
Brief Communication

Pharmacogenomic clinical decision support design and multi-site process outcomes analysis in the eMERGE Network

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ABSTRACT

To better understand the real-world effects of pharmacogenomic (PGx) alerts, this study aimed to characterize alert design within the eMERGE Network, and to establish a method for sharing PGx alert response data for aggregate analysis. Seven eMERGE sites submitted design details and established an alert logging data dictionary. Six sites participated in a pilot study, sharing alert response data from their electronic health record systems. PGx alert design varied, with some consensus around the use of active, post-test alerts to convey Clinical Pharmacogenetics Implementation Consortium recommendations. Sites successfully shared response data, with wide variation in acceptance and follow rates. Results reflect the lack of standardization in PGx alert design. Standards and/or larger studies will be necessary to fully understand PGx impact. This study demonstrated a method for sharing PGx alert response data and established that variation in system design is a significant barrier for multi-site analyses.

Key words: pharmacogenomics, pharmacogenetics, clinical decision support, precision medicine, process outcomes

BACKGROUND AND SIGNIFICANCE

Previous literature identified clinical decision support (CDS) tools integrated into the electronic health record (EHR) as a critical vector for disseminating pharmacogenomic (PGx) knowledge and improving drug prescribing accuracy.^{1–6} A number of organizations have published on their experiences implementing PGx CDS tools and have often taken very different design approaches.^{7–15} There has been little work examining how live PGx CDS systems affect physician experience and behavior, and those studies that do evaluate PGx CDS are generally limited to a single institution.^{16–18}

Clinical genomics is difficult to study at a single institution, in part due to limited sample sizes. This is one reason a number of

institutions have formed multi-center collaborations to integrate genetic and genomic knowledge into clinical care, including the Electronic Medical Records and Genomics (eMERGE) Network^{19–21} and the Clinical Sequencing Exploratory Research (CSER) Consortium.²² Prior work from the eMERGE Network demonstrated successful PGx CDS implementations, with ten sites successfully implementing at least one rule in a clinical environment.¹⁵ However, technical matters are only one aspect of successful IT implementation—the solution must also be effective in addressing the intended issue. A first step towards determining whether PGx CDS will be effective in improving prescribing decisions is to examine process outcome measures, such as physician uptake and response.

To-date, multi-site analysis of PGx CDS process outcomes has not been well documented in the literature. Multi-site data aggregation may enable studies that would not be possible at a single site, but it remains unclear whether such aggregated analyses are feasible, due to technical and design differences. Current EHR systems may make it possible to perform such studies through the use of logging and auditing data.

OBJECTIVE

This study aimed to demonstrate the feasibility of multi-site PGx CDS process outcome analysis across the eMERGE Network. The first objective was to understand and characterize PGx CDS design differences that could affect data aggregation. The second was to develop, and perform a pilot evaluation of, a common data dictionary that would enable multi-site data collection of physician response to PGx CDS alerts.

MATERIALS AND METHODS

The study population included seven sites from the eMERGE-PGx workgroup. Major site characteristics are summarized in [Figure 1](#) with additional details in [Supplementary Tables SA and SB](#). Due to variation in EHR and CDS infrastructure,¹⁵ it was necessary to establish standards for data sharing. Over the course of regular workgroup calls, the group reached consensus on a standardized data dictionary. This included data fields that described alert scenarios implemented at each site, as well as data that described individual instances in which alerts fired in the EHR during clinical encounters. Each site queried its local database for the requested fields, formatted and de-identified data to the agreed specifications, and then submitted it to the first author for aggregation and analysis. Data were divided into three primary categories (the complete data dictionary is described in [Supplementary Table SC](#)):

- *Alert Scenario*: Describes the structure and design of a particular alert, including a name, description, and the recommendation the alert provides.
- *Alert Instance*: Describes a specific instance of an Alert Scenario, including a scenario ID, the time the alert was seen by a provider, how the provider responded, and what medications were ordered after it was viewed.
- *Providers*: Describes the provider(s) who interacted with an Alert Instance, including title and specialty.

Objective 1: analysis of PGx CDS implementation characteristics

TMH and JP conducted informational discussions with subject matter experts at each site to determine general themes of PGx CDS design within eMERGE. These discussions informed development of a data collection tool addressing implementation strategies. In addition to alert characteristics, we also collected operational characteristics. One representative from each site submitted responses via e-mail. Additional implementation characteristics were assessed through review of the submitted Alert Scenario data.

Alert characteristic analysis focused on the drug-gene interactions (DGI) for which alerts were defined, use of active or passive alerts, use of pre-test or post-test alerts, use of patient genotype or phenotype as CDS input, type of recommendation, and available alert actions. Active alerts were defined as interruptive alerts that appeared during order entry. Detailed definitions of these terms can be found in [Figure 1](#) and [Supplementary Table SA](#).

Objective 2: cross-site data collection and pilot outcomes analysis

Alert data were collected via the Alert Instance fields in the submitted datasets. These data were combined with the Alert Scenario and Providers data to analyze clinician response. We determined clinician alert response rate by site and by DGI. Clinician response to the alert consisted of the alert response and clinical response (see [Table 2](#) for detailed definitions of these terms). While alert response values could be mapped directly to EHR logging data, local workflow variation required each site to report clinical responses based on local definitions. Because only two sites implemented passive alerts or pre-test alerts, quantitative analysis was limited to active, post-test alerts that contained a prescribing recommendation.

RESULTS

Objective 1: analysis of PGx CDS implementation characteristics

All seven participating sites ([Figure 1](#)) submitted information describing the nature of their PGx CDS alert designs. There was consistency in several of the alert characteristic categories, particularly DGI, active vs. passive, and pre- vs. post-test alert strategies. Adult and pediatric sites differed in which DGIs they implemented. All five adult sites implemented alerts to assist in prescribing at least two out of three of the following drugs: clopidogrel (*CYP2C19*), simvastatin (*SLCO1B1*), and warfarin (*CYP2C9*, *VKORC1*). The two pediatric sites chose to focus on other DGIs more common in children. Cincinnati Children's Hospital Medical Center (CCHMC) implemented alerts for codeine, oxycodone, hydrocodone, and tramadol, all associated with *CYP2D6*. Boston Children's Hospital implemented alerts for phenytoin, which is also associated with *CYP2C9*. Additional detail is in [Supplementary Table SA](#).

All seven sites implemented some form of active alerts. Five of the seven sites implemented only post-test prescribing alerts. CCHMC implemented pre-test alerts to encourage clinicians, when attempting to order a relevant drug, to first order an appropriate genotype test. In addition, they also implemented an alert that would inform clinicians when a genotype test result already exists, if they are attempting to order a duplicate test. Mt. Sinai Health System implemented both pre- and post-test alerts for warfarin only.

There were sixteen total DGIs with alerts defined across the seven sites. Of those: seven algorithms utilized specific genotypes (eg, *CYP2C19*1/*2*) stored in the patient record; five utilized PGx phenotypes in the form of computed observations^{2,4} (eg, intermediate metabolizer); two could utilize either specific genotypes or phenotypes; and one utilized the simple existence of a genotype test result, regardless of its contents.

The mechanism by which recommendations were generated varied by site and specific DGI. For clopidogrel and simvastatin, all sites used static text to relay the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations in their alerts, though Marshfield Clinic also supplemented these recommendations with dynamically calculated values. Warfarin alerts demonstrated the greatest variability: two sites displayed only dynamically calculated doses, one site supplemented dynamically calculated doses with static CPIC recommendations, one site supplemented dynamically calculated doses with static FDA recommendations, and one site did not calculate a dose, but directed clinicians to the WarfarinDosing.org website. There was significant variation among the sites on which actions were available to providers on the pop-up alerts. Details are in [Table 1](#) and [Supplementary Table SA](#).

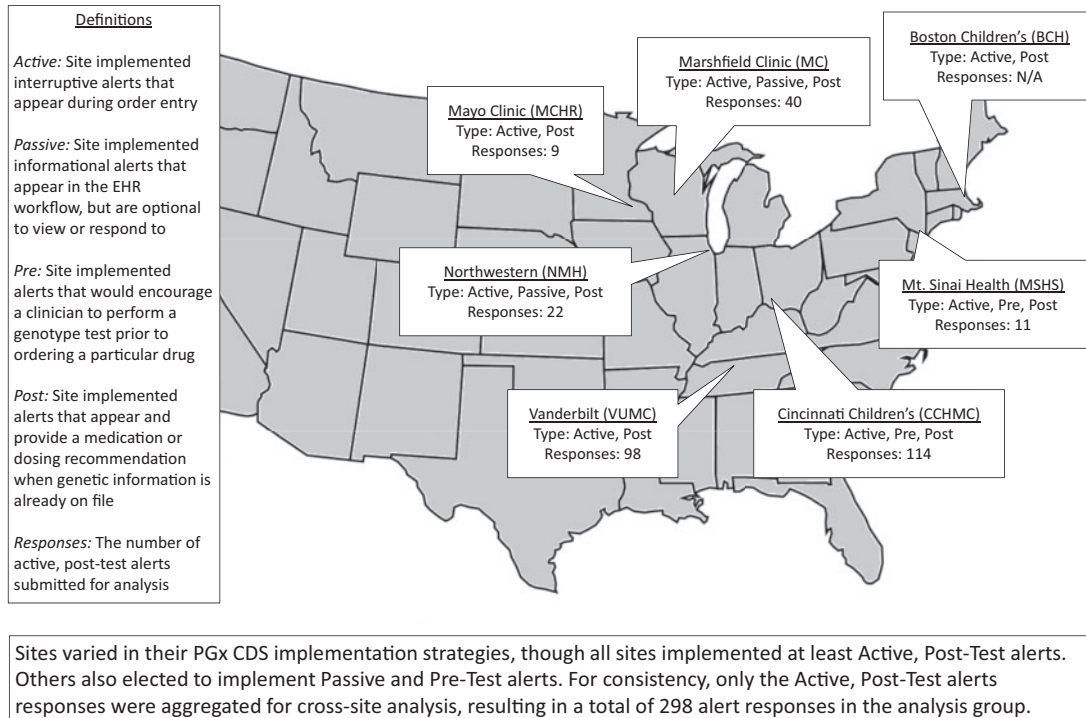


Figure 1. Site characteristics.

Table 1. Available alert actions by site and DGI

Site	Gene	Drug	Accept with No Update	Accept with Update	Explicit Cancel	Implicit Cancel	View Educational Materials	Override with Reason	Override with No Reason	Other
Cincinnati Children's	CYP2D6	codeine	X			X				
		oxycodone								
		hydrocodone tramadol								
Marshfield Clinic	CYP2C19, SLCO1B1, CYP2C9, VKORC1	clopidogrel	X			X	X			
		simvastatin	X			X	X			
		warfarin	X			X	X			
Mayo Clinic	CYP2C19, SLCO1B1, CYP2C9, VKORC1	clopidogrel	X			X	X			
		simvastatin	X			X	X			
		warfarin	X			X	X			
Mt. Sinai	CYP2C19, SLCO1B1, CYP2C9, VKORC1	clopidogrel		X	X	X	X	X	X	X
		simvastatin	X		X	X	X	X	X	X
		warfarin	X	X	X	X	X	X	X	X
Northwestern	CYP2C19, SLCO1B1, CYP2C9, VKORC1	clopidogrel	X		X		X	X		
		simvastatin	X		X		X	X		
		warfarin	X		X		X	X		
Vanderbilt	CYP2C19, CYP2C9, VKORC1	clopidogrel		X	X		X	X		
		warfarin					X			X

Sites varied in the actions that they provided to users on PGx CDS alerts, which affected the Accept, Override, and Ignore rates found upon aggregation. Table includes only the 6 sites that submitted data for aggregation in Table 2.

Objective 2: cross-site data collection and pilot outcomes analysis

Six sites participated in the alert-level analysis and submitted 294 active, post-test alert instances across all DGIs, using the agreed-upon data structure. Alert responses were aggregated by site and

DGI (Table 2). CCHMC and Vanderbilt University Medical Center accounted for 212 of the 294 (72%) alerts, with submissions ranging from 9 to 114 instances. The most common alerts were for codeine and warfarin, accounting for 70% of submitted instances. Overall, 62% of alerts were accepted and 26% overridden.

Table 2. Pilot study – provider responses by site and by DGI

Site / DGI	Total Alerts	Alert Response				Clinical Response		
		Accept	Override	Ignore	Unknown	Followed	Not Followed	No Action
Cincinnati Children's	114	102 (89%)	0 (0%)	10 (9%)	2 (2%)	69 (61%)	18 (16%)	27 (24%)
Marshfield Clinic	40	39 (98%)	0 (0%)	1 (3%)	0 (0%)	17 (43%)	23 (58%)	0 (0%)
Mayo Clinic	9	4 (44%)	0 (0%)	5 (56%)	0 (0%)	4 (44%)	5 (56%)	0 (0%)
Mt. Sinai	11	8 (73%)	3 (27%)	0 (0%)	0 (0%)	8 (73%)	1 (9%)	2 (18%)
Northwestern	22	9 (41%)	0 (0%)	13 (59%)	0 (0%)	5 (23%)	14 (64%)	3 (14%)
Vanderbilt	98	21 (21%)	72 (73%)	5 (5%)	0 (0%)	21 (21%)	65 (66%)	12 (12%)
Total by Site	294	183 (62%)	75 (26%)	34 (12%)	2 (1%)	124 (42%)	126 (43%)	44 (15%)
Codeine	114	102 (89%)	0 (0%)	10 (9%)	2 (2%)	69 (61%)	18 (16%)	27 (24%)
Clopidogrel	65	14 (22%)	46 (71%)	5 (8%)	0 (0%)	10 (15%)	40 (62%)	15 (23%)
Simvastatin	24	22 (92%)	1 (4%)	1 (4%)	0 (0%)	11 (46%)	13 (54%)	0 (0%)
Warfarin	91	45 (49%)	28 (31%)	18 (20%)	0 (0%)	34 (37%)	55 (60%)	2 (2%)
Total by DGI	294	183 (62%)	75 (26%)	34 (12%)	2 (1%)	124 (42%)	126 (43%)	44 (15%)

Alert response varied across sites. Variation in response rate is likely due to significant differences in alert design. As a result, it is difficult to draw any broad conclusions about how physicians are responding to PGx CDS alerts in general. Instead, it will be necessary to analyze alert response in relation to the different design choices made at each site to understand how those choices influence physician behavior.

Definitions.

Alert Response: How the clinician responded to the actual alert that appeared in the EHR interface.

Clinical Response: How the clinician behaved in caring for the patient after viewing the alert.

Accept: Provider explicitly used the CDS-provided “accept” functionality to dismiss an alert.

Override: Provider explicitly used the CDS “acknowledge” or “override” functionality to dismiss an alert.

Cancel: Provider closed an alert without interacting with its contents.

Followed: Provider performed the recommended action within a pre-defined time window after seeing an alert.

Not Followed: Provider performed a clinically relevant, but not recommended, action within a pre-defined time window after seeing an alert.

No Action: Provider performed no clinically relevant action within a pre-defined time window after seeing an alert.

Clinically, 42% were followed and 43% not followed. By DGI, simvastatin (92%) and codeine (89%) alerts were most likely to be accepted, clopidogrel most likely to be overridden (71%), and warfarin most likely to be ignored (20%). Codeine alerts were most likely to be followed (60%), while clopidogrel alerts were most likely to be not followed (62%). Codeine (24%) and clopidogrel (23%) alerts were also most likely to have no action taken.

DISCUSSION

This study successfully characterized the PGx CDS alert design strategies within eMERGE-PGx and demonstrated the ability of the eMERGE-PGx sites to share and aggregate PGx CDS alert data from disparate systems.

The eMERGE Network provided participating sites the freedom to implement PGx CDS as they each saw fit. This study found wide variation in implementation strategies, but also revealed an emerging consensus on how to structure PGx CDS alerts. The most common alerts implemented were active, post-test, and were based on CPIC recommendations, confirming a preference for a central authority of PGx recommendations,² and in line with other studies of PGx implementation.²³ There is also a trend towards preferring dynamically calculated recommendations for warfarin dosing.

Despite these areas of commonality, there is significant variation in how PGx CDS alerts are designed throughout the eMERGE Network. This demonstrates the current lack of EHR standards for storing and using genomic data and lends support to previous calls for such standards.²⁴ (Other work has shown that this sort of variation is not unique to PGx alerts.²⁵) Informal follow-up discussions with participating sites revealed a variety of site-specific factors that led to these differences. Common themes in those discussions included

differences in: EHR functionality; availability of informatics and programming expertise; laboratory data formats; level of resources (funding and personnel); level of clinician buy-in and participation; previous experience with CDS; and concerns about risk of alert fatigue. Previous publications shed some light on site-specific decision making.^{8,13,15}

Sites were almost evenly split as to whether to use genotype or phenotype as algorithm input. Northwestern Memorial Hospital expressed a preference for use of phenotype in CDS to simplify programming logic and to provide results that were more easily interpreted by clinicians. MCHR reported that they were influenced by the reporting format and interface from their testing laboratory. Their algorithms prioritized phenotype where available and defaulted to genotype if a phenotype was not present. Most sites showed a preference for dynamic warfarin dosing, and commonly accepted algorithms require genotype as input. Concordantly, all sites that developed warfarin alerts used genotype, even when using phenotype elsewhere.

Sites also varied significantly in what responses they allowed to pop-up alerts. For instance, some sites used explicit “cancel” buttons, while others did not. Some sites allowed users to “accept” an alert recommending a medication change without automatically updating the order, while other sites would automatically update the order. In some cases, these sorts of variations occurred across DGIs within the same site.

While the pilot study was able to aggregate PGx CDS alert data from disparate systems, the variations in design and small sample size constrain generalized conclusions about physician response to PGx CDS. For instance, accepting an alert is not necessarily a meaningful act if it is the only explicit action available. Therefore, the results reported in Table 2 should *not* be viewed as a definitive representation of the current state of PGx CDS adoption. Though, with

that caveat, it is worth noting that override rates for PGx CDS alerts were lower than in studies of other medication-related CDS.^{26–28} Results from other PGx CDS studies that examined effectiveness are limited and varied, making them difficult to compare, but it seems likely that local design differences influence effectiveness.^{9,11,16,29} These results should be interpreted in context as a pilot study, providing strong evidence that comprehensive studies of PGx CDS may be more complex than expected, due to design variation. Additionally, the relatively low firing rate of the majority of alerts in this study suggests that a larger sample size will be needed to draw definitive conclusions. The consolidation of the EHR market, and the inclusion of PGx CDS as a built-in EHR feature, may reduce inter-site variability and increase PGx CDS usage, thus facilitating multi-site aggregation in the future. Until then, multi-site studies must be carefully focused on areas where sites share common design approaches.

Aside from the issues of site variability and sample size, the pilot study is limited in that it did not examine the relevance of PGx CDS alerts, such as alerts potentially firing in inappropriate situations or providing incorrect recommendations. Nor did it assess the correctness of the clinical actions taken. Sample sizes also made it difficult to determine how often PGx CDS alerts fire on a per patient basis or how clinician demographics affect alert response. Such questions, and others relating to usability and user-acceptance, are unanswered by this study and are the subject of both previous^{17,18,30,31} and in-progress work within the eMERGE Network.

The eMERGE Network is comprised of large, research-oriented institutions. Their priorities, experience levels, and resources dedicated to genomics may not represent national norms for the use of PGx CDS.

CONCLUSION

This study serves as a proof of concept for multi-site PGx CDS analysis. We successfully characterized PGx CDS design across the eMERGE Network. We found heterogeneity in design choices, with notable consensus around the use of active, post-test alerts relaying CPIC recommendations. We found variation in whether sites utilized phenotype or genotype in CDS algorithms, and in the actions that users may perform on any particular alert. This variation was unsurprising and likely due to a lack of genomic medicine standards in the EHR. We successfully created a data dictionary and shared alert logging data across sites with different EHR infrastructures. Finally, a pilot analysis using shared data showed that system variations currently make it difficult to quantitatively analyze physician response to PGx CDS across sites. Such studies should be narrowly focused on areas of commonality until PGx CDS designs become further standardized.

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CONTRIBUTORS

All authors contributed to the concept and design of this project. TMH collected, analyzed, and interpreted the data and drafted the manuscript. All other authors provided feedback and final approval of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

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