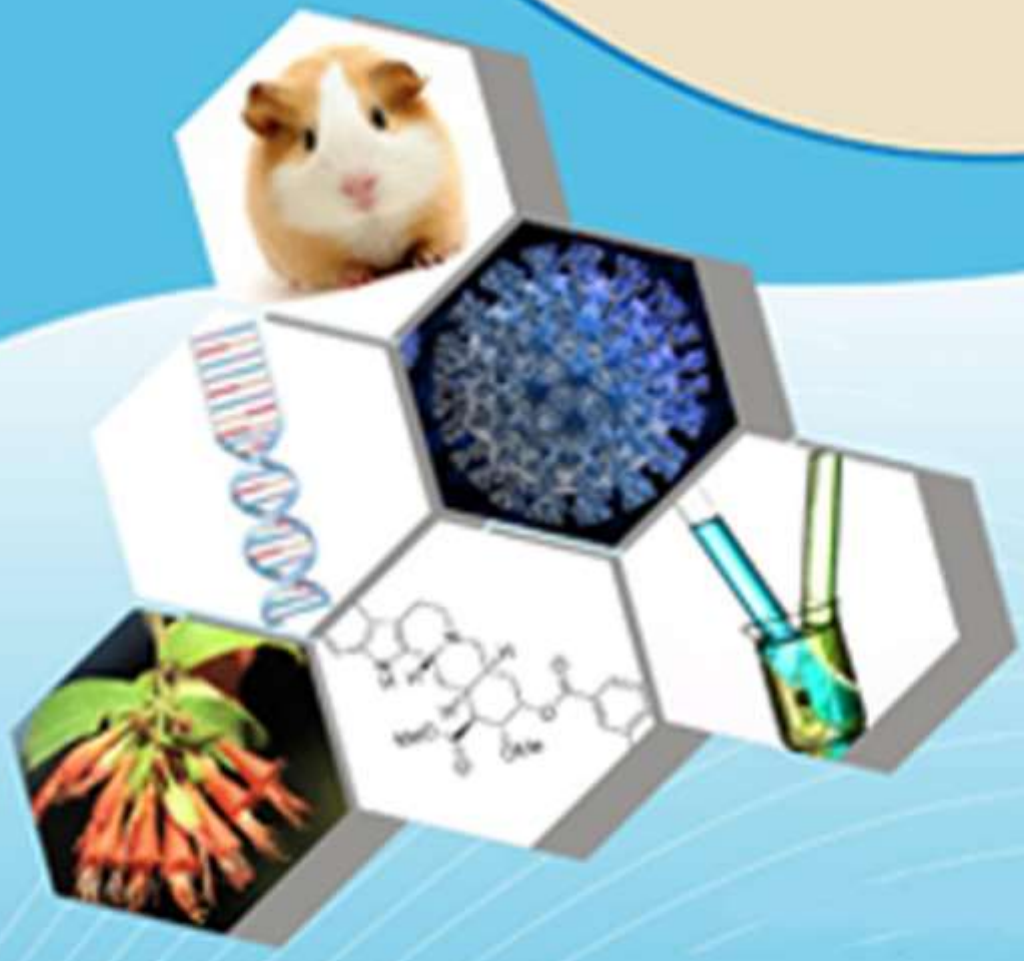
ISSN : 2347-2251

Indo-American Journal of Pharma and Bio Sciences



iajpb.editor@gmail.com
editor@iajpb.com

www.iajpb.com

ISSN 2347-2251 www.iajpb.com
Vol. 6, Issuse 3, July 2018

Indo-American Journal of Pharma and Bio Sciences

Perspectives from various regions on pharmacogenomics EHR development and implementation

S. Kusuma Kumari, C. renuka Thejeswini, R. Jona Methusala

Abstract

There are few documented instructions to implementation, yet the design of electronic health records is vital to the effective introduction of novel genomic services.

In this study, we followed the four-year development process of a locally produced electronic health record that serves a major pharmacogenomics program at a tertiary-level academic medical facility.

Electronic health record (EHR) procedures for ordering a pharmacogenomics panel in anticipation of clinical need (preemptive genotyping) or in response to a particular therapeutic indication were developed and implemented by program personnel. As a result, panel-based genotyping results were kept separate from the EHR until clinically actionable evidence of drug-gene interactions was found. A

The drug-response phenotype prediction service supplied a summary of drug-gene interactions, prompted inpatient and outpatient clinical decision support, updated laboratory records, and produced gene results inside online personal health records.

Conclusion: Generalizability of a locally constructed electronic health record that incorporates pharmacogenomics into its design. Scalability of the model to larger collections of genomic data is examined, as is the difficulty of putting genomic data in a way that is both understandable and therapeutically useful.

Key words; electronic health records; implementation; pharmacogenomics

Introduction

As the price of genotyping reduces dramatically1 and new studies demonstrate the utility of testing, the use of diagnostic gene tests in clinical care has expanded significantly in the United States. 2 Since many commonly given medications now have increasingly well-validated connections to adverse events or lower efficacy when gene variations are present, pharmacogenomics is primed to see comparable expansion. 3–5 In addition, the cost of panel tests comprising hundreds of genes has decreased thanks to developments in genotyping technology, opening the door to the possibility of testing individuals once and utilizing their genetic data frequently for the rest of their lives. There is a high probability that a patient may be exposed to a medicine with published pharmacogenomic connections, given the labels of 119 US Food and Drug Administration-approved pharmaceuticals presently include germ- line or tumor pharmacogenomic information. Sixty-five percent of ambulatory-care patients tracked longitudinally at our institution were exposed to at least one drug with a documented pharmacogenomic connection during a 5-year time period, demonstrating the great potential for using variations from a pharmacogenomic panel test. 6 Communicating the importance of genetic data to practicing physicians and managing genomic data across a fragmented care-delivery system are crucial to realizing the promise of translating pharmacogenomics to clinical practice. 7 Electronic health records (EHRs) and clinical decision support (CDS) are only two examples of the health information technology (HIT) that has become essential in modern medicine. However, there is little documentation of successful clinical pharmacogenomics implementations of these technologies. 8,9 Fortunately, the voids are being filled by a number of NIH-funded consortiums. Knowledge management and clinical decision support (CDS) best practices have been created and published by the Clinical Pharmacogenetics Implementation Consortium.

Pharmacy Practice

Dr.K.V. Subba Reddy Institute of Pharmacy
(Approved by AICTE,P.C.l New Delhi& Permanently Affiliated to JNTUA Anantapuramu
MOU with Government General Hospital &KMC, K urnool

The recommendations of the Clinical Pharmacogenetics Implementation Consortium are well annotated, backed by a hierarchy of evidence, and accessible for no cost. 10–14 To further facilitate translation, two multi-institute consortia, the Electronic Medical Records and Genomics Network (also known as the eMERGE Network) and the Translational Pharmacogenomics Project of the Pharmacogenomics Research Network, are actively piloting efforts to integrate genomic information with EHRs. SPECIAL ARTICLE of pharmacogenomics to the clinical setting and to capitalize on the wealth of clinical data contained in the EHR for research.

Vanderbilt University Medical Center (VUMC) has estab- lished a large pharmacogenomic program known as PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment).[15] PREDICT is based on the principles that pharmacogenomic testing should be preemptive and harness HIT to facilitate ordering, storage, and timely dissemination of genetic results at the point of care. The design and implementa- tion model presented here arose out of a 4-year development process to adapt a largely locally developed EHR[16] to enable the maintenance, interpretation, and distribution of panel-based pharmacogenomic data to a broad base of providers and patients(**Figure 1**). For this article, the term EHR is inclusive of all clini- cal information systems that manage or manipulate genomic information while serving clinician information needs. In addi- tion, we include a brief description of the connection between the EHR and the personal health record (PHR). We believe ourexperiences can inform adaptations of both locally developedand commercial EHRs for pharmacogenomics.

EHR DESIGN PRINCIPLES FOR A PHARMACOGENOMICS IMPLEMENTATION

PREDICT was established as a quality-improvement program in 2010 to apply clinically significant gene variants designated by the US Food and Drug Administration as pertinent to deci- sions involving drug selection and dosing.[15] EHR features were developed with the expectation that panel-based pharmacoge- nomic testing will become pervasive, and genomic consider- ations will routinely influence prescribing. Accordingly, the design of supportive EHR functions has followed 10 objectives (**Table 1**), which seek to give universal, comprehensible, and timely access to clinically significant genetic variants. Displays of pharmacogenomics results were created to be highly visible,

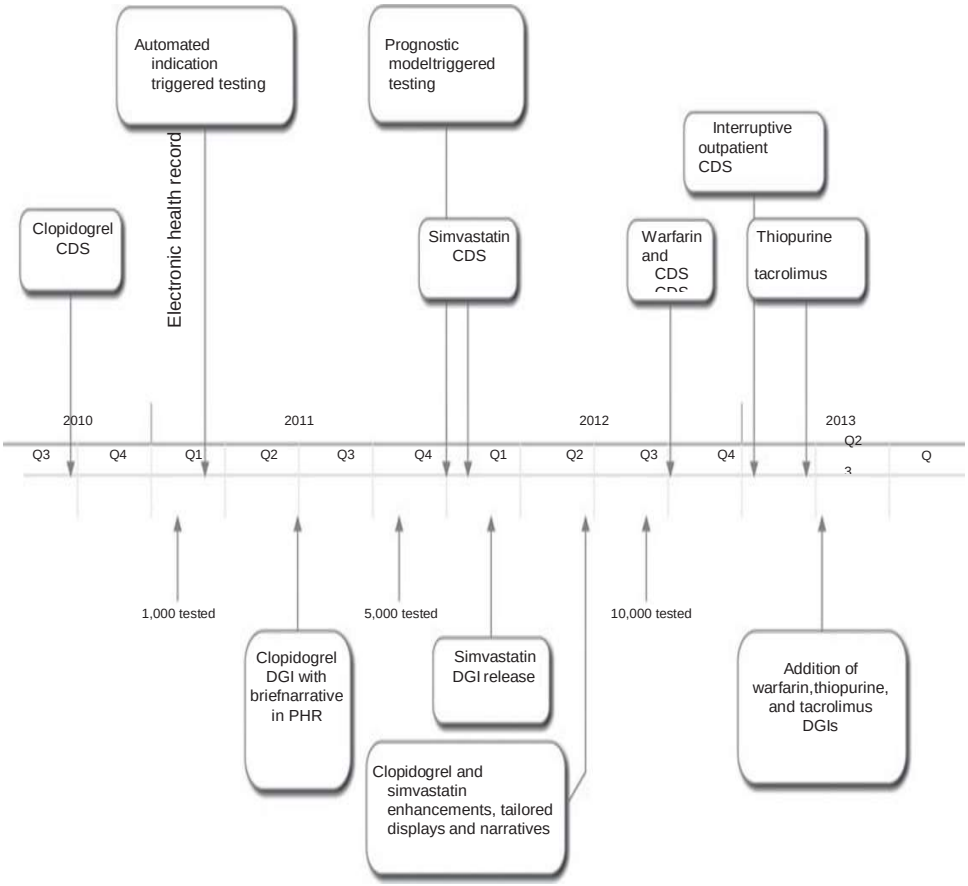


Figure 1 PREDICT EHR development timeline. PREDICT has undergone a 4-year process of design, implementation, and iterative refinement. Several milestones, including new drug–genome interaction implementation as well as high-impact EHR design features, are highlighted. CDS, clinical decision support; DGI, drug–genome interaction; EHR, electronic health record; PHR, personal health record; PREDICT, Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment.

Table 1 Design objectives for a pharmacogenomics-enabled electronic health record

1. Display universally accessible and highly visible gene variant and phenotype information within EHR
2. Flag patients likely to benefit from knowledge of genomic variants in advance of clinical need (preemptive genotyping)
3. Facilitate genotyping among patients with an immediate clinical need (indication-based genotyping)
4. Sequester all variants with selective promotion of actionable variants to EHR upon institutional pharmacy and therapeutics approval
5. Create and maintain a centralized service to translate genotype to phenotype
6. Create a centralized knowledge base of therapeutic alternatives and dosing algorithms for clinical decision support
7. Rapidly distribute genetic results to laboratory, patient portal, inpatient and outpatient prescribing environments, and the associated clinical decision support subsystems
8. Implement surveillance and quality assurance interventions for post–prescription drug–genome “conflicts”
9. Create notification to patients of their genomic results with patient-friendly interpretations
10. Ensure systems are scalable to genomic variant data sets that are much larger than those currently in clinical use

The above objectives were prospectively addressed in the design and implementation of pharmacogenomics CDS within VUMC’s EHR.

CDS, clinical decision support; EHR, electronic health record; VUMC, Vanderbilt University Medical Center.

in an effort to prevent priority results from being “buried” among other laboratory data. Preemptive identification of patients who were expected (based on statistical prediction models) to benefit from panel-based gene variant data to tailor future therapies was incorporated into outpatient workflow. All gene variant data were stored long term, but selective, clinically actionable drug–gene combinations that met the burden of evidence for a significant drug–genome interaction (DGI) and attained institutional approval for release, and for which we had developed CDS logic to guide the physician, were promoted to the EHR. The design for disseminating results features a sin- gle source for both genetic variant data and genotype to drug phenotype interpretation, reinforcing the consistency and reli- ability of genotype reporting. Knowledge and data sources were constructed using service-based software architecture such that both genetic variant data and the DGI knowledge base could be easily updated and the updates would propagate to all linked systems. Finally, the EHR mechanisms for reporting the results and delivering CDS were initially designed to serve a small set of targeted DGIs but easily scale to support a large quantity of pharmacogenomic variants.

A LOCALLY DEVELOPED EHR PERSPECTIVE

The biomedical informatics and genomics fields foresaw the need to store, manage, analyze, display, and communicate genetic data early in the process of developing the translation of genomic medicine to clinical practice. 17 Locally designed clinical information systems are ideal for pharmacogenomics adoption since hospitals have more say over the structure and compatibility of their HIT. Historically, "homegrown" EHRs have been acknowledged for serving as a proving ground for novel HIT concepts, allowing for the evaluation of clinical efficacy, and offering proof-of-concept implementations for the broader informatics community. 18–21 Furthermore, locally designed EHRs benefit from a dedicated user base that developers can interact with face-to-face to get input and make iterative adjustments that enhance the software's usability and functionality. While many big academic medical facilities and integrated health systems have invested decades in technological infrastructure and programming, few have maintained this competence as clinical information demands have grown. The existing monolithic architecture of EHRs, in which huge HIT ecosystems from a single vendor or institution are interoperable internally but lack the capacity to connect outside, is another possible drawback. For instance, due to the difficulties in standardizing EHR systems, three of the eMERGE pharmacogenomics implementation sites are pursuing either partial or complete development separately. When it comes to information sharing and dissemination, eMERGE and the Translational Pharmacogenomics Project locations

standards for design and information management that may be used as a guide by other businesses. From prescription to clinical application, pharmacogenomics relies on electronic health records (EHRs), and this article will detail how these records and their associated features facilitate this process (Figure 2).

IMPLEMENTATION OF PREEMPTIVE AND INDICATION-BASED PHARMACOGENOMIC TESTORDERING

For most of the prescribing scenarios currently covered by PREDICT, including the drugs warfarin, simvastatin, clopidogrel, tacrolimus, and thiopurines, the genomic information contributes diminishing returns to clinical outcomes after the patient has achieved a stable dose or drug selection through experience or sequential drug trials. 3–5,22–25 The clinical impact of genetic data, such as VKORC1 and CYP2C9 variant status, is thought to wane considerably after a stable international normalized ratio is achieved, an event which generally occurs within the first 2 weeks of therapy. This is because warfarin dosing is sto- chastically adjusted in response to serial international normalized ratio measurements. Like CYP2C19 variant individuals, those taking clopidogrel had a greater chance of developing in-stent throm- bosis during the first 30 days after stent implantation. Thus, in order to optimize the

influence of the genotype data on clinical treatment, the program has emphasized testing before to or simultaneously with medication commencement.

Due to this, two pharmacogenomics ordering methodologies, preventative and indication-triggered testing, were developed. All patients with upcoming general care or cardiology appointments now get an alert in the EHR if a statistical risk score hits or exceeds the thresh- old, allowing for preventative genotyping. With a risk score of 40%, the molecular diagnostics lab would be fully used, predicting a patient's likelihood of obtaining simvastatin, warfarin, or clopidogrel over a 3-year time horizon. When a patient's record is marked, the outpatient order entry system generates a draft order for the PREDICT test, which the treating clinician must then approve. Indication-specific testing has been implemented by adding the PREDICT panel test to order sets or preprocedure planning prior to cardiac catheterization (to capture catheterization patients who receive intracoronary stents and antiplatelet therapy such as clopidogrel) and certain orthopedic procedures (e.g., joint replacements) for which warfarin-based anticoagulation is standard. Preemptive genotyping is advantageous because it removes the need to wait for the genotype, which typically takes between 2 and 5 days to get.

In light of the declining cost of genotyping, the potential exposure to multiple medications with pharmacogenomic indications, and the very high cost of severe adverse events, we propose significant cost savings using a preemptive panel- based genotyping strategy as compared to serial single-gene tests.

6,26,27 Over the course of a patient's lifetime, multiplexed gene testing will most likely be used.

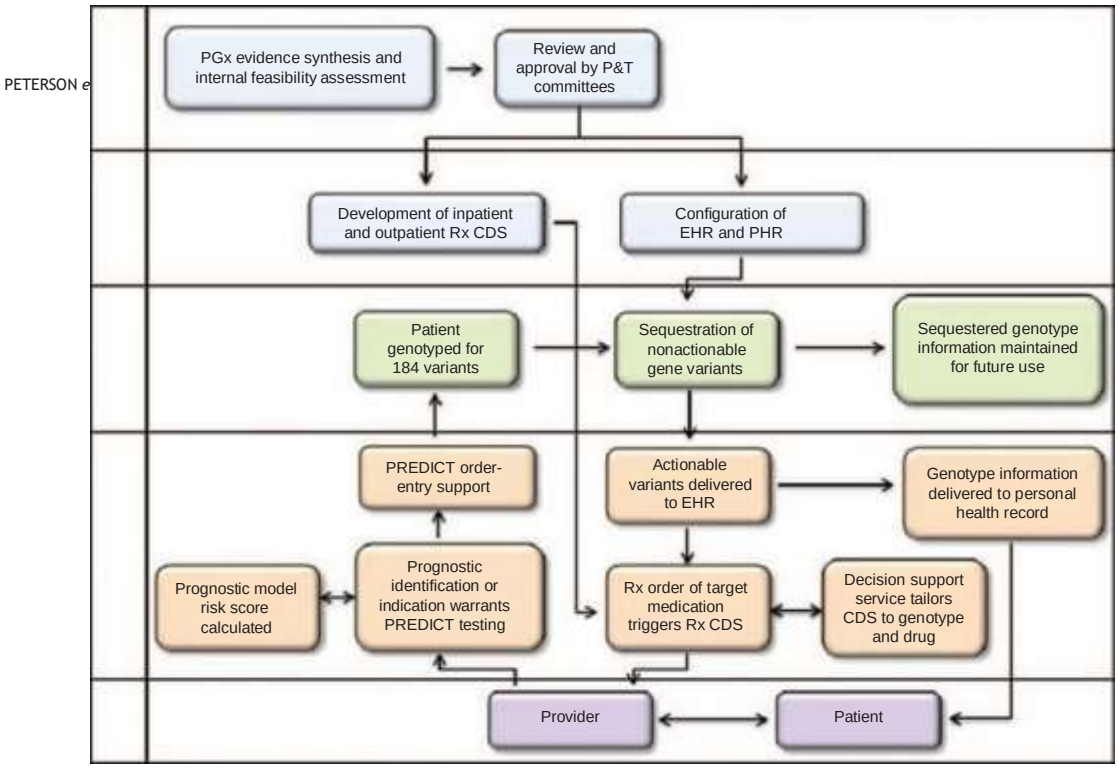


Figure 2 EHR development and operational processes. Pharmacogenomics implementation requires preimplementation research and assessment, technical development of informatics infrastructure, and integration with laboratory and clinical operations. Accessibility to users, both patients and providers, is integral. CDS, clinical decision support; EHR, electronic health record; P&T, pharmacy and therapeutics; PGx, pharmacogenomics; PHR, personal health record; PREDICT, Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment; Rx, prescription.

to be less expensive relative to the potential benefit, particu- larly in patients with a common set of cardiovascular risk fac- tors likely to need associated therapies. However, no health economic studies have determined the value of panel-based genetic tests outside of oncology, and there is a paucity of evi- dence relating panel-based genetic tests to health-care spend- ing. VUMC has supported the PREDICT program costs with institutional funds, including assay costs, reagents, labor, instrumentation for processing, empiric research among patients and providers, development of patient informational materials, decision-support tools that provide point-of-care interventions and drug/dosing guidance based on test results, and education and training given the associated dearth of knowledge and familiarity among prescribers.[15] A key goal of this investment is to catalyze further pharmacoeconomic analyses of this approach.

EHR STORAGE MODEL FOR SEQUESTRATION AND REPOSITORY

National data standards for genetics are in early stages; a model to exchange genetic testing results is proposed by HealthLevel 7,[28] with contributions by Pharmacogenomics ResearchNetwork–affiliated academic groups[29,30] and EHR vendors.[31,32] In the absence of established standards in

2010, and to meet the immediate needs of the program, PREDICT developers created a coded storage model to meet local requirements for

CDS and distribution to multiple clinical information systems. Future adaptation to emerging standards such as Health Level7 is planned to support communication with external sys- tems. Genetic variant data produced by the Illumina VeraCode Absorption, Distribution, Metabolism, and Excretion Core Panel for PREDICT are provided either as a Portable Document Format or as plain text. As the former does not provide com- putable results, automatic parsing of the text format is required to extract the gene name, variant result in star nomenclature, and a call rate, which indicates the ability of the panel to yield a result at a specific variant. In the event of a call rate <98.7%, the test result is manually reviewed and generally retested by Molecular Diagnostics Laboratory staff; otherwise, it is released to an Oracle database, which initially sequesters all results from the main EHR storage.

The Oracle database is exposed to downstream systems through a filtered view limited to actionable approved variants. An automated script queries the filtered database view hourly to extract new or updated entries and, if discovered, creates a new or updated entry in the genotype section of the Patient Summary Service, a central Web service that is available to all components of the EHR and CDS (see **Supplementary Figure S1** online). Examples of four components of the EHR that use Patient Summary Service are shown in **Figure 3**. Patient Summary Service serves as a single source of patient-specific knowledge for medications, diagnoses, allergies, and othe

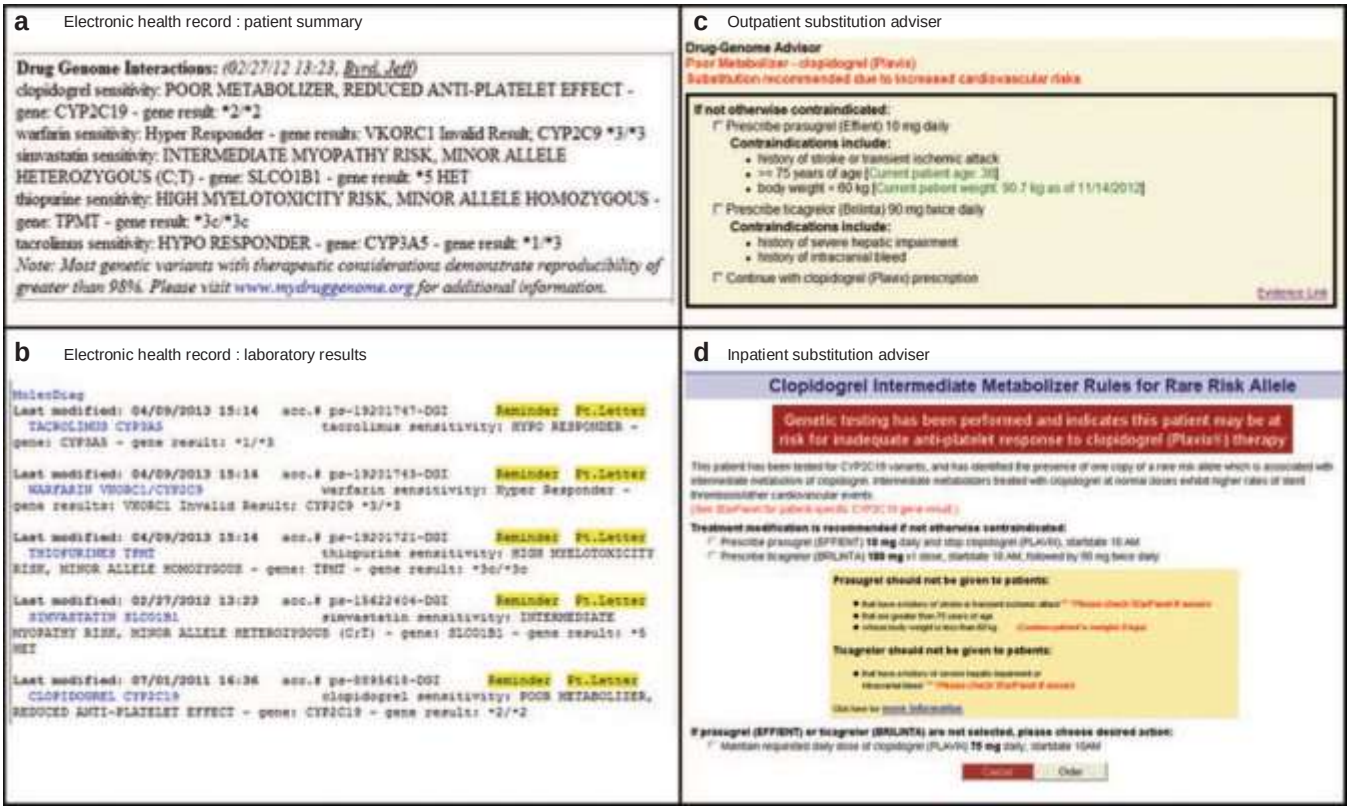


Figure 3 Task-specific views of genomic results present in the EHR. (**a**) The patient summary, which serves as the front page of each patient's record, includes a drug-genome interaction section detailing the patient's genotype in star allele nomenclature as well as phenotype and implications for prescribing. (**b**) Genomic results and phenotypes are also available in the lab results section of the EHR. When a drug is ordered for a patient with an actionable genotype, clinical decision support (CDS), such as the representative (**c**) outpatient substitution adviser, is presented to the ordering clinician. Similarly, parallel mechanisms offer CDS in the (**d**) inpatient setting.

significant family and social history, and this infrastructure was expanded to manage genomic variants and their interpretations.

GENOTYPE-TO-PHENOTYPE TRANSLATION

Although the advantages of multiplexed genetic testing are becoming increasingly apparent, there are clear challenges asso- ciated with managing panel-based genetic data. Raw genotype output is not typically delivered in a standardized format and does not include phenotypic interpretations, which may be drug and patient specific. In order for the genetic results to be useful for clinical implementation through PREDICT, results were individually categorized to create a translation layer, which assigns a coded phenotype category and generates the DGI text string used for display in the EHR and CDS, when triggered (see **Supplementary Figure S1** online). The assigned phenotypes are drawn from a translation table, which relates the raw genotype text string to drug and metabolism effect categories (**Table 2**). Translations are made based on actionable variants, defined as variants that have been reviewed and approved for clinical implementation by the VUMC Pharmacy and Therapeutics Committee; however, a large proportion of variants on the PREDICT platform are not actionable due

to insufficient evi- dence. For *CYP2C9*, for example, only 2 of the 13 variants tested on the platform have been approved for implementation. Genetic

variants that are not deemed actionable are sequestered withina separate database, outside of the EHR, and are not accessible to patients or providers. The genotype data will only be released into the EHR as new genotypes are deemed actionable and new DGIs are incorporated into clinical care.[15]

The model for the current genotype-to-phenotype transla- tion table is to assign a value to every result produced by the Absorption, Distribution, Metabolism, and Excretion plat- form, even if rare. For variants without sufficient evidence to be deemed actionable, a category labeled "indeterminate" was created (**Table 2**).

For purposes of CDS implementation, no change to usual care is recommended for indeterminate genotypes. Other pharmacogenomics implementation sites have used similar approaches,[33] and several consortia have been established to develop and maintain consistent guide- lines for translation of genotype test results, including the Clinical Pharmacogenetics Implementation Consortium and the Translational Pharmacogenomics Project.[34] The translated interpretations are viewable by providers via the EHR and incorporated into the EHR advisers; however, they are not tailored to background level of provider pharmacogenomic knowledge. Therefore, developing phenotype interpretations that are meaningful and clinically useful for providers presents its own set of challenges.

Table 2 Example genotype-to-phenotype translations

			Phenotype	
Gene name(s)	**Raw genotype result**	**Simplified genotype**	**Phenotype category**	**Phenotype detail**
CYP2C19	*17 VAR	*17/*17	Clopidogrel sensitivity	Rapid metabolizer
CYP2C19	*4 VAR	*4/*4[a]	Clopidogrel sensitivity	Poor metabolizer
SLCO1B1	*1A/*1A	*1/*1	Simvastatin sensitivity	Normal risk
SLCO1B1	*1B HET;*2 HET;*5 HET	*1/*5	Simvastatin sensitivity	Intermediate risk
VKORC/CYP2C9	*VKORC1* -1639G>A No Call, *CYP2C9* *1A/*1A	*VKORC1* indeterminate; *CYP2C9* *1/*1	Warfarin sensitivity	Normal responder
VKORC/CYP2C9	*VKORC1* -1639G>A No Call, *CYP2C9* *2 HET;*11 HET; *15 No Call	*VKORC1* indeterminate; *CYP2C9* *1/*2	Warfarin sensitivity	Hyper-responder
VKORC/CYP2C9	*VKORC1* c.-1639 VAR, *CYP2C9* *2 HET	*VKORC1* -1639 AA; *CYP2C9* *1/*2	Warfarin sensitivity	Hyper-responder
VKORC/CYP2C9	*VKORC1* NMD, *CYP2C9* *2 No Call	*VKORC1* -1639 GG; *CYP2C9* indeterminate	Warfarin sensitivity	Indeterminate

Translation entries exist for all encountered genotype combinations and phenotype categories shown in the table, which ultimately drive decision support. Currently, there are a total of 971 unique, observed diplotype genotype entries, mapping to 19 phenotypes.

[a]Denotes a rare variant.

EHR REPRESENTATIONS OF GENOTYPE ANDPHENOTYPE

The centralized service architecture of the genotype-to-phe- notype translation layer allows simultaneous population of multiple clinical information systems, supporting the clini- cian through EHR views and patients through their access toa PHR hosted on a patient portal (see **Supplementary Figure S2** online). For each client system, the service responds to requests for new or updated genomic results. Whenever a phenotype assignment is changed (such as when *CYP2C19**3 heterozygotes are added to an actionable "poor metabolizer" status for clopidogrel), the translation table within the service is updated manually, which triggers automatic revision of theresults displayed in the EHR and PHR. Following the principle of high visibility and universal access, four task-specific views of genomic results are supported in the EHR (**Figure 3a–d**). First, the program team created a space for genomic variants to be visible within the patient summary that serves as the "front page" of the electronic chart and adjacent to the medication list. Much like an "allergy" section, this space is intended to communicate significant genomic variant information whena target medication is contemplated and before initiating a prescription. During review of the design, clinicians and the Pharmacy and Therapeutics Committee required the display of any pharmacogenomic result whether indicating a variant or not, such that there was a quick method of determining if apatient had already been tested. This current presentation for- mat does not scale to many implemented DGIs; therefore, a redesign is in progress.

Second, the phenotype delivered by Patient Summary Service triggers CDS within the outpatient e-prescribing environment as well as the inpatient computerized physician order entry environment when a prescription or medication order con- flicts with the phenotype status (see **Supplementary Figure S1** online). For example, providers prescribing clopidogrel for a

patient with an intermediate-metabolizer or poor-metabolizer phenotype will receive therapeutic guidance to switch to an alternative antiplatelet therapy (see **Supplementary Table S1** online). Finally, new pharmacogenomic information is released from the laboratory. This mechanism (along with the patient

summary) supports reconsideration of patient therapy when- ever new DGIs are released. Among the challenges encoun- tered, EHR designers must decide how to represent risk; the potential impact of phenotype labeling and the utility of add- ing quantitative-risk measures to these brief interpretations are currently unknown.

DISPLAY OF GENOMIC RESULTS IN PHRs

PREDICT genetic results are released into the patient's EHR to guide therapy and clinical decision making. In addition, given the burgeoning body of literature suggesting the importance of empowering patients with health information and increased efforts surrounding the Health Information Technology for Economic and Clinical Health Act,[35] PREDICT genetic results have also been made available to patients through VUMC's patient portal, My Health at Vanderbilt, a resource that allows patients to view EHR data, message their health-care provid- ers, and read general health information tailored to their medi- cal history. Through PREDICT, we have added content in My Health at Vanderbilt related to a patient's genetic test results (see **Supplementary Figure S2** online). The first release of genomic results contained a simplified copy of what was displayed to pro- viders in the EHR: the genetic test result with a brief interpreta- tion, e.g., "CYP2C19, one copy of the variant, poor metabolizer of clopidogrel." Feedback from focus groups overwhelmingly indicated that patients preferred detailed, descriptive back- ground information related to drug side effects and how genet- ics may affect a patient's risk for adverse events. On the basis of this feedback, more comprehensive narratives with graphics are being developed and provided at a seventh-grade reading level.

EVOLUTION OF PREDICT SINCE LAUNCH

PREDICT was launched in September 2010 with genotype- tailored dosing guidance for clopidogrel.[15] The decision to focus on clopidogrel was made following the Food and Drug Administration black box warning alerting physicians and patients to the role of *CYP2C19* variants in medication response.[3] The Food and Drug Administration did not indicate how to incorporate *CYP2C19* variants into clinical decision making; however, an efficacious alternative, the antiplatelet drug prasugrel, was not affected by *CYP2C19* genotype.[36–39] Therefore, the initial clopidogrel adviser was designed to acti- vate when patients were homozygous for *CYP2C19**2 or *3 allele and displayed recommendations to increase clopidogrel maintenance dose to 150 mg daily or switch to prasugrel bar- ring any contraindications.

Since launching the program, over 75 articles have been pub- lished with the potential to influence genotype-to-phenotype mappings or the content of the clopidogrel CDS. Following publication of a large meta-analysis[3] and our internal analysis,[40] which both showed significant reduction in clopidogrel efficacy in individuals heterozygous for *CYP2C19* variants, we added such individuals to the program. Moreover, new, rare *CYP2C19* variants were determined to impair clopidogrel metabolism,[14] and new, effective alternatives to clopidogrel were released on the market. These advances warranted modifications to both the genotype–phenotype translations and the clopidogrel CDS recommendations. Updating the knowledge base and chang- ing the user interface for the CDS to add additional choices required comparatively less effort than the initial development, partially because of the separation of these components into Enterprise Services (see **Supplementary Figure S1** online). However, modifications to the phenotype map often changed the risk status of patients who were already genotyped, requir- ing providers to reconsider the initial drug selection or dosing. For each of these scenarios, we organized a communication plan, identifying affected patients and manually notifying pro- viders using secure electronic messaging within the EHR.[41]

The program continues to expand and incorporate CDS for additional DGIs into the EHR, including recommendations for warfarin, simvastatin, thiopurines, and tacrolimus. Two of the released DGIs are relevant to pediatric populations and required the development of guidelines applicable to both adult and pediatric populations, as well as DGI-specific suppression of genetic results and EHR advisers for those DGIs that were not applicable to a pediatric population (e.g., warfarin advis- ers). Infrastructure available at the time of these deployments allowed for a simple, alternative set of text for adult and pediat-ric patients. This required changes in both the database model and the presentation layer to determine, on the basis of the age of the patient, which text was appropriate for display.

DISCUSSION

The design and implementation of EHR features to support a large multi-DGI pharmacogenomics program required iterative refinements, in part because there is little published guidance on how to leverage HIT to translate genomic medi- cine to clinical practice. We described our initial design choices and subsequent changes in an effort to inform other institu- tions that are contemplating or have initiated a similar effort. One of the major successes in the past 5 years is the formation of cooperative efforts from pioneering institutions associated with the Pharmacogenomics Research Network to organize and curate the pharmacogenomics knowledge base relat- ing genomic variation to therapeutic decision making in the form of clear, accessible guidelines.[10–14] Similar efforts to share implementation practices among members of the Translational Pharmacogenomics Project and the eMERGE Network have made substantial progress.[34] Overall, the gap between the con- ceptual model of personalized medicine and actual clinical implementation is closing but remains wide for most health systems.[42] The PREDICT implementation approach is distinct because of the scope of drug–genome interactions that are tar- geted for adult and pediatric populations, the duration of the program, and the emphasis on preemptive testing. In addi- tion, the ability to leverage on-site developers familiar with the locally developed EHR allowed efficient implementation. Although the specific form of this implementation is institution specific, the abstracted challenges described in this article are generalizable.[33]

We found the major challenges for incorporating PREDICT relate to the complexity of raw genotype data and the lack of existing standards to store and transmit genomic data. Genotyping platforms do not output results in a coded refer- ence standard and are not accompanied by interpretations. Integrating with downstream EHR tasks required parsing of the gene result report and a translation layer able to contend with undefined variants. Manufacturers of genotyping instruments can improve the ease of implementation by adhering to coded standards (as they are developed) and providing more detailed documentation of potential genomic output. Second, we sought to preemptively map all variants but discovered rare variants that were undefined; an automated process within the EHR infrastructure to track and examine new, undefined variants would be valuable to ensure the timely updating of a trans- lation table and could eventually serve as a tool for discovery of potential variant function. Third, EHR integration of genomic data requires a process to manage the release of new or materi- ally updated drug–genome data as thousands of patient records are affected. Such releases also require significant communica- tion and education efforts to inform providers of emerging or changing evidence. Finally, the scalability of EHR integration is challenged by several technical factors, including limited screen "real estate" to display significant variants and inflexible models of displaying results that may not yet be pertinent to patient care.

LIMITATIONS OF THE PREDICT EHR MODEL

The application of pharmacogenomic testing to clinical care is complex and requires established and comprehensive infra- structures to support implementation. With quickly genotyping (and genome sequencing) technologies, emerg- ing evidence, and changes in therapies, these infrastructures must be prepared to accommodate rapid modifications and an explosion in genetic variants. Although PREDICT represents one viable model for implementation of pharmacogenomic information into the EHR, there are limitations and challenges that offer opportunity for improvement and fine-tuning of the program. Despite attention to the succinct and understandable interpretation of genomic results, the EHR displays may not be sufficient for providers without specific pharmacogenomics training. The brief interpretations provided presume a baseline knowledge of pharmacogenomics and are not intended to be educational. Furthermore, PREDICT affects providers in mul- tiple specialties, creating even greater provider education challenges. The provider EHR displays are not currently customiz- able by specialty, health-care role, or baseline knowledge, but such flexibility may be needed as the number of implemented DGIs increase. Moreover, results may be returned outside of the context of a clinical encounter, for example, when a DGI is released into the EHR many years after the patient's initial genetic testing. Similarly, although significant effort has been made to develop understandable and meaningful PHR dis- plays, further research is warranted to elucidate more effective methods of communicating complex genomic information to patients. In addition, there is currently no infrastructure in place to automatically and reliably deliver genetic results to pro- viders outside of Vanderbilt's EHR system; thus, some patients may be tested through PREDICT but not benefit from future decision support after they return to their primary providers outside of the Vanderbilt network. Although PREDICT rec- ommendations are based on the most up-to-date evidence and expert opinions, incorporating genomic information with clin- ically relevant nongenomic factors in CDS recommendations is currently outside of the scope of the program.

PHARMACOGENOMIC ADOPTION: THE WAY FORWARD

The challenges and lessons learned from PREDICT imple- mentation highlight the need for improved EHR integration and interoperability. For patients not receiving care exclusively at VUMC, improved communication and transfer of genetic results to external providers is the first step toward this inte- gration and is necessary to advance genotype-tailored decision making. Clinical notification of high-priority genetic results (e.g., those associated with life-threatening adverse events or with prolonged clinical utility) could be achieved by leveraging national electronic messaging infrastructures and will pave the way for full EHR integration. Pharmacogenomic adoption is limited by provider knowledge and usability of EHR-displayed genomic information. Maintaining awareness of evolving phar- macogenomic evidence and emerging therapies and incorpo- rating this information into clinical practice require procedures for systematic evidence review and an informatics infrastruc- ture that enables prompt modifications of genomic advisers within the EHR system.[15] Improved advisers and information displays that can be modified easily and incorporated within the EHR with very little informatics support will be vital as existing DGIs are updated and additional DGIs continue to be implemented. Moreover, portability of internally developed CDS across EHR systems will be critical for dissemination of clinical pharmacogenomics. We believe that use of Internet- based Web services to encapsulate genetic results and securely communicate relevant guideline-based recommendations and knowledge across institutional boundaries will compel efficient and widespread clinical adoption of pharmacogenomic evi- dence in real-world medical practice.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

ACKNOWLEDGMENTS

Sources of funding for this work include support from Vanderbilt University, the Centers for Disease Control and Prevention (U47CI000824), the National Heart Lung and Blood Institute and the National Institute for General Medical Sciences (U19HL065962), the National Human Genome Research Institute (U01HG006378), and the National Center for Advancing Transla-

REFERENCES

Gullapalli RR1, Desai KV1, Santana-Santos L1, Kant JA2, Becich MJ3. Clinical applications of next-generation sequencing: pathology and biomedical informatics implications and obstacles. With a 2012:3:40 edition of the Journal of Pathol Informatics.

Two Johnson JA, two Burkley BM, two Langaee TY, two Clare-Salzler MJ, two Klein TEs, and one Altman RB. Creating a personalized pharmacogenetics genotyping array at an affordable price for use in the implementation of personalized medicine. Clinical Pharmacology and Therapeutics 2012;92:437–439.

Thirdly, Mega JL, T. Simon, J. P. Collet, et al. Clinical outcomes in patients treated with clopidogrel primarily for PCI and the presence of the reduced-function CYP2C19 genotype: a meta-analysis. JAMA 2010;304:1821–1830.

International Consortium for Warfarin Pharmacogenetics. 4. Clinical and pharmacogenetic data estimation of warfarin dosage. The New England Journal of Medicine.

5 Members of the SEARCH Collaborative Group. An extensive genomic analysis of the relationship between SLCO1B1 mutations and statin-induced myopathy. The New England Journal of Medicine.

Sixthly, Schildcrout JS, Denny JC, Bowton E, et al. The benefits of proactive genotyping in pharmacogenetics for improving medication outcomes. To cite this article: Clin Pharmacol Ther 2012;92:235-242.

Xu H, Denny JC, Wilke RA, et al. How EMRs are becoming more important in the field of pharmacogenomics. Journal of Clinical Pharmacology and Therapeutics.

PH O'Donnell, A. Bush, J. Spitz, et al. Implementing pharmacogenomics in clinical practice: lessons from the 1200 patients initiative. Clinical Pharmacology and Therapeutics 2012;92:446-449.

Johnson JA, LH Cavallari, AL Beitelshees, JP Lewis, AR Shuldiner, and DM Roden. The role of pharmacogenomics in the treatment of heart disease. Reference: Clin Pharmacol Ther. 2011;90:519-531.

CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Relling MV, Klein TE. 2010. 10. 2011;89:464-467 Clin Pharmacol and Ther.

Clinical Pharmacogenetics Implementation Consortium; Relling MV, Gardner EE, Sandborn WJ, et al. Guidelines for thiopurine methyltransferase genotype and thiopurine dose from the Clinical Pharmacogenetics Implementation Consortium. 2011;89:387-391 Clin Pharmacol and Ther.

The Clinical Pharmacogenomics Implementation Consortium; Wilke RA, Ramsey LB, Johnson SG, et al (CPIC). Clinical Pharmacogenomics Implementation Consortium (CPIC) recommendations for SLCO1B1 and simvastatin-induced myopathy. Clinical pharmacology and therapeutics 2012, 92(1):111–117.

Clinical Pharmacogenetics Implementation Consortium; Johnson JA, L. Gong, M. Whirl-Carrillo, et al. CYP2C9 and VKORC1 genotypes and warfarin dose recommendations from the Clinical Pharmacogenetics Implementation Consortium. Journal of Clinical Pharmacology and Therapeutics 2011;90:625.

Guidelines for the use of clopidogrel in patients with a cytochrome P450-2C19 (CYP2C19) genotype deficiency: 2013 update. Scott SA, Sangkuhl K, Stein CM, et al. Research in Clinical Pharmacology and Therapeutics 2013;94:317–323.

14 Pulley, John M.; Denny, John C.; Peterson, John F.; et al. Prospective genotyping for personalized medicine: planning the Vanderbilt PREDICT project for operationalization. 92(2012):87-95 Clin Pharmacol and Ther.

In: Denny JC, Giuse DA, Jirjis JN (Eds.). 2015. Use of EHRs at Vanderbilt University Medical Center. 2005, Vol. 16, No. 6, Pgs. 59-68 of the Semin. Colon. Rectal. Surg.

Altman RB, Klein TE, 2016;Chapter 16. The future of biomedical informatics and pharmacogenomics: challenges and opportunities, Annu Rev Pharmacol Toxicol 2002;42:113-133.

...Wu S, Wang J, and B. Chaudhry, among others. Impact of health IT on healthcare quality, efficiency, and costs: a systematic study. Medical Journal of the American Medical Association 2006;144:742-752.

Silow-Carroll S, John N. Edwards, and Daniel Rodin. What top hospitals have learned from using EHRs to improve efficiency and care. Commonwealth Fund Issue Brief. 2012;17:1.

19 Shortliffe, E. H., R. Davis, S. G. Axline, B. G. Buchanan, C. C. Green, and S. N. Cohen. The MYCIN system's ability to explain and acquire rules for use in clinical therapy consultations through computer. Comput This article first appeared in Biomedical Research, Volume 8, Issue 3, pages 303–320, 1975.

Twenty. Zeng Q, Cimino JJ, and Zou KH. Evaluating a knowledge-based system's ability to provide concept-oriented interpretations of clinical data. Journal of the American Medical Informatics Association 2002;9:294-305.

Eby CS, Deych E, Ferder NS, et al. Therapeutic warfarin dosage prediction in the first weeks of treatment based on VKORC1 and CYP2C9. The year 2010 saw volume 8 of the journal Thromb Haemost go from page 95 to page 100.

Schildcrout JS, Ramirez AH, Shi Y, et al. Dosage adjustments for warfarin based on genetic testing of European- and African-American patients with access to their medical records. The year 2012 had issue 13 of the journal Pharmacogenomics, which included pages 407-418.

Higgs JE, K. Payne, C. Roberts, and W. G. Newman. Is there an increased risk of myelosuppression while using thiopurine medicines in individuals with moderate TPMT activity? pharmacogenomics 2010;11:177-188.

To cite this article: Hesselink DA, van Schaik RH, van der Heiden IP, et al. Pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus in relation to genetic variations in the CYP3A4, CYP3A5, and MDR-1 genes. Clinical Pharmacology and Therapeutics 73, no.

NHGRI, How Much Does DNA Sequencing Cost? 25. http://www.genome.gov/sequencingcosts.

Kwong WJ, Biskupiak J, Ye X, Ghate SR, Brixner DI. Total and bleeding-related healthcare expenditures for atrial fibrillation patients using warfarin. 2011;17:672-684 J Manag Care Pharm.

Those are the words of Shabo Shvo A., who is the 27th. The semantics of pharmacogenomics should be made plain in medical records if they are to be used meaningfully. 2010;11(10):81-87, Pharmacogenomics.

In reference to reference 28, Zhu Q, Freimuth RR, Lian Z, et al. A case study on the harmonization and semantic annotation of the Pharmacogenomics Research Network's data dictionaries. 2013;46:286-293 in the Journal of Biomedical Informatics.

M. Samwald, A. Coulet, I. Huerga, et al. The advancement of customized therapy via semantically enabled pharmacogenomic data. The year 2012 saw the release of volume 13 of pharmacogenomics, which included articles numbered 201-212.

30. Hoffman, Michael, Cristina Arnoldi, and I. Hoffman Chuang. To that end, we've created the Clinical Bioinformatics Ontology (CBO): a semantic network built on top of RefSeq data that has been carefully vetted. 2005;139-150 Pac Symp Biocomput.

Authors: Noy NF, Rubin DL, and Musen MA. Facilitating the use of biological ontologies and related ontology resources. 2004;19:78-81 Ieee Intell Syst.

To cite this chapter: Hicks JK, Crews KR, Hoffman JM, et al. Automatic method for incorporating pharmacogenetic interpretations into the electronic medical record, directed by clinicians. The year 2012 saw the publication of "Clin Pharmacol and Ther" (92:563-566).

Shuldiner RA, Relling MV, Peterson JF, et al. Overcoming barriers to practical application in the translational pharmacogenetics program of the Pharmacogenomics Research Network. Journal of Clinical Pharmacology and Therapeutics 2013; 94:207-210.

D. Blumenthal, "Launching HITECH," New England Journal of Medicine 2010;362:382–385.

R. Marcucci, A.M. Gori, R. Paniccia, et al. Reactive platelets to ADP identified at the point-of-care predict cardiovascular mortality and nonfatal myocardial infarction in patients with acute coronary syndrome undergoing coronary stenting: a 12-month follow-up. 119:237-242 (Circulation) in 2009.

In a 36-author study by Hulot JS, Collet JP, Silvain J, et al. Systematic meta-analysis evaluating the association between the presence of the cytochrome P450 2C19*2 loss-of-function allele and an increased risk of cardiovascular events in clopidogrel-treated patients. In 2010, the journal JAMA Internal Medicine published 56:134-143.

D. Trenk, W. Hochholzer, M.F. Fromm, and others 37 P450 2C19 681G> Cytochrome Adverse 1-year clinical outcome after elective percutaneous coronary intervention with drug-eluting or bare-metal stents is related with a polymorphism and significant on-clopidogrel platelet reactivity. For the full citation, please use: J Am Coll Cardiol. 2008;51:1925–1934.

TRITON-TIMI 38 Investigators; Wiviott SD, Braunwald E, McCabe CH, et

al. Those with acute coronary syndromes may benefit more from prasugrel than from clopidogrel. The New England Journal of Medicine.
Specifically: Delaney JT, AH Ramirez, E Bowton, et al. The use of DNA samples linked to a patient's electronic health record for predicting clopidogrel response. 2012, Volume 91, Issue 4: Pages 257–263.
Jirjis, J., J.B. Weiss, D. Giuse, and S.T. Rosenbloom. Supporting healthcare delivery with a framework for clinical communication. Article in: AMIA Annual Symposium Proceedings 2005:375-379.
Starren J, Williams MS, Bottinger EP. The omic divide: now is the moment for omic support infrastructure. JAMA 2013;309:1237–1238.