Published in final edited form as:

Clin Pharmacol Ther. 2016 November ; 100(5): 427–430. doi:10.1002/cpt.425.

Implementing Algorithm-Guided Warfarin Dosing in an Ethnically Diverse Patient Population Using Electronic Health Records and Preemptive *CYP2C9* and *VKORC1* Genetic Testing

A Owusu Obeng^{1,2}, T Kaszemer¹, NS Abul-Husn¹, O Gottesman¹, A Vega³, E Waite³, K Myers⁴, J Cho^{1,5,6}, EP Bottinger^{1,7}, SB Ellis¹, and SA Scott^{1,5}

¹The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

²Department of Pharmacy, Mount Sinai Medical Center, New York, New York, USA

³Mount Sinai Faculty Practice Associates Primary Care Program, Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁴Information Technology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁵Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁶Department of Medicine, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁷Berlin Institute of Health, Berlin, Germany

Abstract

Implementation of pharmacogenetic-guided warfarin dosing has been hindered by inconsistent results from reported clinical trials and a lack of available algorithms that include alleles prevalent in non-white populations. However, current evidence indicates that algorithm-guided dosing is more accurate than empirical dosing. To facilitate multiethnic algorithm-guided warfarin dosing using preemptive genetic testing, we developed a strategy that accounts for the complexity of race and leverages electronic health records for algorithm variables and deploying point-of-care dose recommendations.

Correspondence: A Owusu Obeng (aniwaa.owusu-obeng@mssm.edu); SA Scott (stuart.scott@mssm.edu).

CONFLICT OF INTEREST

O.G., E.P.B., and S.B.E. are co-inventors on patent applications related to personalized clinical decision support. The other authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.O.O. designed and S.A.S. consulted on the dosing strategy. A.O.O., T.K., and S.B.E. executed the dosing strategy clinical decision support. A.O.O., T.K., N.A.H., O.G., A.V., E.W., E.P.B., S.B.E., and S.A.S. developed and executed the IPM implementation program. T.K., O.G., K.M., E.P.B., and S.B.E. designed and consulted on the information technology infrastructure. A.O.O., A.V., and E.W. managed patient recruitment. A.O.O., N.A.H., and O.G. oversaw provider education. S.A.S. oversaw genetic testing. J.C. and E.P.B. supported the program. A.O.O. and S.A.S. drafted the manuscript. All authors reviewed and revised the manuscript.

Warfarin pharmacogenetics: Evidence and ancestry

Warfarin continues to be a commonly prescribed oral anticoagulant, despite its narrow therapeutic range and the recent availability of novel oral anticoagulants. Therapeutic warfarin dose requirements are influenced by clinical variables (e.g., age, body weight, and gender) and variation in genes involved in warfarin pharmacokinetics (*CYP2C9*) and pharmacodynamics (*VKORC1*), which prompted the development of multivariable pharmacogenetic algorithms to predict personalized warfarin doses. However, despite their availability and the *CYP2C9* and *VKORC1* genotype-based dosing tables incorporated into the warfarin label by the US Food and Drug Administration (FDA), warfarin is still commonly initiated at a fixed empirical dose and titrated based on international normalized ratio.

Implementation of pharmacogenetic algorithm-guided warfarin dosing has been hindered by inconsistent results from reported clinical trials.¹ For example, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial concluded that pharmacogenetic-guided dosing was more accurate than standard practice fixed dosing in their white patients. However, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial found no differences between pharmacogenetic and clinical algorithm-guided dosing in their more diverse cohort (73% white and 27% African American). Moreover, African American (COAG) patients subjected to pharmacogenetic-guided dosing actually had worse outcomes compared with clinical algorithm-treated patients. In addition to highlighting the need for pharmacogenomics research in non-white populations, which recently identified novel variants that influence warfarin dosing among African Americans,² these results indicate that implementation of pharmacogenetic algorithm-based warfarin dosing using only *CYP2C9* (*2, and *3) and *VKORC1* (c.-1639G>A) should be restricted to white patients.

Similarly, although the 2011 Clinical Pharmacogenetics Implementation Consortium guideline recommends pharmacogenetic-guided dosing if genetic information is available, it also cautions that *CYP2C9* variants prevalent among African Americans (*5, *6, *8, and *11) are not included in most algorithms.³ Despite the complexities and contradictions of the current warfarin pharmacogenetics evidence base, we developed a novel warfarin dosing strategy for our multiethnic clinical pharmacogenetics implementation programs, which use electronic health records (EHRs) and preemptive *CYP2C9* and *VKORC1* genetic testing to deploy personalized point-of-care dose recommendations using a pharmacogenetic algorithm, the FDA label dosing tables, or a clinical algorithm.

Clinical pharmacogenetics implementation programs at the Icahn School of Medicine at Mount Sinai

In 2013, the Charles Bronfman Institute for Personalized Medicine (IPM) at the Icahn School of Medicine at Mount Sinai initiated IPM PGx, which enrolled 1,000 patients from the IPM BioMe Biobank for preemptive genotyping of actionable pharmacogenetic variants by the clinical Mount Sinai Genetic Testing Laboratory.⁴ IPM PGx is enabled by the Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics

(CLIPMERGE) platform,⁴ which is an advanced data management and clinical decision support (CDS) system that is external to, but communicates with Mount Sinai's local EHR (Epic). A parallel implementation program at Mount Sinai is the National Institutes of Health-funded eMERGE-PGx, which is a multicenter network project preemptively interrogating genes involved in drug response for both research discovery and clinical implementation.⁵ Approximately 700 patients were recruited from the Mount Sinai Faculty Practice Associates Primary Care clinic for this program, which used targeted gene sequencing with the PGRNseq platform and orthogonal clinical genotyping. As with IPM PGx, data management and CDS are provided through CLIPMERGE.

The patient cohorts for both implementation programs are highly diverse, with ~40% Hispanic, 30% African American, 20% white, and 10% from other racial/ethnic groups. As such, the multidisciplinary implementation working group at Mount Sinai, which is composed of medical and molecular geneticists, pharmacists, and bioinformaticians, concluded that the available evidence did not support pharmacogenetic algorithm-guided warfarin dosing for all patients.

Multiethnic algorithm-guided warfarin dosing strategy

The logic used to determine the most appropriate warfarin dosing CDS is detailed in Figure 1. When warfarin is ordered through the EHR, two conditions must be met for the patient to be eligible for algorithm-guided dosing: (1) warfarin has been recently initiated, and (2) the patient is enrolled in one of the implementation programs. Although the timeframe that the EHR is queried for when warfarin was initiated is currently set at 6 weeks, this will be adjusted as the program moves forward based on dosing recommendation acceptance rates and provider responses. When these two initial criteria are met, CLIPMERGE then determines the availability of *CYP2C9* and *VKORC1* genotype results for the patient.⁴ For patients with no genotype data available, CDS for a clinical algorithm-guided dose will be displayed to the ordering provider if the necessary clinical variables are available in the EHR; otherwise, no CDS will be displayed and the patient will be dosed empirically. For patients with available genotype data, CLIPMERGE determines whether the patient is *CYP2C9**2/*2, *2/*3, or *3/*3. If yes, CDS will recommend either a pharmacogenetic algorithm-guided dose or the FDA label-recommended dose, depending on whether the necessary clinical variables are available in the EHR. If the patient is recorded as being white in the EHR and is *CYP2C9**1/*1, *1/*2, or *1/*3, CDS for either a pharmacogenetic algorithm-guided dose or the FDA label-recommended dose will be displayed to the ordering provider, depending on whether the necessary clinical variables are available. For white patients who carry other low frequency *CYP2C9* alleles that are not included in the pharmacogenetic algorithm (e.g., *5 and *6) and for all other non-white patients, CDS will recommend a clinical algorithm-guided dose if the necessary clinical variables are available in the EHR; otherwise, no CDS will be displayed.

In summary, this strategy only provides pharmacogenetic algorithm-guided dosing for whites and the non-white patients who carry *CYP2C9* *2/*2, *2/*3, or *3/*3 diplotypes. Most non-white patients will trigger a clinical algorithm-guided dose recommendation,

which we believe is an appropriate interpretation of the current warfarin pharmacogenetics literature.

CDS for algorithm-guided warfarin dosing recommendations

The pharmacogenetic algorithm is derived from the International Warfarin Pharmacogenetics Consortium (<https://www.pharmgkb.org/chemical/PA451906>), which predicts starting warfarin doses based on *CYP2C9* (*1, *2, and *3) and *VKORC1* (c.-1639G>A), age, height, weight, race, and other concomitant medications (carbamazepine, phenytoin, rifampicin, and amiodarone). In addition to the recommended dose, the pharmacogenetic algorithm-guided dosing CDS includes a description of the algorithm and a table listing the patient-specific genetic and clinical information used in the calculation. The CDS also includes factors for prescribers to consider before accepting the dose recommendation, a link to an IPM-developed warfarin pharmacogenetics summary, and contact information (Figure 2A). The FDA label-recommended dosing CDS includes *CYP2C9* and *VKORC1* genotypes and phenotypes, and informs the prescriber that the recommendation is derived from the package insert (Figure 2B). The clinical algorithm-guided dosing CDS is identical to the pharmacogenetic algorithm-guided dosing CDS, but without information on *CYP2C9* or *VKORC1* (Figure 2C). Importantly, all CDS recommendations explicitly state that these algorithms assume a target international normalized ratio of 2–3 and to disregard the recommendation if the patient's target international normalized ratio is not 2–3.

When a CDS recommendation is accepted, an image of the CDS message is copied onto the order entry window to facilitate accurate prescribing of the dose recommendation. The contents of every CDS message, whether accepted or rejected, are made available as a laboratory report in the EHR. Prescribers who choose to reject the recommendation are prompted to provide a reason, which include “not relevant to this patient,” “insufficient evidence,” “do not understand advice,” or “other reason.” These responses, including additional data from follow-up provider questionnaires, are being collected to better understand the provider experience and to inform future best practices for pharmacogenetic implementation. In addition, given that it is unclear whether genotype-guided dose information is useful after warfarin has been initiated, our study may provide valuable data toward resolving this issue.

Multiethnic algorithm-guided warfarin dosing: challenges and limitations

Our multidisciplinary implementation working group meets biweekly to review progress, challenges, and new evidence related to algorithm-guided warfarin dosing. The most consistent challenge has been the lack of professional recommendations on algorithm-guided warfarin dosing, particularly in relation to non-white patients. Another is the paucity of publically available pharmacogenetic algorithms that include *CYP2C9* variants beyond *2 and *3, which prompted the decision to have our CDS logic divert patients who carry *5 or *6 to the clinical algorithm regardless of race/ethnicity. Extracting current medication information from the EHR has been an informatics challenge and to err on the side of

sensitivity, any concomitant medications in the EHR without a discontinuation date are treated as current.

CONCLUSIONS AND FUTURE DIRECTIONS

The field of warfarin pharmacogenetics is significantly conflicted by the inconsistent results from reported clinical utility trials¹ and increasing evidence underscoring the importance of race/ethnicity.² As such, we developed a warfarin-dosing strategy for the diverse Mount Sinai patient population that reconciled the available data on algorithm-guided dosing and ancestry, and that could be enabled by preemptive genotyping and our CLIPMERGE platform.⁴ Outcome and provider data from our implementation programs are currently being collected and analyzed, and we are planning to expand the program to additional anticoagulation clinics across the Mount Sinai Health System. Future iterations of the CDS logic will incorporate pharmacogenetic dosing algorithms specific to non-white populations as they become available. Importantly, our approach of incorporating genetic variables only for selected patients can be a model for other pharmacogenetic gene/drug pairs in which there is limited evidence to support clinical actionability in specific patient subpopulations.

Acknowledgments

Funding for this program was provided by the Andrea and Charles Bronfman Philanthropies and The Icahn School of Medicine at Mount Sinai. A.O.O. and E.P.B. are supported in part by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health, through Grant U01HG006380 (eMERGE Network). S.A.S. is supported in part by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health, through grant K23GM104401. The authors would like to thank Ana Mejia, Yolanda Keppel, Stacy Paris, Rajiv Nadukuru, Bernadette Liggay, Patrick Shanley, the Mount Sinai Genetic Testing Laboratory, the Mount Sinai Epic team, Mount Sinai Information Technology, the IMA Coumadin clinic staff, and the Epic Corporation for their contributions to the clinical pharmacogenetics implementation programs at Mount Sinai.

References

1. Scott SA, Lubitz SA. Warfarin pharmacogenetic trials: is there a future for pharmacogenetic-guided dosing? *Pharmacogenomics*. 2014; 15:719–722. [PubMed: 24897277]
2. Perera MA, Cavallari LH, Johnson JA. Warfarin pharmacogenetics: an illustration of the importance of studies in minority populations. *Clin Pharmacol Ther*. 2014; 95:242–244. [PubMed: 24548987]
3. Johnson JA, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther*. 2011; 90:625–629. [PubMed: 21900891]
4. Gottesman O, et al. The CLIPMERGE PGx Program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. *Clin Pharmacol Ther*. 2013; 94:214–217. [PubMed: 23588317]
5. Rasmussen-Torvik LJ, et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. *Clin Pharmacol Ther*. 2014; 96:482–489. [PubMed: 24960519]

Figure 1.

Illustration of the algorithm-guided warfarin dosing clinical decision support (CDS) logic. Once a prescription for warfarin is submitted through the electronic health record (EHR), the Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics (CLIPMERGE) platform determines if a patient is eligible for algorithm-guided warfarin dosing and if preemptive *CYP2C9* and *VKORC1* genotype data are available. Please see the “Multi-ethnic algorithm-guided warfarin dosing strategy” section for additional information on the warfarin initiation EHR query timeframe. The light gray box highlights the data used to determine the most appropriate dosing method based on patient race/ethnicity and *CYP2C9* genotype. The CDS logic diverts most non-white patients (and any patient who carries nonalgorithm *CYP2C9* alleles) to clinical algorithm-guided warfarin dosing when the necessary clinical variables are present in the EHR. If the necessary clinical variables are not available in the EHR, the recommended dose for these patients is then derived from the US Food and Drug Administration (FDA) warfarin label.

Figure 2. Images of the clinical decision support (CDS) alerts for each algorithm-guided warfarin dosing method. Example of CDS images of warfarin dose recommendations delivered through the electronic health record (EHR) using: (a) a pharmacogenetic algorithm, (b) the US Food and Drug Administration (FDA) warfarin label tables, or (c) a clinical algorithm.