Implementation of Pharmacogenomic Decision Support Algorithms in the Electronic Health Record: Determination of Drug Dose based on a Patient’s Genotype and Phenotype Data

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I. Introduction

Pharmacogenetics and Pharmacogenomics (PGx) are the study of the linkage between an individual’s genotype and the impact of medications. The pharmacological effect of a drug depends on pharmacodynamics (interaction with the target or the site of action) and pharmacokinetics (absorption, distribution, metabolism and excretion (ADME)). Drug metabolism is one of the major determinants of drug clearance and the factor that is most often responsible for inter-individual or sub-population differences in pharmacokinetics. The differences in response to medications are always greater between members of a population than they are within the same person or between monozygotic twins at different times. The existence of large population differences with small intra-patient variability is consistent with inheritance as a determinant of drug response. Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to inter-individual differences in the efficacy and toxicity of many medications. Although inter-individual variations in drug response result from effects of age, sex, disease or drug interactions, genetic factors represent an important influence in drug response and efficacy and remain constant throughout life. It is estimated that genetics can account for 30 to 95% of variability in drug disposition and effects. Pharmacogenomics links genotype and phenotype as shown in Figure 1.

Figure 1: Pharmacogenomics as a link between Genotype and Phenotype

The terms “pharmacogenomics” and “pharmacogenetics” are often used interchangeably. “Pharmacogenomics” is now in more common usage, with the emergence of inexpensive DNA sequencing and powerful analysis capabilities. This transformation enables large-scale systematic application of genomics to understand basic mechanisms of genetic variation, and apply them to tailor drug therapy to specific patients and for patient stratification during drug development.

Each year, medications may kill as many as 100,000 Americans and cost hospitals $3.5 billion — a staggering expense that does not take into account lost wages or additional health care costs. Many strategies are needed to prevent drug-related adverse events. One of the most effective strategies available is the provision of computer-based Clinical Decision Support (CDS) in the course of workflow. For example, in a study conducted at Brigham and Women’s Hospital in Boston, the provision of CDS within a computerized provider order entry (CPOE) system reduced the incidence of serious medication errors by 86%, with increasing benefits resulting from the incorporation of more advanced CDS capabilities into the system ($p=0.0003$). An important contributor to adverse drug events is the significant differences in drug response that exists between individuals.

1 Personal Communication, Dr. Issam Zineh, Associate Director of Genomics, FDA.
PGx Clinical Decision Support is universally viewed as the first usable genomic medicine application by clinicians for therapeutic decision-making in the context of the Electronic Health Record (EHR). One solution is to provide a Clinical Decision Support (CDS) system in the course of workflow, so that the physician or other prescriber can recognize when a personalized approach needs to accommodate genetic variants, drug-drug interactions, anthropomorphic variables (e.g., body surface area), and laboratory data. The advantages of CDS are optimized when integration is seamless in the clinical setting, and drug choices and dosage adjustments are clear, accurate and rapid.

II. Warfarin (Coumadin®) Therapy: Application of Pharmacogenomics in Cardiology

Warfarin (Coumadin®) is the most commonly prescribed oral anticoagulant for the treatment and prevention of thromboembolic events. Approximately 2 million patients in the U.S. are initiated on warfarin therapy each year. Indications for warfarin therapy include: (1) Prophylaxis and treatment of venous thrombosis and pulmonary embolism, (2) Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and (3) Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. Figure 2 provides an overview of warfarin PGx (modified, with permission, from 7).

![Figure 2. Panels A and B show Manhattan plots of P values (negative log10) for the association between SNPs across the genome and the final warfarin dose. The horizontal line indicates a P value of 1.5×10−7, which is the level of genomewide statistical significance. In Panel A, the results of univariate regression analysis highlight SNP signals in or near CYP2C9 and VKORC1. In Panel B, the results of multivariate regression analysis with adjustment for the contributions of CYP2C9 and VKORC1 show the CYP4F2 signal on chromosome 19. The label *2 indicates the nonsynonymous SNP rs1799853, *3 indicates the nonsynonymous SNP rs1057910, and the *2*3 composite indicates the SNP rs4917639. Panel C shows the sites of action of warfarin in the vitamin K cycle, as well as the roles of CYP2C9, CYP4F2, and VKORC1 in this process.](image)

The correct maintenance dose of warfarin for a given patient is difficult to predict, the drug carries a high risk of toxicity, and variability among patients means that the safe dose range differs widely between individuals. Complications of warfarin therapy account for over 10% of hospital admissions and 15% of all severe drug-induced adverse events. Studies indicate that the routine incorporation of genetic testing into warfarin therapy protocols significantly ease both the health and financial risks currently associated with this treatment.

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9. Data from the FDA Division of Drug Risk Evaluation.
When genetic information is available, it can help predict therapeutic dose. Common single nucleotide polymorphisms (SNPs) in the cytochrome P450 (CYP) 2C9 system (CYP2C9*2 and CYP2C9*3) are associated with impaired metabolism of warfarin, leading to a decrease in dose requirements and an increase in the time it takes to become therapeutic. In patients who are homozygous for the wild type allele (CYP2C9*1), S-warfarin is cleared normally, resulting in a modest elevation of the International Normalized Ratio (INR). In contrast, patients with the CYP2C9*2 (rs1799853) and/or CYP2C9*3 SNP (rs1057910) have impaired metabolism of S-warfarin. CYP2C9*2 is the SNP in exon 3 (CGT>TGT) and CYP2C9*3 is in exon 7 (ATT>CTT). The CYP2C9 SNPs are associated with a 3-fold increased risk of bleeding and of overdose during warfarin induction.

Single nucleotide variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) also correlate with warfarin sensitivity. In the absence of a coumarin, the vitamin K cycle regenerates reduced vitamin K1 from its epoxide. Reduced vitamin K is a cofactor for post-translational γ-carboxylation of glutamic acid residues on several proteins, including coagulation factors II (prothrombin), VII, IX, and X. Warfarin acts as an antagonist of vitamin K epoxide reductase, whose gene (VKORC1) is highly polymorphic. There are several informative SNPs in the VKORC1 gene that correlate with the therapeutic dose, including VKORC1 6853 G>C (rs8050894), -1639 G>A (rs9923231), and 1173 C>T (rs9934438).

Several clinical dosing nomograms have been proposed over the past 20 years to decrease the toxicity of warfarin induction. These older algorithms have not been widely accepted, though, and their accuracy has been questioned, especially in elderly patients. Major barriers to their implementation are that they were developed for middle-aged inpatients who could tolerate doses of 5–10 mg warfarin daily and who had daily monitoring of the INR. Today, the typical person taking warfarin is elderly and their hospital stays are too short to allow for inpatient dose titration. For example, orthopedic patients are typically discharged 2 or 3 days after joint replacement surgery, so warfarin dose titration is now done in the outpatient setting where daily INR monitoring is not feasible.

The National Heart, Lung and Blood Institute (NHLBI) looked at a number of variables, and several groups of investigators subsequently developed algorithms for genotyping patients (stepwise regression) that predict more accurate warfarin dosing. The following table shows a simple, early example of inputs that predict dosing with high accuracy. Further clinical studies of efficacy are underway, but currently the FDA recommends gene testing prior to warfarin dosing:

<table>
<thead>
<tr>
<th>INPUTS REQUIRED FOR THE ALGORITHM</th>
<th>INDEPENDENT PREDICTORS OF DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-7% per decade</td>
</tr>
<tr>
<td>Height, weight (Body Surface Area, BSA)</td>
<td>+11% per 0.25m²</td>
</tr>
<tr>
<td>Race</td>
<td>-9% (American)</td>
</tr>
<tr>
<td>Smoker status</td>
<td>+10%</td>
</tr>
<tr>
<td>Amiodarone/Cordarone® use</td>
<td>-22%</td>
</tr>
<tr>
<td>Current thrombosis</td>
<td>+7%</td>
</tr>
<tr>
<td><strong>Target Internalized Normalized Ratio (INR)</strong></td>
<td>+11% per 0.5 unit</td>
</tr>
<tr>
<td><strong>Pharmacogenetic</strong></td>
<td></td>
</tr>
<tr>
<td>VKORC1 polymorphism –1639/3673 g&gt;a</td>
<td>-28% per allele</td>
</tr>
<tr>
<td>(The causative allele for the low dose phenotype in warfarin therapy based on both in vitro and in vivo evidence)</td>
<td></td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>-33% per allele</td>
</tr>
<tr>
<td>(This variant has been shown to correlate significantly with warfarin dose)</td>
<td></td>
</tr>
<tr>
<td>CYP2C9*2</td>
<td>-19% per allele</td>
</tr>
<tr>
<td>(This variant has been shown to influence warfarin dose)</td>
<td></td>
</tr>
</tbody>
</table>

In recognition of the clinical relevance of SNPs in CYP2C9 and VKORC1 during warfarin induction, the FDA approved the label change of warfarin to recommend lower initial doses in patients known to have certain SNPs in CYP2C9 or VKORC1. The NIH has funded two multi-centered, prospective, randomized control trials: (1) Clarification of Optimal Anticoagulation through Genetics (COAG) trial (PI: Stephen Kimmel, MD); and (2) Genetic Informatics Trial (GIFT) of Warfarin Therapy to Prevent DVT (PI: Brian Gage, MD). The trials will quantify the benefit of genotyping for CYP2C9*2, CYP2C9*3 and VKORC1-1639 vs. using

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clinical algorithms. Patients in both studies are randomized to either the clinical or the PGx algorithms on www.WarfarinDosing.org. Because of the size and quality of these multi-centered trials, they will define the standard of care for warfarin initiation. They both use the most accurate algorithm for warfarin dosing as a standard developed by Dr. Brian Gage (Washington University), the International Warfarin Pharmacogenetics Consortium (IWPC) and others, which was implemented at www.WarfarinDosing.org by Kraig Robson and IsoDynamic, Inc. It combines clinical data, as well as SNPs from an individual patient to determine optimal starting dose and maintenance dose. Retrospective studies show that clinical data alone provides ~17% accuracy, compared to combining clinical and genotype data from an individual patient that provides ~60% accuracy in predicting starting dose of warfarin. Recently, safer anticoagulant drugs have been introduced into the marketplace, including Dabigatran (Pradaxa®), an oral anticoagulant that is a direct thrombin inhibitor.

Another drug used in cardiology that shows significant inter-patient genetic variation in efficacy is clopidogrel (Plavix®), widely prescribed for the treatment and prevention of myocardial infarction, coronary stent thrombosis, and ischemic stroke. As a pro-drug that requires hepatic activation to 2-OXO clopidogrel, clopidogrel is dependent on CYP2C19 activity. Thus, patients with 1, or especially 2, copies of the CYP2C19*2 allele are unable to activate clopidogrel normally, resulting in low plasma levels and clopidogrel resistance. As a contributor to coronary stent restenosis, recurrent myocardial infarction, and stroke, clopidogrel resistance causes substantial morbidity and mortality. The putative interactions between clopidogrel and proton-pump antagonists provide an opportunity for PGx to provide real-time CDS in the EHR. Finally, an alternative to clopidogrel, prasugrel, does not require CYP2C19 activation, and has been approved by the FDA.

III. Implementation of the Warfarin Dosing Genotype/Phenotype Algorithm in the EHR

Warfarindosing.org represents a multi-year collaboration to decrease the risks of warfarin therapy using CDS. Over the past 5 years, a number of collaborators have developed www.WarfarinDosing.org to guide the initiation of warfarin therapy. The web application includes over a dozen dosing algorithms, many of which have already published. In 2011, the implementation team added PGx and clinical algorithms for days 6-11 of warfarin therapy and the ability to accommodate additional polymorphisms that affect warfarin dose. There is simply no way that paper-based tables can accommodate the increasing complexity caused by new dosing algorithms, new SNPs, and complex calculations.

Despite the growing usage of www.WarfarinDosing.org, there are many more warfarin dosing decisions that are made without the assistance of any CDS. To better increase the adoption of this software by the clinical community, the strategy is to integrate the www.WarfarinDosing.org site into selected EHR systems using secure, standards-based, and web-enabled technologies. For integrating the PGx CDS solution into the EHR, the developers employed an approach that was specifically designed to enable maximum flexibility given the highly diverse system architectures and approaches employed by current EHR systems. To enable such flexible integration, the system was designed using modular and independent components that can be integrated with EHR systems individually or as a package.

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Components include the following:

1. **The core PGx dosing algorithms, available through a standards-based CDS web service.** These standards include HL7 and a collaborating standards development organization known as the Object Management Group (OMG), which has led the development of standards for delivering CDS as a web-accessible software service, known as the HL7 Decision Support Service standard and the OMG Decision Support Service standard. By providing the core algorithms in this manner, EHR systems can interact with the CDS content of [www.WarfarinDosing.org](http://www.WarfarinDosing.org) using what has become a standard approach across industries for interfacing business functions in a highly flexible and agile manner.

2. **User-facing CDS modules** that leverage the PGx web service and provide users with a rich Human-Computer Interface (HCI). These modules were developed for the targeted EHR systems, and components were integrated into Cerner, Epic and other EHR systems.

3. **Supportive software modules** that facilitate clients’ integration of the CDS PGx modules into EHR systems. These modules include the following components:
   - A data access module for retrieving relevant clinical and genetic data from the EHR and for storing relevant data (e.g., smoking status, not routinely captured in EHR but captured by the CDS module).
   - A CDS module for interfacing with the PGx CDS web service (e.g., application programming interfaces provided in C#, Java, and JavaScript platforms).
   - Supplemental CDS web service modules for providing ancillary patient-specific inferences (e.g., to identify that a patient has liver disease based on elevated liver enzyme values).
   - A terminology management module for mapping terms used in the EHR system to terms used by the CDS web service (e.g., for laboratory and medication data).

To validate the approach, the PGx algorithms of [www.WarfarinDosing.org](http://www.WarfarinDosing.org) were encapsulated as CDS modules available within a web service compliant using the HL7 and OMG Decision Support Service standards. The developers integrated this service with the McKesson Horizon Expert Orders™ CPOE system. A screenshot of the prototype system is shown in Figure 4:

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**Figure 4:** Screen-shot of a prototype of the Clinical Decision Support (CDS) contained within a CPOE to estimate warfarin dose for an individual patient, based on clinical data and CYP2C9 and VKORC1 genotypes. ©2011, McKesson Corporation.

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Figure 5 shows a high-level system architecture diagram that outlines the relationships between the standards-based CDS web service, user-facing CDS module, and supportive software modules. In this figure, the numbers on the arrows represent the order of information flow. A clear strength is the use of a flexible, service-oriented architecture so that the various software modules can be combined in different ways depending on the needs and desires of the client EHR systems.

IV. Innovation

The execution of warfarin PGx dosing algorithms within clinical IT systems will challenge existing practice paradigms and improve medical practice, including:

1. Use of patient-specific clinical data and genotype to prescribe a starting and maintenance dose of warfarin (Coumadin®), using the most accurate and best validated algorithms.
2. The use of a standards-based web service to seamlessly integrate CDS for PGx within EHR systems, so that advanced personalized warfarin pharmacotherapy can be a natural part of clinician workflows. This approach has already demonstrated that the CDS capabilities of web applications such as www.WarfarinDosing.org can be efficiently integrated into any EHR system to promote patient safety.
3. The ability to rapidly translate advances in PGx into clinical practice. Through the proposed technical approach as outlined in this paper, updated drug dosing algorithms can be provided to subscribing clients within days of new algorithms being published. For an example of timeliness and accuracy, investigators made available the algorithms developed by the International Warfarin Pharmacogenetics Consortium (IWPC) on the same day (February 19, 2009) that its findings were published in the New England Journal of Medicine.19

4. Another innovation has been to incorporate laboratory data (i.e., INR values) into PGx algorithms\textsuperscript{20}. Before this strategy was pioneered, information from PGx algorithms became superfluous once the INR response was measured.

5. The use of a formal process to improve the usability of the PGx CDS to enhance physician engagement and adoption.

6. A rigorous process used to validate new dosing algorithms. Because it is recognized that no software application or programming language are flawless, separate programmers program each new algorithm in separate software platforms, and research coordinators verify the accuracy of both algorithms.

7. The use of advanced learning technologies to provide relevant PGx learning materials in the context of the pharmacotherapeutic decision. This requires an analysis of what the clinician will tolerate in the busy clinical setting, or what alternatives can be employed, such as distinct CME education or other approaches such as having a website dedicated to genomic and PGx education (see \url{http://pharmacogenomics.ucsd.edu} as an example of a PGx educational service).

\section*{V. Conclusion}

This document provides a brief overview of PGx and one example of where it is being implemented within the context of the EHR. The web service \url{www.WarfarinDosing.org} is an archetype, showing where informatics can optimize genotype-based dose calculation for a widely used drug that has significant implications for patient safety and drug efficacy. PGx is being used in other medical specialties where drug choice and/or drug dose may also be critical, using patient-specific, genotype-based informatics. PGx is one application of genomic medicine that has immediate relevance for translation into clinical practice. It is important to note that though we may conjecture about the disruptive and transformative nature of applying genomic discovery to medicine, routine clinical adoption of PGx by the health care community will require demonstration of its ability to improve patient outcomes and reduce treatment costs.

\textit{Note:} Some of the text in this document about warfarin dosing algorithms is based on language from an NIH grant proposal, authored by Drs. Gage*, Higgins **, Kawamoto***, and Mr. Robson****, and as such, does not constitute a “publication” \textit{per se}, but rather as an overview to provide a foundation for implementation of PGx applications within the context of the OSEHRA “Genomics” Working group at \url{www.osehr.org}. It should not be cited as a peer-reviewed publication, or used for any other purpose than it was intended – to begin a discussion for developing a roadmap for integration of PGx algorithms within OSEHRA.

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