

PERSPECTIVE

Implementing Genomic Clinical Decision Support for Drug-Based Precision Medicine

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The explosive growth of patient-specific genomic information relevant to drug therapy will continue to be a defining characteristic of biomedical research. To implement drug-based personalized medicine (PM) for patients, clinicians need actionable information incorporated into electronic health records (EHRs). New clinical decision support (CDS) methods and informatics infrastructure are required in order to comprehensively integrate, interpret, deliver, and apply the full range of genomic data for each patient.¹

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Numerous challenges exist to the routine personalization of drug therapies using genomic data. The implementation of clinical decision support for pharmacogenomics (PGx) is becoming more common, but there are still many barriers that must be surmounted. Our experience implementing PGx CDS provides some insight into the resources and informatics infrastructure that will be required to support CDS that is based on more comprehensive PM data. In this Perspective, we use the Agency for Healthcare Research and Quality (AHRQ) “Five Rights” framework (Table 1)² to explore challenges to implementing effective PGx CDS. These issues are also likely to be encountered as other types of genomic CDS are implemented.

The challenges encountered when integrating genomic data into clinical systems (Table 1) can be grouped into two general categories: those that are related to information, including data representation and knowledge management, and those that are related to the delivery of information through clinical systems and workflows in the form of CDS interventions. Common challenges encountered by sites implementing PGx CDS are summarized below.

DATA, INFORMATION, AND KNOWLEDGE

Information that is useful to guide clinical decisions is evidence-based, actionable, and pertinent to the clinical circumstance.² Ideally, comprehensive PM would incorporate all patient-specific factors for prescribing (e.g., age, gender, race, comorbidity, socioeconomic status, concomitant medications) tailored to the setting (e.g., intensive, emergency, ambulatory, long-term care), but most clinical guidelines, which are often the basis for CDS interventions, focus on a small subset of data types.

For example, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published 17 guidelines that describe the interactions between 14 genes and 36 drugs.³ The guidelines for the selective serotonin reuptake inhibitor

(SSRI) class of antidepressants provide recommendations based only on a patient’s cytochrome P-450 genotype, but the recommendation also states “drug interactions and other clinical factors can have a major influence for prescribing decisions for SSRIs and should be taken into consideration before initiating drug therapy” (<http://cpicpgx.org/g/25974703>).

Determining which factors are most relevant requires informatics infrastructure that enables the robust capture of patient phenotypes and outcomes data (e.g., detailed information about drug response, including data related to dosing, metabolism, clearance, and adverse events). Those capabilities are essential for collecting the data to generate new evidence that informs the development of more specific clinical guidelines,⁴ which in turn enables the development of tools (e.g., patient level prediction algorithms that explicitly integrate quantitative genomic and nongenomic predictors of drug response) and more precise CDS interventions.

An encouraging example is the collaboration between the Observational Healthcare Data and Informatics (OHDSI) program (www.ohdsi.org) and the Electronic Medical Records and Genomics (eMERGE) Network (<https://emerge.mc.vanderbilt.edu/>). Researchers used a common data model and the OHDSI clinical cohort discovery tool to represent patient phenotype definitions from the Phenotype KnowledgeBase (<https://phekb.org/>), which have been used for a variety of genomic medicine studies using EHR data including genome-wide association studies. Implementing phenotype definitions using a common data model enables a distributed network of researchers to identify patient cohorts at their respective sites, opening up intriguing possibilities for collaborative PM evidence generation that might fill gaps in knowledge, which could result in more effective genomic decision support.

Researchers who have diverse clinical infrastructure and custom, local data models can utilize common phenotype definitions only because those definitions are based on data and terminology standards, which provide common semantics for clinical concepts. Similarly, PGx CDS

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Table 1 AHRQ's "Five Rights" framework for CDS applied to genomic CDS

CDS "Right"	Principle points and examples	Genomic data integration challenges
Right information	<ul style="list-style-type: none"> Evidence-based information that may be derived from a guideline or national performance measure Constrained to relevant clinical information to avoid cognitive overload Supported by links to educational material (e.g., Infobuttons) Targets clinicians and patients 	<ul style="list-style-type: none"> Lack of standardized and structured data for genomic results, clinical observations, and clinical phenotypes Gaps in knowledge of relevant clinical factors Lack of an accepted minimum information model for genomic medicine Few rule definitions that are portable across clinical sites A need for scalable methods to maintain data, knowledge, and rules
Right person	<ul style="list-style-type: none"> An individual who can act on the information Might be a clinician, patient, or caregiver 	<ul style="list-style-type: none"> Localized clinical workflows and team structures limit generalizability of interventions Information must be tailored for each user based on their needs (and kept in sync)
Right intervention format	<ul style="list-style-type: none"> Fits the problem that the intervention is trying to address May be active (e.g., interruptive alerts) or passive Examples include alerts, order sets, infobuttons, dosing calculators, protocols, and decision trees 	<ul style="list-style-type: none"> Lack of evidence comparing different types of interventions Existing clinical systems (e.g., EHRs) and workflows do not fully support integration of genomic data
Right channel	<ul style="list-style-type: none"> Provider-facing clinical systems, such as the EHR or custom applications (e.g., dashboards) Patient-facing systems (e.g., portal or personal health record) Hybrid systems, such as mobile apps that facilitate provider-patient communication or collect personalized health data (e.g., activity tracker, glucose monitor) 	<ul style="list-style-type: none"> Lack of user-friendly tools to deliver complex information Need standard interfaces that enable the integration of tools and methods for delivering genomic information into customized clinical systems
Right time in workflow	<ul style="list-style-type: none"> Information delivered precisely when it will have the best impact on decision making Requires a thorough understanding of clinical workflows Different care settings may make the best use of information at different times within a given workflow 	<ul style="list-style-type: none"> Genomic data may not be available (e.g., from pre-emptive testing), test turnaround time usually exceeds clinical decision making time

CDS can help improve health outcomes if the *Right Information* is communicated to the *Right Person* using the *Right Intervention Format* delivered through the *Right Channel* at the *Right Time in the Workflow*. Some challenges to achieving the "five rights" for genomic data through its integration into clinical systems and workflows are listed in the right-hand column. CDS, clinical decision support; EHR, electronic health record.

implementations require standard representations for drugs and genomic test results if information about those implementations is to be shared. Some standards already exist, such as the RxNorm drug terminology, but there are still many gaps in our ability to consistently represent genomic data (e.g., observed variants) and knowledge (e.g., phenotypic interpretations, drug dosing algorithms).⁵

It is imperative to develop methods for representing knowledge in standards-based, computable forms so that it can be freely shared and used more easily within clinical systems. Portable representations of knowledge (including CDS rules) will improve dissemination, make distributed curation and maintenance possible so that PM knowledge bases can keep up with rapid advances in scientific understanding, and enable the synthesis of high-quality evidence.^{4,6}

Standards make data interoperable and knowledge portable, which are essential for supporting large-scale PM implementations, and therefore the development of standards must be supported at both the national and institutional levels. Furthermore, it is critical that clinical systems adopt data standards and expose standards-based interfaces, which will improve interoperability and facilitate broader data integration.

DELIVERING INFORMATION THROUGH CDS INTERVENTIONS

Healthcare professionals, patients, and caregivers could, each at different times, act on a PM-based recommendation. Recommendations from CDS systems should be presented to individuals who can take action but in a complex, interdisciplinary team practice, identifying the right person to receive a recommendation can be challenging. Moreover, each healthcare discipline may use information differently to personalize patient care.

For example, a physician may initiate an order for a drug but it is likely that a pharmacist will ultimately inform the final decision regarding the selection and dose of the drug. Pharmacists are well positioned to lead and support drug-based PM because they understand and provide leadership for the entire medication use process and are skilled at evaluating and applying patient-specific factors (e.g., renal and hepatic function, age, drug interactions). Pharmacists at many sites are already using PGx data to tailor drug therapy. In addition, in many situations information should be actively provided (or at least be made available) to multiple members of the interdisciplinary

healthcare team, which will promote communication and consistency in team-based patient monitoring. Therefore, to successfully implement CDS for genomic and PM data, a robust and well-integrated electronic infrastructure that enables effective communication among interdisciplinary team members and coordinates the delivery of information is required.

As demonstrated by PGx implementations, it is important to provide educational materials that are tailored to each user's role and level of background knowledge along with each CDS intervention.⁷ Educational materials are needed for both the care team and patients. Patients are increasingly likely to receive PGx testing either through a clinic or direct-to-consumer services, and they may learn that they carry an actionable genotype for a drug they are currently taking. Educational material for patients must clearly explain not only when a modification to their drug therapy is needed but also when it is not, so patients do not make changes to their medications before discussion with a clinician. When designing CDS, patients must be considered a potential consumer of information and infrastructure must enable delivery of information to patients.

It is also important to consider how information is delivered when CDS interventions are designed. Interruptive alerts, such as those used for allergies, drug–drug interactions, or PGx are widely used at the point-of-care in EHRs. High volumes of interruptive alerts can result in alert fatigue, which can condition clinicians to cancel the alert without acting on the recommendation. Increasing alert specificity by incorporating all relevant clinical factors when designing CDS for PM can make interruptive alerts more effective by increasing their relevance at point-of-care and reducing the risk of alert fatigue.⁸

Interruptive alerts are only one type of CDS intervention; other types can also be used to deliver information that can inform clinical decision-making. Dosing calculators integrate clinical and genomic data, and order sets can be modified in real time to include patient-specific genomic information so clinicians can consider those data at the time of order creation. Infobuttons, which provide information on-demand, are an example of noninterruptive CDS that is being tested by eMERGE and ClinGen (<https://www.clinicalgenome.org/>) for PGx.⁹ The Medicine Safety Code is a mobile application that empowers patients to share their PGx results with providers and provides links to guidelines.¹⁰ Note that all CDS implementations that utilize tools outside of the EHR require robust standards to support data exchange between systems.

As CDS implementations become more complex by taking into account genomic and other types of PM data, it will become increasingly important to develop interventions that facilitate and guide, rather than interrupt, clinical decision-making. This will require the development of more tightly integrated clinical systems that can access a wide variety of patient-specific clinical data on demand, use computable knowledge bases to make inferences from those data in real time, and display results and recommendations to clinicians through a variety of channels at logical points within their workflows.

SUMMARY

The AHRQ “Five Rights” framework and our experiences with PGx CDS allow us to reflect on the challenges encountered when integrating genomic data into clinical systems and using those data to personalize drug therapies. As the amount of patient-specific data that is available to clinicians continues to grow, novel approaches will be required to enable scalable knowledge management and delivery of information, and enhancements to clinical electronic infrastructure will be required to support integration of complex data types. The lessons learned from PGx CDS implementations provide valuable insights into the strengths and limitations of different approaches, and successes give us reason to be optimistic for the future utilization of PM data and CDS to individualize drug therapies.

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