A Clinical Decision Support Model for Incorporating Pharmacogenomics Knowledge Into Electronic Health Records for Drug Therapy Individualization: A Microcosm of Personalized Medicine

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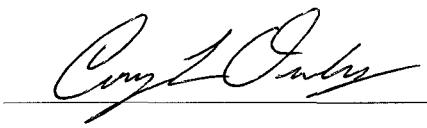
Signature 

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Abstract

A Clinical Decision Support Model for Incorporating Pharmacogenomics Knowledge Into Electronic Health Records for Drug Therapy Individualization: A Microcosm of Personalized Medicine

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Personalized medicine, where treatment may be tailored to individual characteristics, has the potential to improve patient outcomes. As a microcosm of personalized medicine, findings from pharmacogenomics studies have the potential to be applied to individualize drug therapy such that the efficacy is improved and the occurrence of adverse drug events are reduced. In this context, the overarching research question this research project aimed to address was: what needs to be done to incorporate pharmacogenomics knowledge into an electronic health record in a useful way that facilitates drug therapy individualization? Clinical decision support imbedded in the electronic health record was investigated as a model for providing access to pharmacogenomics knowledge to support accurately using and interpreting patient genetic data to individualize drug therapy. The aims of this research were: (1) characterizing pharmacogenomics knowledge resources; (2) determining capabilities of current clinical decision support systems; (3) developing a prototype implementation of a model for pharmacogenomics clinical decision support; and (4) evaluating the utility of the pharmacogenomics clinical decision support model implementation. Findings from this work enhances our understanding of how pharmacogenomics knowledge should be made accessible via clinical decision support in the electronic health record given characteristics of pharmacogenomics knowledge, technical capabilities of current clinical systems and characteristics of clinicians. More generally, the results of this study contribute a model that is directly applicable to the incorporation of genetic and molecular data into electronic health records and its usability by healthcare providers.

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PUBLICATIONS RELATED TO THIS DISSERTATION

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LIST OF ABBREVIATIONS AND ACRONYMS

AHRQ	Agency for Healthcare Research and Quality
AHIC PHC	American Health Information Community's Personalized Health Care
ASCO	American Society of Clinical Oncology
BCM	Baylor College of Medicine
caBIG™	Cancer Biomedical Informatics Grid
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CDS	clinical decision support
CLIA	Clinical Laboratory Improvement Amendments
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPMC	Coriell Personalized Medicine Collaborative
CPOE	computerized provider order entry
CO	clinical outcomes
DTC	direct-to-consumer
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EHR	electronic health record
eMERGE	Electronic Medical Records and Genomics
ePKgene	University of Washington's Pharmaceutics Pharmacogenetics database
FA	functional assays
FDA	U.S. Food and Drug Administration
FURTHeR	Federated Utah Research Translational Health e-Repository
GAPPNet	Genomic Applications in Practice and Prevention Network
GN	genotype
GWAS	genome-wide association study
HHS	U.S. Department of Health and Human Services

HIT	health information technology
HL7	Health Level Seven international standard
HPCGG	Harvard Medical School-Partners HealthCare Center for Genetics and Genomics
I-CD9	International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification coding system
IOM	Institute of Medicine
IT	information technology
LIS	laboratory information system
MIND	Medical Information Network Database
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NLM	National Library of Medicine
NLP	natural language processing
ONC	Office of the National Coordinator for Health Information Technology
ORCA	Online Record of Clinical Activity
PD	Pharmacodynamics
PGx	Pharmacogenomics/Pharmacogenetics
PGRN	Pharmacogenetic Research Network
PharmGKB	Pharmacogenomics Knowledge Base
PK	pharmacokinetics
PLoS	Public Library of Science
PMRD	Personalized Medicine Research Database
PREDICT	Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society

SPL	structured product label
St. Jude	St. Jude Children's Research Hospital
TCC	Moffitt Cancer Center, Total Cancer Care™
UI	user interface
UW	University of Washington
VUMC	Vanderbilt University Medical Center
WGI	Wisconsin Genomics Initiative

1. CHAPTER 1: EXECUTIVE SUMMARY

1.1. OVERVIEW

Personalized medicine is the tailoring of medical treatment to individual characteristics such as environmental factors, demographics, patient history, family history and clinical profile. In this dissertation, the concept of personalized medicine is used in the context of *Genomic Medicine*, or medical practice that incorporates knowledge of an individuals' genetic profile and how certain profile characteristics give rise to certain phenotypes or physical conditions. While studying personalized medicine is too broad in scope, *drug therapy individualization* can provide a useful microcosm or testbed for studying the informatics issues involved with using electronic health records to support achieving the vision of personalized medicine. As with personalized medicine, drug therapy individualization incorporates knowledge of an individuals' genetic profile. However, the scope of healthcare delivery and the evidence-base from which conclusions are drawn is of a more narrow focus. Drug therapy individualization is achieved by using genetic profile data to predict drug disposition, efficacy, toxicity and clinical outcome. *Pharmacogenomics* is the study of how variations in the human genome affect an individuals' response to medications; it provides the evidence-base for making predictions in the context of drug therapy individualization.

Clinical decision support delivered through use of just-in-time information combining clinical data with genomic data and genomic knowledge broadly has the potential to improve clinicians' ability to make genome-tailored or personalized clinical decisions. *Clinical decision support* refers broadly to providing clinicians with clinical knowledge and patient-related information, filtered or presented at particular times, to enhance clinical care (Teich, Osheroff, Pifer, Sittig, & Jenders, 2005). *Just-in-time information* is the right information, provided to the right people, at the right time. Pharmacogenomics clinical decision support provides a useful testbed for looking at the broader question of supporting personalized medicine. To explore pharmacogenomics-related decision support in clinical practice, a model for pharmacogenomics clinical decision support to facilitate the effective communication of pharmacogenomics knowledge in a clinical context was proposed, implemented and evaluated. *Effective communication* was defined in this dissertation as a

process by which pharmacogenomics knowledge to support drug therapy individualization is communicated to the care provider in a format and with supportive information that promotes their appropriate use in making informed health decisions. Characteristics of pharmacogenomics knowledge, technical capabilities of current clinical systems, and characteristics of potential system end-users guided the design of the model presented in this dissertation. As a preliminary step, the characteristics of pharmacogenomics knowledge were assessed and the technical requirements for pharmacogenomics knowledge in a clinical context were determined. The proposed model for pharmacogenomics clinical decision support was then implemented within a local prototype electronic health record system and simulated patient data was incorporated. The utility of the model implementation was assessed in a pilot study investigating the perceived usefulness and the clinical impact of pharmacogenomics knowledge delivered via the model implementation. The remainder of this chapter provides more detail on the process and an overview of the structure of the dissertation.

1.1.1. The potential for clinical decision support systems to facilitate drug therapy individualization

Current clinical decision support technologies exist that could be adapted to support providing pharmacogenomics knowledge in a clinical context. This dissertation incorporates rule-based, data driven computation and information retrieval approaches to implement clinical decision support. Infrastructural prerequisites to develop, implement and maintain just-in-time clinical decision support with genetic/genomic knowledge and data in a production system have previously been suggested. These suggestions have begun to be incorporated into the clinical systems of organizations pursuing personalized health care initiatives. Aspects of the work presented in this dissertation that are unique from these initiatives include the application of methods to evaluate and utilize existing knowledge resources, and the exploration of multiple models for providing clinical decision support that incorporates existing pharmacogenomics knowledge. The potential to use pharmacogenomics knowledge to support drug therapy individualization is apparent given the growing inclusion of information about genomic biomarkers in Food and Drug Administration (FDA) drug labeling. However, the availability of relevant knowledge resources (such as FDA drug labels) and the maturity of the pharmacogenomics knowledge

they provide need to be understood to fully set the stage for the work presented in this dissertation.

1.1.2. Maturity of pharmacogenomics knowledge in the clinical context

Pharmacogenomics resources that provide access to data and knowledge for translational research and potentially for drug therapy individualization: (a) are made available through various venues (e.g. professional organization websites, drug databases), (b) provide access to knowledge that varies in maturity, (c) are increasing in prevalence, and (d) applicability of knowledge to clinical practices varies. Despite this, there are few resources that provide evidence-based guidance on using genetic data in a clinical context. Of particular motivation to this research is that lack of access to appropriate pharmacogenomics knowledge necessary to support clinical decision-making has been cited as a barrier to the use of genetic test results for drug therapy individualization. In this dissertation, a subset of available pharmacogenomics knowledge resources are investigated to determine requirements for representing and providing access to pharmacogenomics knowledge in the drug therapy individualization context.

1.2. Motivation & Overarching gap this work aims to address

Individualized drug therapy based on genetic testing is often beyond the scope of current formal clinical training. As such, an overarching gap this dissertation aimed to address is the need for education and guidance for health care professionals to support accurately using and interpreting patient specific genetic data for drug therapy individualization in face of ever increasing availability of pharmacogenomics knowledge and testing. Clinical decision support embedded in the electronic health record might provide a venue for delivering this form of support, and is therefore the primary mode for delivering personalized healthcare investigated in this work.

1.3. Primary research question

The primary research question of this dissertation is a subset of the broader question of how informatics could facilitate the practice of personalized medicine. The primary research question is: **What needs to be done to incorporate pharmacogenomics knowledge into an electronic health record in a useful way that facilitates drug therapy individualization?** Given the scarcity of resources that provide evidence-based guidance on using genetic data

for drug therapy individualization, this question is addressed by highlighting factors that might influence (a) the implementation of clinical decision support embedded in the electronic health record with available pharmacogenomics knowledge and (b) the ability of current pharmacogenomics knowledge resources to be incorporated into existing clinical decision support frameworks. Suggestions are also made for new directions to improve upon our current ability to present pharmacogenomics knowledge in a way that satisfies the educational and guidance needs of health care professionals.

1.4. Outline of this dissertation

1.4.1. Chapter 2: The potential for clinical decision support systems to facilitate drug therapy individualization

This chapter provides background information on available general-purpose clinical decision support technologies that might be adapted to support providing pharmacogenomics knowledge in a clinical context. Gaps in our related to better understanding the ability to incorporating clinical decision support into existing clinical infrastructures and the appropriateness of various functionalities given characteristics of pharmacogenomics knowledge are introduced in this chapter. In addition, some discussion about the potential for providing just-in-time pharmacogenomics knowledge to support drug therapy individualization via clinical decision support embedded in an electronic health record system is provided in this chapter. Unique challenges to incorporating pharmacogenomics knowledge are introduced in Chapter 3.

1.4.2. Chapter 3: Maturity of pharmacogenomics knowledge in a clinical context

This chapter provides a baseline overview of current resources that provide pharmacogenomics knowledge. Gaps related to the characteristics of pharmacogenomics knowledge that this dissertation aims to fill are introduced in this chapter. In addition, some discussion of the potential for making resources available via clinical decision support tools given the maturity of the knowledge is provided in this chapter and investigated in more depth in Chapter 4.

1.4.3. Chapter 4: Charactering pharmacogenomics knowledge resources (Aim 1)

The research sub-question addressed in this chapter was: **What are the characteristics and the value of current pharmacogenomics knowledge in the context of clinical decision support within an electronic health record?** Characteristics of pharmacogenomics knowledge in a clinical context were assessed by: (a) characterizing the availability of pharmacogenomics knowledge appropriate for use in a clinical context; and (b) characterizing pharmacogenomics knowledge translated into a form suitable to incorporate into an electronic health record system.

1.4.4. Chapter 5: Determining capabilities of current clinical decision support systems (Aim 2)

The research sub-question addressed in this chapter was: **How do current decision support systems align with requirements of characterized pharmacogenomics knowledge in computable form?** Technical requirements for pharmacogenomics knowledge in a clinical context were assessed by: (a) assessing the availability of discrete data to support linking patient-specific data to pharmacogenomics knowledge; and (b) assessing the feasibility of current systems to support technical requirements for presenting pharmacogenomics knowledge in a clinical context.

1.4.5. Chapter 6: Developing a prototype implementation of a model for pharmacogenomics clinical decision support (Aim 3)

The research sub-question addressed in this chapter was: **How can patient genetic test results and just-in-time pharmacogenomics knowledge be presented to users with electronic health record clinical data so that it aligns with requirements of pharmacogenomics knowledge?** A model for integrating clinical decision support into electronic health records to address requirements for presenting pharmacogenomics knowledge was proposed in this chapter. As a preliminary step, user interface requirements for presenting pharmacogenomics knowledge in a clinical context were characterized. The model was then designed such that it supported both technical requirements (identified in Chapter 5) and the user interface requirements for pharmacogenomics knowledge. Lastly, a prototype implementation of the proposed model building on local clinical frameworks was created.

1.4.6. Chapter 7: Evaluating the utility of the pharmacogenomics clinical decision support model implementation (Aim 4)

The research sub-question addressed in this chapter was: **What needs to be done to achieve effective communication of pharmacogenomics knowledge embedded in the electronic health record?** The ability of the proposed model (model designed and prototype implemented in Chapter 6) to support effective communication of pharmacogenomics knowledge was assessed. The assessment was accomplished by delivering pharmacogenomics knowledge via the model implementation and measuring in a simulated context with care providers: (a) the perceived appropriateness of pharmacogenomics knowledge; (b) the clinical impact in terms of uptake of pharmacogenomics knowledge; (c) the clinical impact of knowledge provision on prescribing decisions; and (d) the confidence in prescribing decisions with access to pharmacogenomics knowledge.

1.4.7. Chapter 8: Conclusions

This chapter synthesizes findings across all of the dissertation research aims, discusses their implications for future research, and describes proposed principles for supporting the integration of pharmacogenomics knowledge into clinical decision support frameworks and implementing clinical decision support embedded in an electronic health record.

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2. CHAPTER 2: THE POTENTIAL FOR CLINICAL DECISION SUPPORT SYSTEMS TO FACILITATE DRUG THERAPY INDIVIDUALIZATION

2.1. INTRODUCTION

In the previous chapter, an overview of this dissertation and a summary of the overarching problem being addressed in this work were presented. Specifically, this dissertation aims to address the need for education and guidance for health care professionals to support accurately using and interpreting patient specific genetic data in individual drug therapy. This problem was addressed by answering the overall research question: **What needs to be done to incorporate pharmacogenomics knowledge into an electronic health record in a useful way that facilitates drug therapy individualization?** This chapter provides background information on available general-purpose clinical decision support technologies that could be adapted to support the provision of pharmacogenomics knowledge in a clinical context. Clinical decision support embedded in the electronic health record can provide the support care providers' need to properly tailor treatments to patients; to prevent medical errors from misinterpretation of tests (genetic and otherwise); and to accelerate the translation of research findings into clinical practice (genomic research and otherwise). Gaps in our understanding of requirements for incorporating clinical decision support into exisiting clinical infrastructures and in understanding the appropriateness of various clinical decision support functionalities given characteristics of pharmacogenomics knowledge are introduced in this chapter. The subsequent chapter gives a baseline overview of current resources that provide specifically pharmacogenomics knowledge and the potential for these resources to be made available in the clinical context via general-purpose clinical decision support technologies given the maturity of the knowledge.

2.2. CLINICAL DECISION SUPPORT SYSTEMS AS A TOOL TO PROVIDE JUST-IN-TIME INFORMATION

2.2.1. Just-in-time information for clinical decision support in general

There are several instances in which the just-in-time metaphor has been used in the context of medical decision-making. Examples include the following: "Just-in-time Information" (JITI) librarian consultation service (McGowan, Hogg, Campbell, & Rowan,

2008); the Infobutton Manager that is accessed through a clinical information system, anticipates clinician's questions, and provides links to pertinent electronic resources (Collins, Currie, Bakken, & Cimino, 2008); the MD on Tap application that is installed on smartphones and allows for information retrieval from MEDLINE and other databases (Demner-Fushman et al., 2006); and the MINDscape system, a web based integrated interface that provides access to both patient specific information and knowledge resources that contain information such as drug reference information and clinical guidelines (Tarczy-Hornoch et al., 1997). Each example provides a different approach to presenting just-in-time information to support clinical decisions.

Both Infobutton and MINDscape approaches provide point-of-care access to knowledge, and both focus on methods for automatically selecting and retrieving appropriate knowledge resources. These infrastructures are therefore of particular relevance to this research. The MINDscape system is used as an example electronic health record (EHR) framework against which the feasibility of incorporating PGx knowledge for clinical decision support (CDS) is evaluated (See Dissertation Chapter 5). OpenInfobutton webpages that can be incorporated into an EHR were designed and implemented in this work (See Dissertation Chapter 6). OpenInfobutton is an open source platform for Infobutton established to foster innovations and wide adoption (Del Fiol, Kawamoto, & Cimino, 2011; OpenInfobutton project webpage). The just-in-time model is one of many decision support system models.

2.2.2. Clinical decision support systems in general

Clinical decision support (CDS) systems refer broadly to systems that provide clinicians or patients with clinical knowledge and patient-related information, filtered or presented at particular times, to enhance clinical care (Teich, Osheroff, Pifer, Sittig, & Jenders, 2005). There are various user interface design configurations that impact interactions clinicians or patients have with CDS systems.

2.2.2.1. Clinical decision support system user interface design configurations

User interface (UI) design configurations for CDS may be described as passive, semi-active or active CDS. "Historically, the distinction between passive and active CDS relates to whether or not a clinician must actively retrieve information to support medical decisions (Shortliffe, 1987). Therefore, passive CDS requires that a clinician first recognize when

advice would be useful, then make an explicit effort to access the CDS system. Another view of passive versus active CDS is that passive decision support occurs when a system provides access to relevant data or knowledge for interpretation by the physician e.g. links to relevant external resources; and active decision support implies a higher level of information processing e.g. alerts or pop-ups (Elson & Connelly, 1995)." (Overby et al., 2011) To accommodate both of these definitions, three CDS UI design configurations were defined for this project: passive, semi-active, and active.

The difference between semi-active and active CDS can be illustrated using genetic testing to determine warfarin dosing as an example. "Warfarin is an anticoagulant that has significant individual variability in response and optimal dose. Studies show that the VKORC1 gene accounts for approximately 25% of the phenotypic variability in warfarin dosing, and the CYP2C9 gene accounts for about 6-10% (Rieder et al., 2005). If a clinician has the results of testing for CYP2C9 and VKORC1 genetic variants to assess sensitivity to warfarin, a semi-active approach to improving the interpretation of these tests is to embed educational resources with the result. Active CDS, however, may use an algorithm that combines patient characteristics such as age, gender and weight, with genomic data to determine the starting dose of warfarin for patients initiating anticoagulation." (Overby et al., 2011) Other frameworks for characterizing generalized CDS approaches exist as well.

In a report prepared for the Agency for Healthcare Research Quality (AHRQ) (AHRQ National Resource Center for Health Information Technology, 2011), they use a different framework to describe decision support aids: *classic clinical decision support*, *information retrieval tool,* and *knowledge resource.* These types are described by process for (a) submitting patient-specific information, and (b) retrieving patient-specific information. *Patient-specific genomic information* is of particular focus to this work. Genomic information includes *genotyping data* and *genomic knowledge*, where *genotyping data* includes data produced with use of Single Nucleotide Polymorphism (SNP) arrays, and *genomic knowledge* supports guidance for clinical interventions based on a persons' genotype.

Focusing on patient-specific genomic information, the decision aid types AHRQ defines align with definitions of passive, semi-active and active CDS UI design configurations. *Classic clinical decision support* involves automated submission of patient specific data (e.g.

genotype data) and automated retrieval of patient specific knowledge (e.g. genomic knowledge), therefore an active CDS UI design configuration would be appropriate. An *information retrieval tool* involves automated submission of patient-specific data, but manual retrieval of knowledge (e.g. Infobutton). This type of decision aid would require a semi-active CDS UI design configuration. *Knowledge resources* require manual submission of patient-specific data and manual retrieval of patient-specific knowledge, and the appropriate UI design configuration would be passive CDS. Example knowledge resources include resources such as UpToDate, Epocretes, and MDConsult.

2.2.3. Clinical decision support structural components and knowledge representation model for information retrieval

The basic components of clinical decision support (CDS) systems include the application environment and the CDS module (Greenes, 2007). The application environment includes the clinical IT application (including patient data), and determines how and when the CDS module gets invoked. The systems' back-end processing occurs in the CDS module that provides a method of transforming input parameters (e.g. submitted patient-specific data) to a patient-specific output (e.g. retrieved patient-specific knowledge).

2.2.3.1. Clinical decision support back-end processing

Clinical decision support system back-end processing occurs within the CDS module and can incorporate logic-based and text mining approaches. Logic-based approaches involve either data driven computation (react upon detection of an event pattern - also referred to as *forward chaining*) or goal driven computation (given an event pattern, check if the pattern has been satisfied or not – also referred to as *backward chaining*). Text mining approaches may involve information retrieval (retrieving relevant documents or information from knowledge resources), information extraction (extracting facts from relevant documents), and various modes of providing access to extracted information (e.g. question answering, summarization, etc.). An example text mining system (or more specifically, a clinical question answering system) described by Demner-Fushman et al. (Demner-Fushman & Lin, 2007) utilizes MEDLINE abstracts as its core knowledge source and incorporates statistical methods to extract and score the relevance of knowledge about patient population, clinical problem and clinical intervention discussed in the abstracts.

This thesis incorporates rule-based, data driven computation and information retrieval approaches to implement the CDS module. A general CDS system might incorporate a knowledge base, and an inference engine that generates results of a calculation or retrieval operation (e.g. in the form of an alert message or "resources page"). Within a rule-based CDS system, the knowledge base and inference engine are part of a rules engine (the software component of a rule-based system) that assesses individual rules and determines their applicability to a particular patient (Musen, Shahar, & Shortliffe, 2006). The knowledge-base consists of rules represented in a computational format. In order for an inference engine to reason about patient data and clinical knowledge, knowledge-base rules need to be represented in a computer accessible format (Lavrac & Mozetic, 1989) (Aguirre, Barron, Brena, & Garcia, 1993). Such a format within a rules engine implementation can be referred to as the *knowledge representation model*. A rule-based knowledge representation model that is commonly used to represent medical knowledge and can be connected with information retrieval processes is a *production rules representation model*.

2.2.3.2. Production rules representation model and information retreival

Production rules represent knowledge in terms of rules that draw conclusions if the stated conditions are met. While there are many different syntaxes for production rules, all rules are composed of two parts, (a) the *conditions* to be tested, and (b) the *actions* to be performed if the conditions are met (e.g. IF <condition(s)> THEN <action(s)>). The condition part of the rule is also known as the premise, antecedent, or Left Hand Side (LHS). The action part of the rule can be referred to as the consequent, conclusion, or Right Hand Side (RHS). Rules are declarative representations (with pieces of syntax correspond to facts), and therefore fire in response to changes in the facts available to the rules engine. There are several rules engines available to help developers create and edit rule bases. There are two reasoning approaches to executing production rules: data driven (forward chaining) and goal driven (backward chaining). For example, MYCIN (Shortliffe, 1974) is a rule-based, primarily goal driven, system designed to identify severe bacterial infections. The system can first ask the user a number of preset questions then performs backward chaining to identify each possible infection. MYCIN incorporates another level of complexity by representing knowledge as IF-THEN rules, each with a certainty factor (or probability that a conclusion will be true given the evidence). While MYCIN performed well in a clinical

context it was never actually used in practice, primarily due to the ethical and legal issues associated with a computer recommending therapy with various degrees of uncertainty.

Two rules engines that incorporate data driven computation are Java Expert System Shell (JESS) (Java Expert System Shell) and Discern Expert (Cerner Corporation). JESS is an open source data driven rules engine designed to integrate with Java software applications. As another example, Discern Expert is a proprietary data driven rules engine that is part of the Cerner Millennium commercial product. At University of Washington, Discern Expert is installed as part of the implementation of Cerner PowerChart® (the inpatient EHR application), and PharmNet® (the inpatient pharmacy application). The rules use "IF-THEN" logic based on any medical information stored in the EHR and provides a range of automated responses offered (e.g. sending an email, placing an automated order, presenting an on-screen pop-up window, etc.)

Production rules may also be applied to facilitate information retrieval processes given the detection of an event pattern. For example, a knowledge base might contain production rules that define index terms for performing a search or compiling a list of relevant documents or knowledge resources.

Existing UW CDS frameworks provide support for a production rules knowledge representation model. Therefore processes for representing existing genomic knowledge that can be incorporated into this form of model are explored in this work. In addition, UW clinical frameworks provide support for information retrieval (See Section 2.5.2). This thesis describes work that builds on these frameworks while also addressing some technical barriers to incorporating clinical knowledge into existing CDS systems.

2.2.4. Barriers to incorporating clinical knowledge into existing clinical decision support systems

There are technical barriers to incorporating clinical knowledge in general into CDS systems. For example, methods to convert clinical knowledge into computable form (e.g. production rules knowledge representation) are still being developed (AHRQ National Resource Center for Health Information Technology, 2010). There are also social barriers such as clinicans' lack of motivation to use CDS. This may be due to issues with usability (e.g. speed and ease or use), lack of integration into clinical workflow, concerns about

autonomy, and legal & ethical ramifications of adhering to or overriding recommendations made by the CDS system (Berner, 2009). In addition, the evolving and incomplete nature of clinical knowledge makes executing knowledge maintenance activities particularly challenging. These barriers are magnified for genomic knowledge. Providers have cited the fast pace of changes in genetic testing as the greatest obstacle to providing information to their patients (Wilkins-Haug, Hill, Schmidt, Holzman, & Schulkin, 1999).

A systematic review of the literature performed by Kawamoto et al. identified design characteristics associated with successful deployment of CDS (Kawamoto, Houlihan, Balas, & Lobach, 2005). Characteristics include: 1) computer-based decision support is more effective than manual processes for decision support; 2) CDS interventions that are presented automatically and fit into the workflow of the clinicians are more likely to be used; 3) CDS that recommends actions for the user to take are more effective than CDS that simply provides assessments; and 4) CDS interventions that provide information at the time and place of decision making are most likely to have an impact.

The last characteristic describes the provision of just-in-time decision support (see Section 2.2.1 above) as an important design characteristic for successful deployment of CDS. In this research, the design characteristics for successful deployment of CDS are further investigated by evaluating the context under which various CDS functionalities are appropriate given characteristics of available clinical knowledge (See Dissertation Chapter 5 and Ref (Overby et al., 2011)). Clinical knowledge specific to the use of genetic test results in a clinical context is investigated in this work. General CDS models can be applied to present clinical knowledge in the context of incorporating genetic test results into the electronic health record.

2.3. GENETIC TEST RESULTS AND ELECTRONIC HEALTH RECORDS AS AN EXAMPLE OF PRESENTING JUST-IN-TIME CLINICAL DECISION SUPPORT

2.3.1. Requirements for incorporating genetic test results into electronic health records

There have been significant efforts towards understanding the clinical context for making genetic tests results available in the electronic health record. It has been reported that three developments are necessary for the genome-enabled electronic health record to exist:

improved tools to support the capture of genomic results; a controlled vocabulary appropriate for describing clinically significant genomic findings, and the applications capable of enabling clinicians to utilize results to support their decision making (Hoffman, 2007). There have been significant contributions in all of these areas through efforts such as the Personalized Health Care Initiative and by the American Health Information Community's Personalized Health Care (AHIC PHC) Workgroup. The Personalized Health Care Initiative of the U.S. Department of Health and Human Services (HHS) (US Department of Health and Human Services, 2006), launched in 2006, was especially directed at preparing EHRs to accommodate genetic test information and other elements important for personalized healthcare. Through the Initiative, standards for embedding genetic test data were published in 2008.

Towards incorporating clinically useful genetic test information into EHRs, the AHIC PHC Workgroup recommended developing a use case that describes the process of performing a genetic/genomic test (Glaser, Henley, Downing, & Brinner, 2008). To facilitate the development of the use case, the PHC Workgroup developed a matrix reporting on information requirements of various genetic/genomic test types in the context of three phases of genetic testing (US Department of Health and Human Services, 2007). Phases of genetic testing are defined according to the CDC Notice of Intent published in the Federal Register, Vol 65, No 87, 5/4/2000 25928 and include: 1) a pre-analytic phase; 2) an analytic phase and; 3) a post-analytic phase. The pre-analytic phase includes events such as determining which genetic test is appropriate to answer a clinical question and collecting/transporting a sample to the test site; the analytic phase involves sample analysis; and the post-analytic phase includes reporting and interpretation of results. ***Table 1*** summarizes the dataset specific to personalized healthcare (including types of genetic/genomic tests) that were considered relevant to the use case developed by the Workgroup. Data elements are listed for 5 data categories: demographic, personal health information, family history information, personal genetic/genomic data, and family genetic/genomic data. These data elements, while non-exhaustive, lend themselves to standardization to support interoperable personalized healthcare delivery.

Table 1 *Data set for personalized health care considered by AHIC PHC Workgroup*

Data Category	Data elements
Demographic	Name
	Unique identifier
	Race/Ethnicity
	Occupation
Personal health information	History of specific disorders
	Relevant non-genetic laboratory test and pathology data
	Other clinical data such as radiology study results
	Environmental exposure data
	Any prior treatment for specific disorders
Family history information	Disorders of family members
	Disorders of family members
	Ages of condition onset and/or death of various family members
	Environmental exposure data
	Relevant social data
	Pedigree in structured form
Personal genetic/genomic data	Prior genetic/genomic laboratory test results
	Prior genetic status for specific disease
	Full genome scan: deoxyribonucleic acid (DNA)
Family genetic/genomic data	Genetic/genomic data of family members
	Pedigree in structured form when appropriate
	History consanguinity
	Consent/access allowance information

As a result of exploring information requirements for performing a genetic/genomic test, and exploring the above dataset considerations in the context of personalized healthcare delivery, the *Personalized Healthcare Detailed Use Case* document was developed by the Office of the National Coordinator for Health Information Technology (ONC) and published on March 21, 2008 (US Department of Health and Human Services, & Office of the National Coordinator for Health Information Technology, 2008). The use case has a high level focus on the exchange of information between organizations and systems that aligns with the national health information technology (HIT) agenda. Of particular focus is the exchange of personal health history, family health history, and genetic/genomic testing information between consumers and clinicians in two scenarios: *clinical assessment*; and *genetic, testing reporting, and clinical management.* The use case indicates roles and functions from the perspective of a clinician, testing laboratory, and consumer. *Events* detailed in the scenarios are from these three perspectives (***Table 2***). The Personalized Healthcare Detailed Use Case document outlines information exchange requirements for events. The work covered in this thesis, however, focuses on understanding data requirements, functional requirements, and

user interface presentation requirements for providing just-in-time CDS in the context of personalized healthcare delivery. There are four events described in the Use Case document that require either the retrieval of information from genetic/genomic knowledge repositories or consultation with genetic references. Just-in-time CDS might be incorporated into EHRs to support these activities. A prototype system is implemented in this work to particularly provide support for clinicians' performing interpretation and care planning activities.

Table 2. *AHIC PHC Use Case Events*

	Perspectives/Roles		
	Clinician	**Testing Laboratory**	**Consumer**
Scenario 1: Clinical Assessment			Share available family health history information
	Construct a personal & family history and pedigree		
			Receive family health history information & pedigree
	Evaluate relevant genetic testing references and guidelines[a]		
	Order genetic/genomic tests[a]		
Scenario 2: Genetic Testing, Reporting, and Clinical Management		Receive genetic/genomic testing orders	
		Prepare for appropriate test	
		Perform genetic/genomic test	
		Develop & transmit the lab result[a]	
	Receive lab results		
	Perform interpretation and care planning activities[a]		
		Provide supplemental information[a]	
	Provide results to consumer and/or next provider		
			Receive results and Interpretation

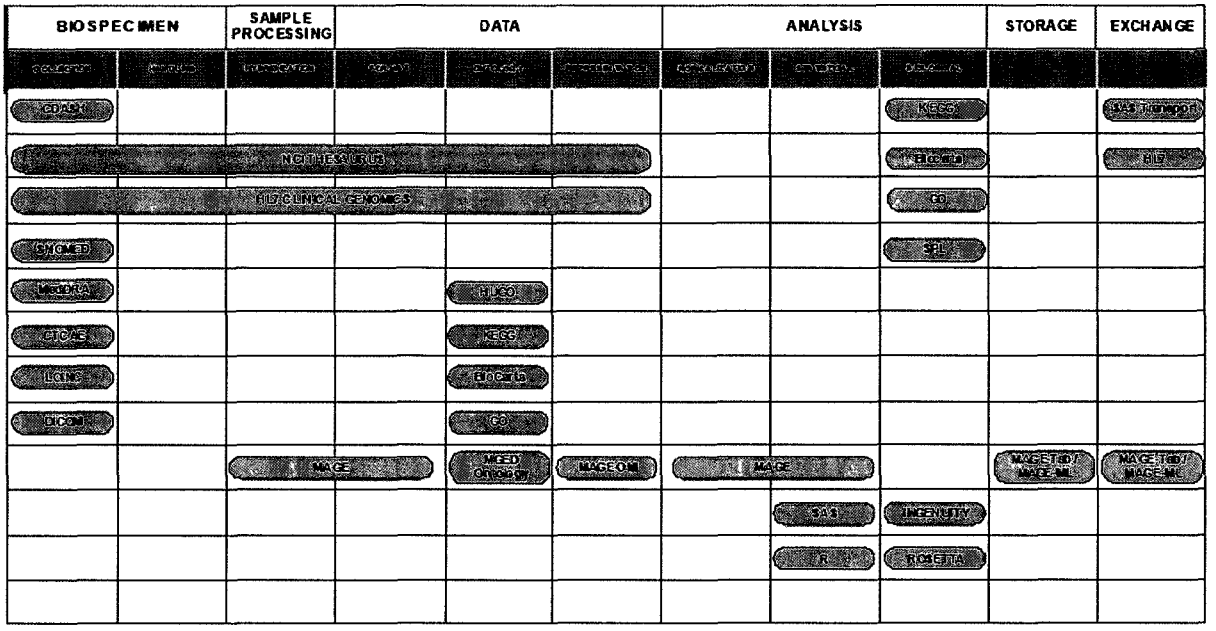
a. Events requiring the retrieval of information from genetic/genomic knowledge repositories or consultation with genetic specialists

There are infrastructural prerequisites to develop, implement and maintain just-in-time CDS with genetic/genomic knowledge and data in a production system. According to an analysis of requirements for a national CDS infrastructure for genomic and personalized medicine performed by Kawamoto et al, "essential components of this infrastructure include standards for data representation, centrally managed knowledge repositories, and standardized approaches for leveraging these knowledge repositories to generate patient-specific care recommendations at the point of care." (Kawamoto, Lobach, Willard, & Ginsburg, 2009). There has been progress in all of these areas.

2.3.2. Standards for representing genetic/genomic data

Standards enable semantic interoperability (understanding data and knowledge) through controlled terminology, and syntactic interoperability (accessing data and knowledge) through structured messaging. The Department of Health and Human Services (HHS) sponsored a stakeholders workshop titled Identifying Opportunities to Maximize the Utility of Genomics Research Data through Electronic Health Information Exchange on Oct 15, 2009 in Washington, D.C. A Clinical Genomics Data Standards Activities to Support Electronic Information Exchange resource guide (US Department of Health and Human Service, 2009) that was distributed as part of the meeting materials describes clinical genomics activities across HHS. The resource guide also describes proposed data elements needed to maximize the utility of data collected for clinical genomics, and standards that are currently in use or under development that apply to the elements. To facilitate providing just-in-time CDS, genetic/genomic data and knowledge should be captured in a computable form. Standards for structuring and processing raw genetic/genomic data are summarized in ***Table 3***. The table aligns existing standards with stages of the genomics data information flow. Column headings are the stages and include collection of a biospecimen, the protocol for its handling, the sample processing (e.g. hybridization to an array), the resulting raw data (e.g. measurement), and the processing of the generated raw data (data analysis, storage, and data exchange). Standards are listed below the applicable stages. The Structured Product Labeling (SPL) standard, associated with representing analyses of biological significance is most relevant to this thesis. SPL defines the content of human prescription drug labeling in an XML format. The US Food and Drug Administration (FDA) adopted SPL as a mechanism for exchanging medical information. An example application of the SPL standard to enable semantic and syntactic interoperability is with the DailyMed website (http://dailymed.nlm.nih.gov) operated by the US National Library of Medicine (NLM). DailyMed uses the SPL standard to publish drug labels and provide free access to consumers and health care providers.

Table 3. *Standards for clinical genomics data capture, analysis, exchange and storage (borrowed directly from Ref. (US Department of Health and Human Service, 2009) with permission from the publishers)*



2.3.3. Current approaches to connect genetic/genomic data to just-in-time clinical knowledge

To understand approaches to connecting clinical data to just in time clinical knowledge, a general framework is helpful. The laboratory information system (LIS), electronic chart, and computerized provider order entry (CPOE) system, are components of an EHR that are most relevant to connecting genetic test results to just-in-time clinical knowledge. The LIS supports electronic or manual reporting of laboratory results to the ordering provider. The electronic chart might combine the ability to view laboratory results and a clinical report. LIS systems and electronic charts can either be fully integrated or interfaced using Health Level Seven International (HL7) messages (http://www.hl7.org). CDS can be configured in the laboratory review context. For example, one form of CDS might be to flag patient genetic/genomic data values that fall above or below expected reference ranges.

CDS can also be configured in the CPOE clinical context. Physicians can use CPOE systems to electronically order medications in an inpatient or outpatient setting. "CPOE systems can assist physicians with writing orders by streamlining and structuring the order entry process." (Osheroff et al., 2007) Automated CDS algorithms, for example, might be integrated with a CPOE system to evaluate the appropriateness of a therapeutic regimen

given patient genetic/genomic test results. However, the ability to implement this form of CDS may be restricted by the way test results are stored within the EHR.

Genetic and genomic test results are often stored as unstructured text-based reports, which limits the ability to integrate LIS systems and implement CDS in EHRs. There are several examples where natural language processing (NLP) algorithms have been applied to code free-text clinical documents so that concepts such as disease presence/absence are represented in computable form (Hripcsak et al., 1995) (Friedman, Alderson, Austin, Cimino, & Johnson, 1994) (Crowley et al., 2010). Once data are represented in computable form, they can be connected to just-in-time clinical knowledge.

There are a few published examples of approaches for connecting genetic test results to just-in-time clinical knowledge (Del Fiol et al., 2006) (Kaihoi, Petersen, & Bolander, 2005) (Maviglia, Yoon, Bates, & Kuperman, 2006). In addition, a number of institutions are already putting an infrastructure in place to connect personal genetic/genomic data with clinical knowledge in a personalized medicine context. In a publication by the US Department of Health and Human Services, *Personalized Health Care: Pioneers, Partnerships, Progress*, institutions including Baylor College of Medicine, National Cancer Institute, Coriell Institute for Medical Research, Harvard-Partners Center for Genetics and Genomics, Marshfield Clinic, Moffitt Cancer Center, University of Utah and Intermountain Healthcare, Vanderbilt University School of Medicine, and others, shared some experiences thus far in their pursuits (US Department of Health and Human Services, 2008). Other organizations making significant steps to establish the infrastructure to connect personal genetic/genomic data with clinical knowledge include Duke University Medical Center (Kawamoto & Lobach, 2007) and direct-to-consumer genetic testing companies (e.g. 23andMe and Navigenics). The infrastructures developed, or being developed, at these organizations are described in more detail below.

2.3.3.1. Baylor College of Medicine (BCM) and Baylor Clinic & Hospital

Baylor College of Medicine (BCM) is currently operating the Baylor Clinic & Hospital, an integrated health-care facility that focuses on personalized, gene-based medicine. The Baylor Clinic & Hospital adopts an Epic Patient Care System that centralizes patient care information and makes it available to both care providers and patients (via MyChart, the online patient interface for the EHR system). BCM partnered with Epic Systems Corporation

to develop this new EHR system that also incorporates (for physicians) alerts to new knowledge about disease states and risks linked to genetic data as it becomes available.

2.3.3.2. The National Cancer Institute, Cancer Biomedical Informatics Grid (caBIG™)

The National Cancer Institute (NCI) launched the Cancer Biomedical Informatics Grid (caBIG™) program with the goal of facilitating the cancer community to share data and knowledge (https://cabig.nci.nih.gov). TRANSEND (TRANslational Informatics System to Coordinate Emerging Biomarkers, Novel Agents, and Clinical Data) is an NCI funded project housed at the University of California San Francisco's Helen Diller Family Cancer Center that incorporates caBIG tools in an information management infrastructure developed to support adaptive clinical trials. Adaptive clinical trials are a class of trial designs that allow modifications of dosing or other parameters over the course of a study to incorporate new knowledge. For example in the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular analysis, http://tr.nci.nih.gov/iSpy) trial that motivated the TRANSEND project, patients are tested and assigned a study arm based on their predicted response to that treatment given their molecular profile. caBIG components utilized in the TRANSEND infrastructure include caTISSUE (a tool for biospecimen tracking), caARRAY (a tool for storage of DNA Miroarray data), and caINTEGRATOR (an analytics portal for analysis of trial data). In addition, the project aims to demonstrate integration with an electronic health record system (Tolven eCHR).

2.3.3.3. The Coriell Personalized Medicine Collaborative (CPMC)

The Coriell Personalized Medicine Collaborative (CPMC) research study is an evidence-based research study designed to determine which elements of personal genetic/genomic data are valuable in clinical decision-making and healthcare outcomes. The study aims to obtain consent for 100,000 participants to have their saliva collected for genotyping. The CPMC provides infrastructure to support dynamic communications between Coriell and study participates using a secure web portal. Genetic variants associated with health conditions considered potentially medically actionable are returned to participants. Participants are also given the option to grant access to their physician(s) to view results and are able to request genetic consultation free of charge. Personal genetic/genomic data are connected with

clinical knowledge via the CPMC web portal. Knowledge presented in the CPMC web portal includes genetic education material written for two audiences: the lay participant and the medical professional. Risks associated with genetic associations are reported to illustrate the known population disease risk and the adjusted risk based on the genetic variant genotype. An educational section of the web portal called "Understanding the Odds" has been created to ensure that participants and healthcare providers understand these results.

2.3.3.4. The Harvard Medical School-Partners HealthCare Center for Genetics and Genomics (HPCGG)

The Harvard Medical School-Partners HealthCare Center for Genetics and Genomics (HPCGG) provides an information technology (IT) infrastructure that is designed to link HPCGG facilities to support research activities, the Laboratory for Molecular Medicine (HPCGG's CLIA certified molecular diagnostic laboratory), and the Partners HealthCare Electronic Health Record. HPCGG has partnered with the Partners HealthCare Information Systems Department and Hewlett Packard Corporation in this endeavor. Components of the Partners HealthCare Genetics IT infrastructure that connect personal genetic/genomic data with clinical knowledge include GeneInsight and the Genetic Variant Interpretation Engine (GVIE) that supports professional genetic experts and other healthcare professionals including genetic counselors. In addition, the EHR is being integrated with CDS to provide support for genetics based clinical decisions. It is planned for patient genetic data to be stored in a secured Genetic Marker Repository (GMR), for test definitions to be stored in a Genetic Test Definition Catalog (GTDC), and for GeneInsight to serve as the EHR's genomics knowledge base. The CDS infrastructure will leverage these repositories within EHR displays, along with an option to view patient genomic profiles within a Patient Genome Explorer (PGE). The ultimate goal is to package the GMR, GTDC, PGE and GVIE/GeneInsight components together to form a Genetics Enabler Kit (GEK) that could be integrated into other EHRs.

2.3.3.5. Marshfield Clinic, Personalized Medicine Research Database (PMRD) and Wisconsin Genomics Initiative (WGI)

Marshfield Clinic leverages clinical information systems to support personalized health care research. For example, their Personalized Medicine Research Database (PMRD) allows

for genotypic and clinical data to be combined for research studies, while protecting the privacy of research studies. Marshfield is engaged in projects that connect personal genetic/genomic data to clinical knowledge. For example, the Wisconsin Genomics Initiative (WGI) is a research effort of Marshfield Clinic, Medical College of Wisconsin, University of Wisconsin School of Medicine and Public Health, and University of Wisconsin-Milwaukee that is providing a scientific platform for integrating genetic, phenotypic, and environmental information databases and providing the ability to efficiently search data for scientific discovery.

2.3.3.6. Moffitt Cancer Center, Total Cancer Care™ (TCC)

An approach to cancer care called Total Cancer Care™ (TCC) is being developed at Moffitt Cancer Center. The infrastructure to support TCC is a multi-dimensional data warehouse that provides user-specific views of patient data via a research, patient or clinician portal. The research portal is being designed to support discovery research (e.g. drug target discovery, molecular signatures to predict therapy response and resistance, and molecular signatures to predict risk for relapse). The patient portal is being designed to provide tailored educational information to help patients/survivors better understand and address their needs. The clinician portal is being designed to provide clinicians with evidence-based treatment guidelines. A goal for this portal is to provide support for physicians to query the most effective treatment guidelines for patients they are seeing with a particular tumor profile. This form of functionality requires connecting personal genetic/genomic data with clinical knowledge.

2.3.3.7. The University of Utah and Intermountain Healthcare, Federated Utah Research Translational Health e-Repository (FURTHeR)

The University of Utah and Intermountain Healthcare are collaborating to establish the Federated Utah Research Translational Health e-Repository (FURTHeR) that will provide the informatics infrastructure for personalized medicine research. FURTHeR is planned to link genotypic, phenotypic, genealogic, clinical, environmental, and public health data from disparate statewide sources for presentation within a Web-based portal to patients, care providers and researchers. Metadata integration services will be used within FURTHeR to classify and describe data from disparate data sources. An example data source includes the

Intermountain Healthcare Enterprise Data Warehouse that builds on the HELP and HELP2 electronic health record systems. These systems integrate embedded e-resources and provide clinicians with access to a wide range of electronic context-specific clinical knowledge (i.e. passive CDS).

2.3.3.8. Vanderbilt University, StarPanel and BioVU

Efforts in personalized medicine at Vanderbilt University include their investment in their local electronic health record system, StarPanel. StarPanel incorporates CPOE capabilities that include delivery of warnings that flag serious drug interactions or potential dosage errors. Ordering capabilities are licensed to be co-developed with McKesson as the Horizon Expert Order (HEO) system. Another effort is the BioVU DNA repository that was developed with the goal of accelerating biologic discovery, and the goal of validating methods to evaluate and deliver personal genetic/genomic data to the bedside. BioVU includes DNA extracted from discarded blood samples coupled with a de-identified version of StarPanel. Vanderbilt is one of five sites participating in the National Human Genome Research Institute's initiative to evaluate the utility of EHRs associated with DNA repositories (the "eMERGE" network).

2.3.3.9. The Duke University Health System, SEBATIAN

The Duke University Health System is actively engaged in efforts to connect personal genetic/genomic data with clinical knowledge to support genetically-guided medicine. One effort, for example, involves providing CDS support for genetically-guided warfarin management. At Duke University, they are using a services-based approach that incorporates the HL7/OMG Decision Support Service standard in their local electronic health record system (SEBATIAN (Kawamoto & Lobach, 2005)). This standard has the potential to allow for personalized medicine algorithms to be interfaced with clinical data sources though a Web-accessible interface.

2.3.3.10. Direct-to-consumer (DTC) genetic testing companies, 23andMe & Navigenics

Direct-to-consumer (DTC) genetic testing companies that connect personal genetic/genomic data with clinical knowledge include 23andMe and Navigenics. 23andMe provides ancestry testing, and testing for 24 clinical conditions including carrier status (e.g

Cystic Fibrosis), disease risks for 91 diseases (e.g. Type 2 Diabetes), drug response for 18 medications (e.g. Clopidogrel Efficacy), and 42 traits (e.g. eye color, food preference). Navigenics provides testing for disease risk (28 conditions, e.g. Type 2 Diabetes), and drug response (e.g. Clopidogrel Efficacy). Navigenics also offers genetic counseling to help people understand their test results. 23andMe views DNA scan data as informational only, where as Navigenics views these data as medical testing (Pollack, 2010). Navigenics therefore has a more restrictive inclusion criteria when compared to 23andMe. In addition to consumers, they market their services to doctors and corporations that might be interested in including their service as part of their employee wellness program. 23andMe, on the other hand, primarily markets to consumers and offers a wider range of results, including those with little medical impact but potentially larger entertainment value (e.g. avoidance of errors).

2.3.4. Unique aspects of this work

This work is distinguishable from current approaches to connecting genetic/genomic data to just-in-time clinical knowledge in the focus on (a) primarily providing support for care providers, (b) evaluating and applying methods to utilize existing knowledge resources, and (c) exploring multiple modes of providing CDS. Of the eleven initiatives, organizations and companies summarized in the previous section, five primarily provide support for care providers. The other six largely provide support for either patients or researchers.

The CPMC initiative, Navigenics and 23andMe appear to have a patient-centric focus. 23andMe has the clearest patient (or consumer) centric focus. While a more minor focus, there are some aspects of the CPMC initiative and Navigenics that involve providing care providers with clinical knowledge to support interpretation and use of patient genetic/genomic data. For example, both provide options for patients to grant physicians access to their genetic data, and support is provided in the form of educational materials and custom reports (e.g. odds ratios specific to an individuals' genotype along with a lay summary of relevant publications).

NCI caBIG™, PMRD & WGI, and Vanderbilt appear to have a primarily research-centric focus. All provide scientific platforms for integrating genetic/genomic data to just-in-time clinical knowledge. Vanderbilt and the NCI TRANSEND projects both integrate with an EHR system, however, the purpose for this integration is to provide support for scientific

research. For example, Vanderbilt has established the BioVU DNA repository that includes a de-identified version of their EHR StarPanel. Given that the EHR portion is de-identified, there is no direct connection between BioVU and the patient record to facilitate the provision of individualized care based on genetic/genomic data contained in BioVU.

Another major distinction between the work pursued in this dissertation and other initiatives is the evaluation and application of methods to utilize existing knowledge resources in this work. The projects and initiatives of CPMC, Harvard-Partners Center for Genetics and Genomics, Moffitt Cancer Center Total Cancer Care™, The University of Utah and Intermountain Healthcare, Navigenics, and 23andMe all have a heavy emphasis on building new knowledge bases for personalized medicine. In contrast, the first aim of this dissertation (Dissertation Chapter 4) focuses on characterizing existing knowledge resources and translating pharmacogenomics (PGx) knowledge from these resources into a form appropriate to integrate into existing EHR frameworks. Formal evaluations of how local clinical system CDS capabilities align with the data requirements, functional requirements (Aim 2, Dissertation Chapter 5) and user interface requirements (Aims 3.1 & 3.2, Dissertation Chapter 6) for providing just-in-time knowledge derived from existing resources were then performed. A conceptual model for PGx clinical decision support embedded in an EHR was derived based on findings from these evaluations (Aim 3.3, Dissertation Chapter 6) and a prototype implementation of the model established (Aim 3.4, Dissertation Chapter 6). This reverse process of implementing a model for the delivery of personalized healthcare based on the characteristics of existing genomic knowledge is unique from any of the approaches taken across the projects presented in this chapter.

In addition, this work explores the appropriateness of multiple modes of providing CDS given the characteristics of existing knowledge resources. The majority of the projects presented in this chapter provide one form of CDS (either semi-active or active CDS). Particularly unique to this work was the scheme applied to determine what implementations of CDS (incorporating both semi-active and active forms of CDS) are most appropriate to achieve effective communication of genomic knowledge in a clinical context prior to implementing just-in-time CDS to support personalized healthcare delivery. The steps for implementing a conceptual model for PGx CDS embedded in an EHR is provided in Dissertation Chapter 6, and the results of evaluating what implementations are most

appropriate to achieve effective communication in the context of drug therapy individualization is presented in Dissertation Chapter 7 (Aim 4). Dissertation Chapter 7 also evaluates the utility of incorporating PGx knowledge into just-in-time CDS for drug therapy individualization (as a microcosm of personalized healthcare delivery).

2.4. JUST-IN-TIME CLINICAL DECISION SUPPORT FOR DRUG THERAPY INDIVIDUALIZATION USING PHARMACOGENOMICS KNOWLEDGE

This dissertation research focuses on incorporating PGx knowledge into just-in-time CDS for drug therapy individualization as a microcosm of personalized healthcare delivery. There are currently few approaches to personalized healthcare delivery being applied in clinical practice that focus specifically on connecting genetic test results with PGx knowledge to support drug therapy individualization. However, the potential for providing such support is great and there are already some suggestions available on how to properly provide physician with the support they need to deliver personalized healthcare.

2.4.1. The potential to use pharmacogenomics knowledge to support drug therapy individualization

The potential for translating knowledge gained from PGx studies into clinical practice is great given current initiatives of the FDA. There has been oversight by the FDA over the field of PGx since 2004 and the white paper titled *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (US Food and Drug Administration, 2004) brought attention to how emerging PGx techniques show promise for improving upon safety, efficacy and quality of drug products. Following, in 2005 the FDA published a white paper *Guidance for Industry on Pharmacogenomics Data Submission* (US Food and Drug Administration, 2005) with the goal of promoting the use of PGx in drug development and encouraging public sharing of data and information on PGx test results. Today, there have already been several FDA approved PGx diagnoistics (genetic tests), and drugs for which there is PGx information in their labels (US Food and Drug Administration, 2011).

Moreover, the decreasing cost and the increasing throughput of genotyping technologies is contributing to progress in personalized medicine. For example, the MammaPrint technology (approved by the FDA in 2007, (US Food and Drug Administration, 2007))

analyzes the expression of 70 genes to determine the risk of breast cancer recurrence in patients with stage I or II node-negative breast cancer. In the future, we can imagine the existence of a technology for profiling drug-metabolizing genes. Such a technology could lead to a scenario where each patient has a PGx profile of drug-metabolizing genes in their EHR. However, our ability to interpret such data and link it with other personal health information remains a bottleneck in the translation of findings into clinical practice. The existence of CDS capabilities, such as automatically providing just-in-time PGx knowledge within an EHR has the potential to support the interpretation of such data by a clinician and support their ability to individualize drug therapy.

2.4.2. Requirements for just-in-time pharmacogenomics knowledge to support drug therapy individualization

Although there is clear support from the FDA to translate the use of genetic tests for PGx-related decisions into clinical practice, it comes with several challenges implicit in which are requirements for future systems. Knowing which genetic variants a patient has does not tell the physician how to adjust drug dose. Much of the knowledge needed to make an informed decision about drug dose adjustments based on genetic test results is beyond the scope of a physicians' formal medical training (Menasha, Schechter, & Willner, 2000). In addition, several other variables affect dosing: demographic details such as age, sex, weight and current health vary between patients; the rate by which the body clears a drug varies by drug; and effects of the same genetic variant may be different in different populations. These are all issues physicians must take into consideration when making drug dose adjustments.

These challenges are reiterated in the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* (Secretary's Advisory Committee on Genetics, Health, and Society, 2008a) which suggests that most practitioners are unfamiliar with guidelines for appropriate use of genetic tests, and few processes are implemented, evaluated, or enforced to support practitioners. In addition, lack of access to appropriate knowledge to support decision-making hinders our ability to incorporate existing PGx knowledge into clinical practice.

A key solution suggested in the report is to enhance education and guidance for health care professionals to support accurate use and interpretation of genetic tests. With a focus on PGx, the SACGHS report, *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges* (Secretary's Advisory Committee on Genetics, Health, and Society, 2008b) suggests that guidance for physicians include support for understanding criteria for PGx genetic testing, recognizing what information should be discussed with the patient; interpreting PGx test results; and understanding use of the results for patient care. The report states that, no research has been done to determine whether the proposed support would result in the appropriate use of PGx test. Providing guidance for health care professionals with CDS embedded in EHR systems has the potential to facilitate overcoming some of the above challenges.

2.4.3. Current approaches to connect genetic test results to just-in-time pharmacogenomics knowledge to support drug therapy individualization

There are currently no examples of research to determine whether providing support for PGx-related clinical decisions would result in the appropriate use of PGx personal genetic/genomic data. This is likely due to the lack of existing CDS systems and tools that provide just-in-time PGx knowledge to support drug therapy individualization. While there are several projects underway with the goal of providing general support for genomic medicine (See Section 2.3.3) few projects are working specifically towards implementing CDS that incorporates just-in-time PGx knowledge. In this work, a model (building on existing infrastructures) that incorporates different approaches to connect and present just-in-time PGx knowledge was implemented to support drug therapy individualization (See Dissertation Chapter 6).

Moreover, as a step towards understanding how PGx knowledge is used for drug therapy individualization, the effective communication of various presentations of just-in-time PGx knowledge was assessed in a clinical context. Also, the clinical impact of presenting just-in-time PGx knowledge on drug therapy individualization was assessed (See Dissertation Chapter 7). Effective communication may be defined as a process by which test results are communicated in a format and with supportive information, when applicable, that promotes their appropriate use by the clinician in making informed health care decisions (definition

from reference (Secretary's Advisory Committee on Genetics, Health, and Society, 2008a), adapted to be more general). Clinical impact represents both the uptake of PGx knowledge and the effect of PGx knowledge provision on clinical decisions. Effective communication and clinical impact were evaluated in simulated clinical context where clinical users interacted with a prototype clinical system. Implementation was performed in one University of Washington (UW) clinical system, however, there are several systems at UW that lend themselves to be viable test environments for providing CDS for drug therapy individualization.

2.5. CURRENT SYSTEM SUPPORT AT UW AS A TESTBED FOR PROVIDING CLINICAL DECISION SUPPORT FOR DRUG THERAPY INDIVIDUALIZATION

University of Washington (UW) clinical systems have to potential to be a testbed for providing CDS for drug therapy individualization. There are several UW clinical systems that are of particular interest to the work pursued in this dissertation.

2.5.1. An overview of University of Washington clinical systems

The UW Department of Laboratory Medicine uses the Misys (Sunquest) Flexilab Laboratory Information System (LIS) with the Multiple (MULHOS) option (www.misys.com). The Sunquest LIS is supplemented by locally developed applications including an online test directory (http://byblos.labmed.washington.edu), a web-based application that provides laboratory and clinical personnel with test information, and a hematopathology database (Hemepath) that supports reporting flow cytometry data.

The Sunquest LIS is also interfaced to four major UW clinical systems and data repositories: EpicCare, Online Record of Clinical Activity (ORCA), Medical Information Network Database (MIND) and Microsoft Amalga. Sunquest receives orders and sends results to EpicCare and ORCA. The EpicCare (www.epic.com) application is primarily used at UW in the outpatient setting. ORCA is a clinical system based on the Cerner Millennium application suite (www.cerner.org) that includes the PowerChart® application, and is primarily used in the inpatient setting. Results are also sent from the LIS to MIND and Amalga. MINDscape (Tarczy-Hornoch et al., 1997), is a web-based (predominantly view only) interface to the MIND database that provides a view of patient specific information and

knowledge resources. Microsoft Amalga (www.microsoft.com/amalga) is a system primarily used for aggregate cross patient queries.

2.5.2. Current approaches to incorporating just-in-time information into existing UW clinical systems

MINDscape and ORCA applications both provide the infrastructure to support the incorporation of just-in-time information. MINDscape's web interface provides primarily view only access to the electronic form of the patient health record (includes demographic information, insurance coverage, clinician-selected problem list entries, laboratory data, and etc). In addition, MINDscape incorporates automated reminder alerts and integrates knowledge resources. Stand-alone online resources may be easily linked through MINDscape. For example, MINDscape provides links to the Federated Drug Reference (FDRx), an online resource developed at UW for formulary, drug reference, and pill images (Ketchell et al., 1996). To alert users to the existence of the reference resource, an "i" icon appears next to each medication in a patients' medication list. Clicking the medication launches a search of FDRx.

The ORCA PowerChart® application is a graphical user interface used by physicians in the inpatient setting at UW. Similar to MINDscape, the application provides access to the electronic form of the patient health record. UW has already moved paper-based records to ORCA and is in the process of moving clinician orders management processes to the EHR using computerized practitioner order entry (CPOE) functionality. CPOE implementation is planned for the spring of 2012 (UW Medicine, 2011a). CPOE will be used by Harborview Medical Center, Seattle Cancer Care Alliance and UW Medical Center in the emergency, procedural and inpatient settings. A sample of CPOE in ORCA was demonstrated in April and May and was well received. Twenty-five proof-of-concept sessions were held and nearly 270 clinicians reviewed the prototype system (UW Medicine, 2011b).

Currently, ORCA incorporates two "Links and Reports" pages: a general page available on the Toolbar and one within a patient chart on the Menu that has options specific to the patient chart. The "Links and Reports" pages provide links to other applications, custom links that can be added, and saved PowerNotes (a note with a template that guides documentation) needing completion are listed. In addition, Discern Expert, the proprietary

rules engine of the Cerner Millennium commercial product is installed as part of the PowerChart® implementation. Discern Expert is currently being used minimally in the PowerChart® application to alert providers if allergies have not been entered in a patient record.

2.5.3. Database details of UW clinical systems

The backend databases to MINDscape and PowerChart® (MIND and ORCA) contains the following number of records (by table): Patients – 1.9 million (127,964 in 2008); Problems – 6.8 million (643,715 in 2008); Medications (2 tables) – 11.6 million (523,000 in 2002); Laboratory values – 114 million (11.7 million in 2008); Inpatient stays – 350,000 (23,792 in 2008); Outpatient visits – 10.2 million (816,000 in 2008). As of November 11th, 2009, the database model includes two databases that are identical in structure, one for each major hospital (UW Medical Center & Harborview Medical Center). Each database contains approximately 357 tables (300 primary data tables, 57 processing tables) and 200 indices (100 primary, 50 ancillary).

2.5.4. Evaluating the ability to build on existing UW clinical systems

In this work, the current CDS capabilities of UW clinical systems were evaluated to support presenting genetic test results and just-in-time PGx knowledge in the context of drug therapy individualization (See Dissertation Chapter 5). Given the results of this evaluation a prototype implementation of the ORCA system was established (See Dissertation Chapter 6).

2.6. SUMMARY

In summary, this dissertation aims to fill some gaps introduced in this chapter. Gaps include the need to better understand what it takes to incorporate clinical decision support in to existing clinical frameworks to support drug therapy individualization, and to better understand what clinical decision support design characteristics are appropriate given characteristics of pharmacogenomics knowledge. Approaches to address these gaps described in this dissertation include: (1) Given the characteristics of pharmacogenomics knowledge (Dissertation Chapter 4), providing a scheme for formally evaluating clinical decision support capabilities of existing clinical systems in the context of drug therapy individualization (Dissertation Chapter 5); (2) providing a model that builds on current infrastructures for connecting and presenting just-in-time pharmacogenomics knowledge in a

prototype system implementation (Dissertation Chapter 6); (3) estimating the appropriateness of various clinical decision support functionalities in the context of evolving pharmacogenomics knowledge to support the use of genetic test results in drug therapy individualization (Dissertation Chapter 7); and (4) estimating how pharmacogenomics knowledge will be used for drug therapy individualization in a simulated clinical context (Dissertation Chapter 7).

Chapter 2 has provided background information on available clinical decision support (CDS) technologies that could be adapted to support providing pharmacogenomics knowledge in a clinical context. However, in order to fully set the stage for the work completed in this dissertation, the availability of relevant knowledge resources and the maturity of the pharmacogenomics knowledge they provide need to be understood. Knowledge from these resources has the potential to be incorporated into CDS technologies, and is therefore the focus of the next chapter titled "Maturity of pharmacogenomics knowledge in a clinical context."

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3. CHAPTER 3: MATURITY OF PHARMACOGENOMICS KNOWLEDGE IN A CLINICAL CONTEXT

3.1. INTRODUCTION

In the previous chapter, background information on available technologies to support the provision of pharmacogenomics knowledge in a clinical context, with a particular focus on clinical decision support, were presented. This chapter gives a baseline overview of current resources that provide pharmacogenomics knowledge and the potential for these resources to be made available via clinical decision support tools given the maturity of the knowledge. Gaps in our understanding of the characteristics of pharmacogenomics knowledge are introduced in this chapter. In the following chapter, the details and results of a formal evaluation of the characteristics and the value of current pharmacogenomics knowledge in the context of clinical decision support within an electronic health record are described. Quoted sections in this dissertation chapter are primarily borrowed from the chapter titled "Pharmacogenomic Knowledge to Support Personalized Medicine: The Current State," (Overby & Hachad, 2011) in the book titled "OMICs: Biomedical Perspectives and Applications" with permission from the publisher.

3.2. EARLY EXAMPLES OF PROJECTS IMPLEMENTING PHARMACOGENOMICS IN CLINICAL PRACTICE

3.2.1. Pharmacogenomics knowledge in drug labels

Drug labels from the US Food and Drug Administration (FDA) are considered an important source of clinical information in clinical practice and in effect serve as a clinical knowledge resource (though not computable). A growing amount of pharmacogenomics (PGx) knowledge is beginning to appear in drug labels and has potential (though unproven) to improve clinical outcomes as discussed below. Researchers have begun to examine the availability and potential utility of PGx knowledge in FDA labels.

In terms of potential clinical impact of PGx, a recent study found that nearly 24% of Americans already receive drugs affected by known biomarkers (Frueh et al., 2008). In addition, over one million Americans seek care for adverse reactions every year (Lazarou, Pomeranz, & Corey, 1998). The occurrence of adverse drug effects and drug-related deaths

might be reduced with use of PGx profile data to make dosage adjustments that prevent drug toxicity.

To illustrate the drugs for which dosage adjustments might be most appropriate and the need for such clinical action, "In the United States, the number deaths from drug-induced causes in 1999 (19,128 deaths) more than doubled by 2007 (38,371 deaths) (Xu, Kochanek, Murphy, & Tejada-Vera, 2010). Drug-metabolizing enzymes, drug transporters, and Human Leulocyte Antigen's (HLAs) are the main three categories of genes currently associated with adverse drug reactions (ADRs) (Nakamura, 2008; Wilke et al., 2007). Type A ADRs in particular are typically dose-related and occur relatively frequently, accounting for more than 50% of all ADRs (Brockmoller & Tzvetkov, 2008). Variants in drug-metabolizing enzymes and drug transporters can affect clearance of drugs and can lead to this form of ADR if no dose adjustment is made. HLAs have been implicated in Type B ADRs that are unpredictable and occur in susceptible individuals. There are currently two drugs for which the FDA recommends genetic testing for an HLA variant prior to drug administration (US Food and Drug Administration, 2011). These drugs include Carbamazepine (HLA-B*1502) and Abacavir (HLA-B*5701). There are 45 drugs for which the FDA provides information, recommendations, or requirements for genetic testing of drug-metabolizing enzymes." (Overby & Hachad, 2011). The number of drugs for which the FDA provides information related to the genetic testing of drug-metabolizing enzymes is summarized in *Table 4*. The cytochrome P450 biomarkers (CYP -2C19, -2C9 and -2D6) are associated with 73% of the drugs with a drug-metabolizing enzyme biomarker, with CYP2D6 biomarker associated with the largest portion.

Table 4. *Drugs for which the FDA provides information on genetic testing of drug-metabolizing enzymes in the drug label*

Drug-metabolizing gene	Number of drugs
Cytochrome P450-2C19 (CYP2C19)	7
Cytochrome P450-2C9 (CYP2C9)	2
Cytochrome P450-2D6 (CYP2D6)	24
Dihydropyrimidine dehydrogenase (DPYD)	2
Glucose-6-phosphate dehydrogenase (G6PD)	3
N-acetyltransferase (NAT)	2
Thiopurine Methyltransferase (TPMT)	3
UGP Glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1)	2
Total	***45***

Drug metabolizing enzymes, such as those listed in *Table 4*, play an important role in pharmacokinetic (PK) response. Variability in PK response (drug absorption, distribution, metabolism and excretion) can be explained in part by PGx evidence. In addition, "it is possible to find equivalent doses for different PK genotypes (Brockmoller & Tzvetkov, 2008), therefore genetic testing might facilitate preemptive genotype-guided prescribing. This practice has already proven more efficient and safer than the traditional 'population average' protocol with Warfarin (the most prescribed anticoagulation therapy worldwide) (Caraco, Blotnick, & Muszkat, 2008)." (Overby & Hachad, 2011). Given this potential to have clinical impact, researchers have begun to study FDA label PGx content. In this work, FDA label PGx content is characterized and translated into a form suitable to present within electronic health record frameworks (Dissertation Chapter 4).

There are three studies to date that have examined the availability of PGx information in drug labels (Frueh et al., 2008) (Zineh et al., 2006) (Zineh et al., 2004). In 2006, researchers reported a lack of specific PGx-based recommendations for prescribing and dosing of drugs (Zineh et al., 2006). Of the top 200 prescribed drugs, they found that 71.3% had published PGx information in the literature, but only three had package inserts with PGx information sufficient to guide individualized dosing. In a 2008 study, authors report that although there remains a gap between published information on PGx and PGx information found in labels, drug approvals have recently included more PGx information (Frueh et al., 2008). In the analysis, they demonstrate that one fourth of all prescriptions are for drugs that contain PGx information in their labeling. Also, preliminary research showed that about 10% of the total number of drug labels included PGx biomarker information (Mummaneni, Amur, Goodsaid, Rudman, & Frueh, 2006). It is evident that the number of products in the United States for which the FDA includes genetic information is growing. The FDA published guidelines on "valid genomic biomarkers" in 2006 (US Food and Drug Administration, 2006). These guidelines originally classified testing as "required," "recommended," or "information only." This classification system was removed in the updated website in July 2009 (US Food and Drug Administration, 2009). Prior to this update, the FDA had identified 21 validated biomarkers for 29 drugs. *Table 5* includes information about the frequency of each test requirement. The distribution of guidance the FDA provided for validated biomarkers in

drug labels indicates that the majority of the labels provided information only, and testing of biomarkers was required for a small portion of the drugs.

Table 5. *Validated FDA genomic biomarkers and genetic testing requirements (prior to July 2009, (US Food and Drug Administration, 2009))*

FDA guideline category	Validated biomarkers
Test required	4
Test recommended	8
Information only	17
Total	***29***

Information contained in the FDA "Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels" prior to July 2009 is summarized in *Table 6*. The FDA table information was originally organized by biomarker, but is organized by drug in *Table 6* with the belief that providers are more interested in ordering PGx tests by drug. The FDA table in its current form (as of May 2011 (US Food and Drug Administration, 2011)) now provides an easy way to sort table content. Specifically, options to sort by drug, therapeutic area, biomarker, and label sections are available. Notably, content categories have changed as updates were made to the FDA table (e.g. removal of guideline categories). Therefore, the way in which drug labels containing genomic information are identified, the routes to which the FDA provides access to drug label content, and the accessibility of various details about drug labels containing genomic information is constantly changing. All of these variables affect the ability to translate knowledge contained in drug labels into a form suitable for electronic health record (EHR) frameworks (Dissertation Chapter 4).

Table 6. *Drugs for which the FDA has required, recommended, or provides information only on genetic testing for a biomarker (adapted from Ref. (US Food and Drug Administration, 2009)). See Chapter 4 for a more current list of drugs and associated biomarkers.*

Drug	Category of testing	Biomarker
Abacavir	Recommended	· HLA-B*5701 allele presence
Atomoxetine	Information only	· CYP2D6 Variants
Atorvastatin	Recommended	· Familial Hypercholestremia (deficiency, and/or mutation, of receptors for low density lipoprotein -LDL)
Azathioprine	Recommended	· TPMT Variants
Busulfan	Information only	· Philadelphia Chromosome-positive responders
Capecitabine	Information only	· DPD Deficiency
Carbamazepine	Recommended	· HLA-B*1502 allele presence
Celecoxib	Information only	· CYP2C9 Variants
Cetuximab	Required	· EGFR expression with alternate Context
Clopidogrel	Information only	· CYP2C19 Variants
Codine sulfate	Information only	· CYP2D6 (UM) with alternate context
Dasatinib	Required	· Philadelphia Chromosome- positive responders with alternate context
Eriotinib	Information only	· EGFR expression
Fluoxetine HCL	Information only	· CYP2D6 with alternate context
Imatinib mesylate	Information only	· C-KIT expression
Irinotecan	Recommended	· UGT1A1 Variants
Lenalidomide	Information only	· Deletion of Chromosome 5q(del(5q))
Maravironc	Required	· CCR5 - Chemokine motif receptor
Nilotinib	Information only	· UGT1A1 variants with alternate context
Panitumumab	Information only	· KRAS mutation (Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients with mCRC Containing KRAS Mutations)
Prasugrel	Information only	· CYP2C19 Variants with alternate context (no effect of Variants)
Primaquine	Information only	· G6PD Deficiency with alternate context
Rasburicase	Recommended	· G6PD Deficiency
Rifampin, isoniazid, and pyrazinamide	Information only	· NAT Variants
Trastuzumab	Required	· Her2/neu Over-expression
Tretinoin	Information only	· PML/RAR alpha gene expression (Retinoic acid receptor responder and non-responders)
Valproic acid	Recommended	· Urea Cycle Disorder (UCD) Deficiency
Voriconazole	Information only	· CYP2C19 Variants with alternate context
Warfarin	Recommended Recommended Recommended	· CYP2C9 Variants Alternate Context · Protein C deficiencies (hereditary or acquired) · Vitamin K epoxide reductase

In addition, there are ongoing changes being made to drug label. As of July 2011, there were 25 validated biomarkers for 71 drug listings on the most current updated website (US Food and Drug Administration, 2011). This is over twice the number of drugs that were listed on the FDA "Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels" in 2009 (See *Table 5*). The increasing prevalence of PGx biomarker information in drug labels emphasizes the evolving nature of evidence and the maturity of PGx knowledge in a clinical context.

There has also been growth in the number of medications for which the FDA identifies multiple validated biomarkers. In 2009, warfarin was the only drug listed by the FDA as having multiple validated biomarkers (i.e. CYP2C9, vitamin K epoxide reductase, subunit 1 (VKORC1)). Since then, multiple validated biomarkers have been associated with particular drugs including: cetuximab (i.e. epidermal growth factor receptor (EGFR), v-Ki-ras2 Kristen rat sarcoma viral oncogene homolog (KRAS)), imatinib (i.e. v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene (c-KIT), Philadelphia chromosome, platelet-derived growth factor receptor (PDGFR), F1P1L1-PDGFRα fusion protein), nilotinib (i.e. Philadelphia chromosome, UGT1A1), and panitumumab (i.e. EGFR, KRAS). All of the factors highlighted in this section affect the way in which PGx knowledge contained in drug labels can be made accessible in a computable manor.

3.2.2. Pilot use of high-throughput molecular technologies in a clinical context

Given increasing recognition by the FDA that multiple biomarkers impact the efficacy of particular drugs, high-throughput molecular technologies will likely become a primary source of genetic information to help with PGx decisions. Roche's AmpliChip CYP450 and Genomic Health's Oncotype DX are two existing technologies that have PGx uses. "Oncotype DX is a gene expression assay primarily used for breast cancer prognosis (Dobbe, Gurney, Kiekow, Lafferty, & Kolesar, 2008). However, the test also has PGx uses with respect to administering adjuvant chemotherapy in conjunction with tamoxifen (used for estrogen receptor-positive breast cancer tumors). The AmpliChip CYP450 test is a microarray-based PGx test that provides detection of gene variations in CYP2D6 and CYP2C19 genes. The assay aids in dosing decisions for drugs metabolized through these genes (e.g. tamoxifen) (Jain, 2005)." (Overby & Hachad, 2011). The use of these and other high-throughput molecular technologies is not widespread but has already begun.

Two institutions, St. Jude Children's Research Hospital (St. Jude) and Vanderbilt University Medical Center (VUMC), are utilizing commercial high-throughput molecular technologies in their personalized medicine initiatives. Both organizations provide approaches to communicate results generated by these technologies to care providers and are made available in the electronic health record with clinical decision support to aid with making prescribing decisions. Technologies include the Affymetrix DMET™ and Illumina VeraCode® chips designed primarily for use in PGx studies.

The DMET™ chip is being used by St. Jude in their PG4KDS project that aims to migrate array-based pharmacogenetic tests from the laboratory into routine patient care, to be available preemptively (St. Jude Children's Research Hospital, 2011a). The primary research objective is to estimate the proportion of patients who have high-risk or actionable pharmacogenetic results entered in their EHR decision support, a secondary object is to incorporate CDS tools linking test results to medication use, and assess their level of utility. Currently, customized decision support is integrated with their local EHR. Specifically, a Pharmacogenetics tab has been added to patient records and for all clinically eligible genotypes, a gene-specific consult with test interpretation is provided. In addition, genotypes identified as "high-risk" are entered into the Problem List. High-risk genotypes are linked to active decision support in the context of two phases of genetic testing: the pre-analytic phase (e.g. "You have ordered a medication for which genetic testing may be important") and the post-analytic phase (e.g. "Warning, this patient is a CYP2D6 poor metabolizer") (Relling, 2011). This EHR implementation is currently available for genes identified as Priority (Clinically Eligible) genes including Thiopurine Methyltransferase (TPMT) and Cytochrome P450 2D6 (CYP2D6) (St. Jude Children's Research Hospital, 2011b).

The Illumina VeraCode® chip is being used by VUMC in their Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment (PREDICT) project to screen 34 genes (185 SNPs) involved in drug absorption, distribution, metabolism and excretion. During Phase I of the project, a process to enable decision support to providers for drug dosing based on DNA findings has been developed. Clopidogrel metabolizer status is now identified from patient test results and presented to care providers at VUMC to guide therapy decisions (Hughes, 2010). The CDS implementation is a scalable process to allow expansion to other SNPs with associated decision support. As actionable items for dosing are

developed, they are able to connect decision support to the genotype data of patients included in the PREDICT database (currently around 1500 patients) and auto-populate the EHR over time. Phase II of the project involves mining electronic health records for particular ICD9 codes to identify "at risk" patient populations for preemptive genotyping (Vnencak-Jones, 2011).

The VUMC and St. Jude efforts are among the earliest example applications of CDS to support the use of patient PGx data in a clinical context, and have therefore encountered several challenges. Challenges include managing evolving genomic knowledge, managing complex data for clinical interpretation, and agreeing on methods for quality control. Even with pilot efforts such as these, adoption of high-throughput molecular technologies in a clinical context remains low. The work completed for this dissertation seeks to investigate how CDS could be implemented in a way that overcomes some previously identified barriers such that translation of PGx knowledge into clinical practice is better supported. For example, suggested areas to pursue to overcome barriers associated with managing evolving genomic knowledge and managing data for clinical interpretation are provided (e.g. providing modes for identifying updates to genomics knowledge that also carry provenance information) from a clinical organization perspective and from the perspective of organizations managing knowledge resources (e.g. clinical organizations importing data about knowledge resource updates, and organizations managing knowledge repositories enhancing access to these data) (See Dissertation Chapter 8).

3.2.3. Barriers to the uptake of high-throughput molecular technologies

Challenges highlighted in pilot uses of high throughput technologies are among the general barriers to broad and routine clinical use of PGx and other types of personalized medicine that other researchers have also identified (Deverka, Doksum, & Carlson, 2007). For example, "lack of clinical uptake may in part be due to the challenge of dealing with rapidly changing genetic knowledge. This reflects the need for accelerated translation of genomic knowledge into a form that will assist clinicians in their use of genomics-based molecular diagnostics. Basing prescribing decisions on genetic tests is also often beyond the present scope of medical training (Menasha, Schechter, & Willner, 2000), if not human cognitive ability. Moreover, most practitioners are unfamiliar with guidelines for use of genetic tests; and few are implemented, evaluated or enforced (Secretary's Advisory

Committee on Genetics, Health, and Society, 2008a). In the study conducted by Medco Health Solutions, Inc. and the American Medical Association, they found that only 10% of physician survey respondents believe they are adequately informed about PGx testing (Medco Health Solutions, & American Medical Association, 2009)." (Overby & Hachad, 2011) This thesis attempts to address the challenge of dealing with genetic knowledge that is evolving and of various levels of maturity by determining appropriate user interface design configurations for presenting clinical decision support (CDS) given particular characteristics of the knowledge (See Dissertation Chapter 5). In addition, this work investigates (in a simulated context) how practitioners' prior experience, knowledge and opinions of the use of patient genetic test results in a clinical context impact drug therapy individualization practices (See Dissertation Chapter 7).

CDS is implemented in a prototype system as a mode for providing PGx knowledge to support drug therapy individualization in a simulated context (See Dissertation Chapter 6). Given that individualizing drug therapy based on genetic tests is often beyond the scope of formal clinical training, CDS embedded in the EHR might provide a venue for educating physicians. To further support the importance of education in this context, "a 2003 study on barriers to the adoption of genetic counseling, testing and interpretation services concluded that educational programs are needed to facilitate implementation of genetic services across a broader set of physicians (Suther & Goodson, 2003)" (Overby & Hachad, 2011) indicating that education and guidance for healthcare professionals are key requirements for accurate use and interpretation of genetic tests for personalized medicine.

With a focus on the use of PGx knowledge for drug therapy individualization (as one form of personalized medicine), "the SACGHS report, *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges*, (Secretary's Advisory Committee on Genetics, Health, and Society, 2008b) suggests that guidance for physicians include support for understanding criteria for PGx genetic testing; and understanding use of results for patient care. CDS software that provides PGx knowledge (e.g. genetic testing protocols) at the point-of-care can aid in this process, and will become especially important for multi-gene pharmacogenomic protocols expected in the future (McKinnon, Ward, & Sorich, 2007)." (Overby & Hachad, 2011). Participation in translational research can help us to understand clinicians' acceptance and utilization of these forms of CDS in a clinical context, and to

better understand technical bottlenecks preventing translation of PGx knowledge from "bench" into clinical "bedside" practice.

3.3. TRANSLATIONAL RESEARCH TO SUPPORT THE UPTAKE OF PHARMACOGENOMICS KNOWLEDGE IN CLINICAL PRACTICE

3.3.1. Overview of T0-T4 translational research in general

Translational research is required to effectively move PGx discoveries and the resultant knowledge to evidence-based practice, and has been described as four iterative phases with feedback loops to allow integration of new PGx knowledge (Khoury et al., 2007). In summary, "Phase 0 (T0) translational research is discovery research; Phase I (T1) is research to develop a candidate health application; Phase II (T2) is research that evaluates a candidate application and develops evidence-based recommendations; Phase III (T3) is research that assesses how to integrate an evidence-based recommendation into clinical care and prevention; and Phase IV (T4) is research that assesses health outcomes and population impact." (Overby & Hachad, 2011). Findings from translational research can be particularly helpful for effectively implementing and diffusing healthcare interventions. For example, research to determine appropriate clinical practice guidelines for using data generated by singe gene/variant-based and high throughput molecular technologies (T3 research), and research to determine appropriate methods to deliver test results in a way that achieves effective communication in the context of drug therapy individualization (T4 research).

3.3.2. Translational research efforts to improve uptake of pharmacogenomics discoveries in clinical practice

While it is clear that translational research efforts have the potential to facilitate the translation of PGx discoveries into clinical practice, the number or research efforts in this area remains low. Nearly a decade ago, the Institute of Medicine (IOM) expressed concerns about the chasm between basic discoveries and translation to clinical and public health practice (Richardson, Berwick, & Bisgard, 2001). Even so, it has been estimated that no more than 3% of genomics research focuses on translational research that aim to validate genomic discoveries for use in practice (T2-T4 research) (Khoury et al., 2007).

In addition to the fact that only a small percentage of genomics research is translational, there is a barrier in terms of appropriate information resources to apply new genomics

knowledge (e.g. PGx knowledge bases). For example, the "lack of access to appropriate information necessary to support clinical decision-making hinders the ability to incorporate existing pharmacogenomic test results into clinical practice. In order for clinicians to adopt genomics-based molecular diagnostics such as those for which relevant content is provided for information in FDA drug labels, T3 and T4 research is required." (Overby & Hachad, 2011). As an example of the limitations of FDA drug labels, much of the information that is made available in labels about genomics-based molecular diagnostics does not provide guidance on what testing should be performed, for whom, and how test results should be interpreted (See Dissertation Chapter 5, (Overby, Tarczy-Hornoch, Hoath, Kalet, & Veenstra, 2010).

To further highlight limitations of FDA drug labels, "in 2006, a study reviewing PGx information in the drug labels and in the literature for the top 200 prescribed drugs showed that 71.3% of the drugs had published PGx information in the literature, but only 3 had drug labels with information sufficient to guide dosing (Zineh et al., 2006). T3 research on the most appropriate testing practices and patient management given test results is required to develop clinical practice guidelines and programs for incorporating genomics-based molecular diagnostics." (Overby & Hachad, 2011) Although the percentage of translational research pursuits to validate genomic discoveries remains low, current T3 research findings must be made accessible for developing clinical practice guidelines in the context of drug therapy individualization.

3.3.3. Approaches to providing access to T3 research findings

With a focus on T3 research, the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) has suggested providing access to T3 research findings in a way that enables applying information retrieval techniques. Information retrieval techniques might then be applied in a way that provides just-in-time access to knowledge to support evaluation and use of PGx test results for drug therapy individualization. Specifically, "SACGHS has recommended that a Web-based registry or repository of information be made available to provide up-to-date and accurate information for available genetic tests Secretary's Advisory Committee on Genetics, Health, and Society, 2008a). Providing these forms of support with PGx knowledge sources integrated at different points of need within a clinicians' workflow, have the potential to influence uptake of PGx tests in clinical practice. For example, a study

in 2004 describes a conceptual framework for evaluating PGx tests and consists of the following: 1) medical need; 2) clinical validity and utility of a test; 3) ease of use of the test; and 4) choice of treatments based on the results of the test (Shah, 2004)." (Overby & Hachad, 2011). PGx knowledge resources (including T3 research findings) that might support these points of evaluation (i.e. clinically meaningful resources) are described in the following section.

3.4. PHARMACOGENOMICS KNOWLEDGE RESOURCES CONTAINING T0-T4 RESEARCH FINDINGS

3.4.1. Stakeholder organizations

Given findings that low adoption of genetic tests is closely correlated with endorsements of patient groups and medical organizations (Yoo, 2009), the need for translational research (particularly T3 diffusion research) by both professional organizations and patient groups is evident. A list of organizations within the United States that are participating in T2-T4 evaluations regarding use of PGx data in clinical practice are shown in ***Table 7***. For each organization, the table presents information on relevant resources they create and provides examples of each. This non-exhaustive list illustrates both types of stakeholder organizations that are involved in the T2-T4 evaluations (a mix of regulatory, professional and payor organizations), and the types of resources that are created across organizations (types vary e.g. survey results, evidence synopses, recommendations; published primarily in the form of full-text publications or reports).

***Table** 7. Regulatory agencies, professional organizations and payor organizations within the United States that are participating in T2-T4 evaluations regarding use of PGx data in clinical practice (table expanded from Ref. (Overby & Hachad, 2011)) (continued on the next page)*

Organization	Resources	Examples
Regulatory organization - Centers for Disease Control (CDC), Office of Public Health Genomics, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) (Teutsch et al., 2009)	Evidence Reports	Can UGT1A1 Genotyping Reduce Morbidity and Mortality in Patients with Metastatic Colorectal Cancer with Irinotecan? (Palomaki, Bradley, Douglas, Kolor, & Dotson, 2009)
Regulatory organization - National Institutes of Health (NIH), National Institute of General Medical Sciences (NIGMS), Pharmacogenetic Research Network (PGRN), Clinical Pharmacogenetics Implementation Consortium (CPIC) (Relling & Klein, 2011)	Recommendations for implementing specific pharmacogenomic tests and practices	Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing (Relling et al., 2011). Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy (Scott et al., 2011).
Regulatory organization - US Food and Drug Administration (FDA), Interdisciplinary Pharmacogenomics Review Group (IPRG) (Goodsaid & Frueh, 2007)	Review Voluntary Exploratory Data Submissions (VXDS) Qualification of exploratory biomarkers into valid biomarkers Technical Recommendations	Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels (US Food and Drug Administration, 2011)
Regulatory organization - Agency for Healthcare Research and Quality (AHRQ)	Technology Assessments	Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia (Teruhiko Terasawa, Dahabreh, Castaldi, & Trikalinos, 2009)
Professional organization - American Society of Clinical Oncology (ASCO)	Clinical Practice Guidelines Provisional Clinical Opinion ASCO Guideline Endorsements Clinical Evidence Review	Testing for KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy (Allegra et al., 2009)
Professional organization - National Comprehensive Cancer Network (NCCN)	Clinical Practice Guidelines (NCCN Guidelines ™) NCCN Task Force Reports	ER and/or PgR testing in breast cancer (Allred et al., 2009).

Organization	Resources	Examples
Professional organization - College of American Pathologists (CAP)	Reference Resources and Publications	ER/PgR Guideline and Resources (CAP and ASCO joint guideline) (Hammond et al., 2010) HER2 Testing Guidelines (CAP and ASCO joint guideline) (Wolff et al., 2007)
Payor organization - Medco Health Solutions	Medco Research Institute, Pharmacogenomics Community	Warfarin study (Medco/Mayo Clinic) (Epstein et al., 2010) Physician survey (Medco/American Medical Association) (Medco Health Solutions, & American Medical Association, 2009) Physician Adoption Study (Medco Health Solutions, 2010)
Payor organization - CVS/Caremark Pharmacy Services	Pharmacogenomic testing program (in partnership with Generation Health Inc.)	Pegasys and Copegus (treatment of hepatitis C); Gleevec, Tasigna, Sprycel , Tarceva, and Tykerb (oncology drugs) (CVS Caremark, 2010)

3.4.2. Drug databases with pharmacogenomics knowledge

While T2-T4 translational research results are primarily prepared by stakeholder organizations in the form of publications and reports (e.g. summarizing findings across PGx studies), there are several examples of PGx knowledge resources for T0 and T1 translational research that provide primary research findings in a form that is more computer accessible. Freely available PGx resources including Chembank (Seiler et al., 2008), Drugbank (Wishart, 2008), PharmGED (Zheng et al., 2007), PharmGKB (Altman, 2007) and SuperCYP (Preissner et al., 2010) databases have architectures for representing knowledge such as curated facts from primary research articles (e.g. study details like population genotypes and diseases/phenotypes), drug/chemical compound information, and drug target/metabolizing enzyme information. A more detailed overview of the forms of knowledge represented in these resources is provided in Ref. (Overby & Hachad, 2011). While these resources provide PGx knowledge compiled from multiple sources in a computer accessible manner, much of the knowledge does not lend itself to providing evidence-based guidance given the variable maturity of the knowledge (i.e. more breadth than depth in content coverage).

3.4.3. Databases with evidence-based guidance on using genetic data use in clinical practice

There are a few examples of freely available databases that synthesis findings from T2 – T4 research from multiple sources (including knowledge produced by stakeholder organizations). Resources include "the GeneTests knowledge base (Pagon et al., 2002), Genetic Test Registry (Kuehn, 2010) (Khoury, Reyes, Gwinn, & Feero, 2010), the GAPP Knowledge Base (GAPP Knowledge Base), and the PLoS Currents: Evidence on Genomic Tests publication (Gwinn, Dotson, & Khoury, 2010). The GeneTests knowledge base provides an online laboratory directory (laboratories offering in-house molecular genetic testing, specialized cytogenetic testing, and biochemical testing for inherited disorders); an online genetic clinic directory (providers of genetic evaluation and counseling services); and provide geneReviews documents (contain clinical guidance in areas such as testing strategy, interpretation genetic test results, and genetic counseling). The Genetic Testing Registry, expected for public release in late 2011, will encourage providers of genetic tests to publically share information about the availability and utility of their tests; provide information on the locations of laboratories that offer particular tests; and facilitate genetic and genomic data-sharing for research and new scientific discoveries. The GAPP Knowledge Base, being developed by the Genomic Applications in Practice and Prevention Network (GAPPNet), is an online resource that provides access to information on applications of genomic research for use in public health and health care. Current features include the GAPPFinder (a searchable database of genetic tests in transition to practice), Evidence for Genomic Applications (an online, open access journal that links to published evidence reviews and recommendations), Evidence Aggregator (an application that facilitates searching evidence reports, systematic reviews, recommendations or guidelines in genetic tests and genomic applications), and Project Locator (an online database for archiving genomic translational research projects). The PLoS Currents: Evidence on Genomic Tests is an open access publication provided by the US Centers for Disease Control and Prevention (CDC) and the Public Library of Science (PLoS). The publication provides brief summaries of evidence for the clinical validity and clinical utility of genomic tests and is intended to complement other efforts described above." (Overby & Hachad, 2011). While these databases provide T2 - T4 genomic research evidence compiled form multiple resources,

some provide little information on PGx (e.g. the GeneTests knowledge base) and most provide knowledge in the form of full-text documents that require additional processing to be computer accessible (e.g. PLoS Currents Evidence on Genomic Tests).

3.5. Primary sources of pharmacogenomics knowledge explored in this work

In this work, a range of translational resources to determine requirements for a CDS model for incorporating PGx knowledge into EHRs to support drug therapy individualization are investigated. Resources spanning T0-T4 translational research that represent PGx knowledge in a way that the maturity of the knowledge can be evaluated (e.g. statistical significance of results is provided), and that are likely to provide clinically meaningful knowledge were selected. Specific resources explored in this work that synthesize T0-T2 resource findings include PharmGKB and e-PKgene. PharmGKB (www.pharmgkb.org) is an open source resource financially supported by NIH/NIGMS and managed at Stanford University (Altman, 2007). e-PKGene (www.pharmacogeneticsinfo.org) is a manually curated knowledge resource developed within the department of Pharmaceutics and the University of Washington (Hachad et al., 2011). T3-T4 resources that provide evidence-based synopses and guidelines that are explored include: Drug labels included in the FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels (US Food and Drug Administration, 2011), Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Relling & Klein, 2011), and the PLoS Currents: Evidence on Genomic Tests publications (Gwinn et al., 2010).

3.6. Summary

This chapter provides a baseline overview of pharmacogenomics knowledge resources that provide access to data for translational research and potentially for drug therapy individualization. Pharmacogenomics knowledge from resources described in this chapter vary in how knowledge is represented and in its maturity in a clinical context. This dissertation overall focuses on addressing gaps in our understanding of pharmacogenomics knowledge characteristics by translating pharmacogenomics knowledge from resources discussed in this chapter into the clinical domain, evaluating clinicians' acceptance and utilization of patient-specific pharmacogenomics knowledge, and investigating technical

bottlenecks preventing translation of phamacogenomics knowledge into clinical practice. This work overall is thus an example of the Phase III (T3) class of translational research that is needed to understand issues related to integrating interventions into existing clinical system infrastructures.

A subset of pharmacogenomics knowledge resources are investigated in the drug therapy individualization context by: (1) formally evaluating the maturity of pharmacogenomics knowledge contained in FDA drug labels that provide information about, recommendations for use, or require the use of genetic test results in the context of drug therapy individualization (Dissertation Chapter 4); (2) investigating characteristics of pharmacogenomics knowledge resources in order to better understand the requirements for translating knowledge into a form that can be incorporated into clinical decision support frameworks (Dissertation Chapter 5); and (3) evaluating the perceived usefulness of providing access to current pharmacogenomics knowledge resources to support drug therapy individualization in a simulated clinical care context (Dissertation Chapter 7).

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4. CHAPTER 4: CHARACTERIZING PHARMACOGENOMICS KNOWLEDGE RESOURCES (AIM 1)

4.1. INTRODUCTION

The previous chapter gives a baseline overview of current resources that provide pharmacogenomics knowledge and the potential for these resources to be made available via clinical decision support given the maturity of the knowledge. In this chapter, the details and results from a formal evaluation of the characteristics and the value of current pharmacogenomics knowledge in the clinical context are provided. The research question addressed in this chapter is: What are the characteristics and the value of current pharmacogenomics knowledge in the context of clinical decision support with an electronic health record? Related to the overarching aim of this research, answering this research question helps understand the steps needed to translate pharmacogenomics knowledge contained in various resources into a form that can be presented electronically in an electronic health record. As a logical next step to the work described in this Chapter, as described in the next Chapter, an evaluation of functional and user interface requirements for providing pharmacogenomics knowledge in the context of clinical decision support embedded in an electronic health record was performed. Quoted sections in this dissertation chapter (Chapter 4) are primarily borrowed from the publication titled "Feasibility of incorporating genomic knowledge into electronic medical records for pharmacogenomic clinical decision support," (Overby, Tarczy-Hornoch, Hoath, Kalet, & Veenstra, 2010) with permission from the publisher.

4.2. RELATED WORK AND SIGNIFICANCE

There are several resources containing potentially clinically relevant pharmacogenomics (PGx) knowledge (See Dissertation Chapter 3). In addition, clinical decision support (CDS) is already beginning to be applied in a pilot setting to address challenges to drug therapy individualization in a clinical setting (See Dissertation Chapter 3, Section 3.2.2). However, in order for CDS to be applied for drug therapy individualization on a broader scale, methods for characterizing and determining the value of the PGx knowledge in this context need to be

established. This work begins to address this need by determining the requirements for translating PGx knowledge into a form that can be incorporated into an EHR.

4.3. METHODS

4.3.1. Aim 1.1: Characterize the representation of knowledge in pharmacogenomics resources

An analysis of clinically relevant information contained in PGx knowledge resources was performed. FDA drug labels listed on the "Table of valid genomic biomarkers in the context of approved drug labels" (FDA biomarker-drug pairs) and PharmGKB were resources of particular focus in this sub-aim. Both resources were originally reviewed during September 2009 (US Food and Drug Administration, 2009). The evaluation of these resources was updated reflecting all FDA drug labels as of May 2011 and is reported in this dissertation. However, some methods of this particular sub-aim were unable to be applied for the most recent table of FDA biomarker-drug pairs due to the removal of primary literature citations in the latest version of the table (US Food and Drug Administration, 2011).

To characterize the representation of PGx knowledge contained in FDA drug labels and in PharmGKB the focus was on two aspects; (1) the degree of overlap of evidence coverage in FDA drug labels and within PharmGKB, and (2) the types of electronically available knowledge produced by the FDA and contained within the PharmGKB. To determine the evidence coverage for FDA drug labels and PharmGKB the following were identified: (a) the supporting primary literature citations for each FDA biomarker-drug pair; and (b) citations curated as containing evidence of the biomarker-drug relationship within the PharmGKB.

Thus work evaluated the types of available knowledge from FDA drug labels made electronically accessible from the DailyMed (http://dailymed.nlm.nih.gov) website was evaluated in this work. DailyMed is one of two electronic resources that facilitate access to FDA drug labels. The other resource is the FDA website, Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda), that provides search access to current and archived drug labeling and drug-approval reviews. In collaboration with the National Library of Medicine, the FDA provides access to the most recent labels submitted to the FDA via the DailyMed website. Labeling submitted after November 2005 conforms to the Structured Product Labeling (SPL) format (See Dissertation Chapter 2, Section 2.3.2).

The DailyMed online resource is focused on in this evaluation because it provides the most up-to-date labeling information.

Several forms of curated knowledge relevant to this research were identified in the PharmGKB database. Categories of curated knowledge as defined by PharmGKB include "categories of evidence, pathway evidence, variant evidence, genotype data, phenotype data, and clinical PGx section (Sangkuhl, Berlin, Altman, & Klein, 2008). The PGx literature is curated using five categories of evidence and standardized vocabularies of genes, drugs and diseases. These categories include: clinical outcome (CO); pharmacodynamics (PD); pharmacokinetics (PK); molecular and cellular functional assays (FA); and, genotype (GN). In the PGx literature, CO, PD, PK and FA are forms of phenotypic evidence. Pathway evidence includes knowledge of biochemical pathways associated with the use of a particular medication. Variant evidence includes knowledge of genetic variants associated with individual response to therapy. Genotype and phenotype data designate the existence of these types of data. Clinical PGx section designates drugs for which all related knowledge has been compiled within PharmGKB." (Overby et al., 2010). For each drug listed on the table of FDA biomarker-drug pairs, forms of curated knowledge defined by PharmGKB are catalogued.

For both PharmGKB and DailyMed, electronically available knowledge is classified as *encoded*, *tagged* or *computable*. A distinction can be made between these forms of knowledge, "encoded and tagged information may be described as computer accessible, and computable knowledge as computer-readable. An example of *tagged information* would be a wiki page that contains a table of contents. The information on the wiki page is free text, but tagged for particular sections identified in the table of contents. Resources containing encoded information utilize controlled vocabularies in order to add structure to information and facilitate more complex computer access. For example, PubMed contains *encoded information* about publication authors, titles, journals, etc. A user is then able to specify encoded data as search terms and execute complex queries across all publications. *Computable knowledge* is knowledge described in a language for communication with the computer. If knowledge is computable, then it can be described as an algorithm or rule, and implemented as such in a computer program or application." (Overby et al., 2010). Given the characteristics identified in this sub-aim, the feasibility of translating knowledge

contained in PhamGKB and DailyMed was then assessed.

4.3.2. *Aim 1.2: Assess the feasibility of translating pharmacogenomics knowledge into computable form*

FDA drug labels are a rich source of information to guide drug therapy decisions and were therefore the focus of this sub-aim investigating the feasibility of translating PGx knowledge into a computable form, suitable to code within an EHR framework. In the original evaluation (conducted September 2009), 28 drug labels of the FDA biomarker-drug pairs were investigated by first, identifying passages containing clinically relevant knowledge; and second (wherever feasible) translating passages into an if-then rule representation. Given that PGx knowledge contained in drug labels are primarily in free-text form, these steps were performed manually. In addition, PGx knowledge was clustered into general categories and appropriate user interface (UI) presentations were determined. A general category may be, for example, "knowledge that provides support for determining 'who should be screened for a genetic variant prior to administering a particular treatment.' UI presentation types characterize how actionable a THEN statement is, of an IF-THEN rule. Types include: *information only*; *recommendation*; and, *warning*. A statement is classified as *information only* if no direct action is specified within the statement, or actions are specified using language with a low degree of certainty (i.e. might, may, could). Conversely, a statement is classified as a *recommendation* if a clear action is specified using language with a medium to high degree of certainty (i.e. should, will, are, is, must, was, do); and as a *warning* if potential consequences are specified (language may be of any degree of certainty). In cases where a statement falls into multiple categories, a choice is made according to the following prioritization: *warning*, then *recommendation*, then *information*. That is, if a statement is identified as being both a recommendation and a warning, it is classified as a warning. Similarly, if a statement is identified as both information only and a recommendation, it is classified as a recommendation." (Overby et al., 2010). The designated classifications refer to the type of UI presentation that is most appropriate given how actionable the IF-THEN rule.

This evaluation was updated in this dissertation to include drug labels for the 71 FDA biomarker-drug pairs listed as of May 2011 (up from the 28 listed in September 2009). In the

updated evaluation, passages containing gene specific keywords in DailyMed drug label webpages were extracted in an automated fashion using a Perl script (rather than manually extracted as previous). As previously, passages were manually translated into one or more if-then rules. An example of an extracted passage and its translated if-then rules are as follows:

Passage from mercaptopurine FDA drug label (DailyMed HTML page)

- Most patients with heterozygous TPMT deficiency tolerated recommended PURINETHOL doses, but some require dose reduction. Genotypic and phenotypic testing of TPMT status are available. (See CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections.)

Manually translated IF-THEN rules

- IF patient is [being considered for] taking mercaptopurine AND patient is heterozygous TPMT deficient THEN most patients with heterozygous TPMT deficiency tolerated recommended PURINETHOL doses, but some require dose reduction.
- IF patient is [being considered for] taking mercaptopurine THEN genotypic and phenotypic testing of TPMT status are available.

In addition, two approaches were applied to cluster PGx knowledge contained in FDA drug labels into general categories: 1) sub categories were applied to the entire rule (as previous, e.g. "Advice related to testing"), and 2) sub categories were applied to the pre-condition (IF statement) and post- condition (THEN statement) of a rule. For example, the rule "IF patient is [being considered for] taking mercaptopurine THEN genotypic and phenotypic testing of TPMT status are available," had pre-condition: *Drug* and post-condition: *Testing is available*. All other methods were applied to the 71 FDA drug labels as previously described.

4.4. RESULTS

4.4.1. Aim 1.1: Representation of knowledge in pharmacogenomics resources

4.4.1.1. Evidence coverage by FDA drug labels and PharmGKB

The original evaluation of 28 drugs listed on the "Table of valid genomic biomarkers in the context of approved drug labels" (FDA biomarker-drug pairs) (US Food and Drug Administration, 2009) is reported in this sub-aim. Methods of this sub-aim were unable to be applied for the most recent table of FDA biomarker-drug pairs due to the removal of primary literature citations in the latest version of the table. Overall in the 2009 evaluation, there was little overlap between citations containing evidence of biomarker-drug relationships. For example, "there were 185 articles containing evidence listed on the FDA website and 268 articles with evidence of biomarker-drug relationships of interest contained in the PharmGKB. Only 28 (6.4%) of the total set of articles containing evidence were found in both the PharmGKB database and on the FDA website. Of the 28 articles contained in both resources, eleven (39%) were not designated as containing evidence of the particular drug-biomarker relationship of interest in PharmGKB." (Overby et al., 2010). PharmGKB might serve as a good source to supplement FDA approved drug label evidence given that there were 240 articles curated by PharmGKB as relevant to FDA drug-biomarker pairs that are not cited by the FDA. The ability of PharmGKB to supplement knowledge contained in the FDA drug labels can be estimated by investigating the mismatches further. The eleven articles contained in both resources, but that were not designated as containing evidence of the drug-biomarker relationship of interest in PharmGKB are shown in *Table 8*. The table includes citations for which there was a mismatch between the FDA "Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2009) and the PharmGKB drug-biomarker relationship classifications. The first column is a list of references (PMIDs), the second column is the drug-biomarker relationship for which the reference listed in the first column was identified as providing evidence for FDA drug labels (FDA drug-biomarker relationship column), and the third column contains gene, drug and disease associations for the references that were identified by PharmGKB (PharmGKB Gene/Drug/Disease Relationships column). Of the eleven mismatches, four indicated the same biomarker across the two resources, but PharmGKB does not curate the associated drug

denoted by the FDA. This indicates partial mismatchs, rather than a complete mismatch (partial or complete mismatch is indicated in column 4 of *Table 8*, shown on the next page). In addition, of the seven complete mismatches, three do not indicate any associated medications. These two findings suggest that PharmGKB curation efforts may be more gene-focused than medication-focused. PharmGKB also provides no gene, drug or disease curations for three publications. These may be articles that were identified as containing PGx knowledge, but the curation of these articles were missed or has not yet occurred. This finding indicates that there may be other instances of publications that were missed for curation and are therefore not considered in this evaluation. In summary, the degree of overlap between publications cited by the FDA and publications curated by PharmGKB determined in this evaluation may be an overestimate due to the existence of articles with missing curations. In addition, PharmGKB may have a more gene-centric process to curating publications. This suggests that publications curated for FDA biomarker-gene pairs by PharmGKB might require an additional level of evaluation of its relevance to drug therapy individualization before being designated as providing supplemental knowledge.

Table 8. *Mismatched evidence of drug-biomarker relationships contained on the FDA "Table of valid genomic biomarkers in the context of approved drug labels" and within PharmGKB.*

References (PMIDs)	FDA drug-biomarker relationship (Accessed 9/2009)	PharmGKB Gene/Drug/Disease Relationships (Accessed 9/2009 & 8/2011)	Mismatch (partial or complete)
11259359	***Drug***: Rifampin, isoniazid, and pyrazinamide ***Biomarker***: NAT variants	UGT1A1, Irinotecan, Neoplasms	Complete
15037866	***Drug***: Celecoxib ***Biomarker***: CYP2C9	CYP2C19, antidepressants, Depression	Complete
15037866	***Drug***: Fluoxetine HCL ***Biomarker***: CYP2D6	CYP2C19, antidepressants, Depression	Complete
15828850	***Drug***: Fluoxetine HCL ***Biomarker***: CYP2D6	ABCB1, CYP3A4, CYP3A5, imatinib	Complete
16336752	***Drug***: Cetuximab ***Biomarker***: EGFR expression	None listed	Complete
17900275	***Drug***: Prasugrel ***Biomarker***: CYP2C19	CYP2C19, clopidogrel	Partial
17906972	***Drug***: Warfarin ***Biomarker***: Vitamin K epoxide reductase (VKORC1)	None listed	Complete
18085998	***Drug***: Carbamazepine ***Biomarker***: HLA-B*1502 allele presence	None listed	Complete
18192896	***Drug***: Carbamazepine ***Biomarker***: HLA-B*1502 allele presence	HLA-B, allopurinol, lamotrigine, sulfamethoxazole, Steven-Johnson Syndrome	Partial
19108880	***Drug***: Clopidogrel ***Biomarker***: CYP2C19	CYP2C19, Myocardial Infarction	Partial
19429918	***Drug***: Prasugrel ***Biomarker***: CYP2C19	CYP2C19, clopidogrel	Partial

The 240 publications in PharmGKB that do not overlap with those listed by the FDA were also investigated further to determine representation of categories of evidence for the biomarker-drug relationships. The distribution of "evidence categories" for these publications was CO – 49(19%); PD – 80(32%); PK – 141(56%); FA – 27(11%); and, GN – 171(68%). Percentages do not total 100% because some publications cover multiple categories of evidence. These designations may be useful to determine the relevance of publication contents to drug therapy individualization and its potential to enhance knowledge

contained in FDA drug labels. For example, articles curated for both "GN" (genotype information) and "CO" (clinical outcomes) may be most promising to consider. In addition to providing access to curated publications, PharmGKB also provides electronic access to evidence summaries that might be more immediately applicable to drug therapy individualization. Both PharmGKB and DailyMed were investigated further to characterize the forms of electronic knowledge they provide that might support drug therapy individualization.

4.4.1.2. Electronically available knowledge in DailyMed and PharmGKB

Resources were further characterized by investigating the forms of electronically available knowledge in DailyMed (i.e. FDA drug label content) and PharmGKB. Drug labels for all but one drug evaluated in this work (telaprevir) were available electronically from DailyMed. The full list of drugs and associated biomarkers investigated in this work is shown in *Table 9* (shown on the next page). The first two columns include the list of 71 drugs and valid biomarkers in the context of approved drug (US Food and Drug Administration, 2011). The third column includes information about the last drug label revision at the time of the most recent evaluation (according to Drugs@FDA). The fourth column indicates the date each drug label was accessed from DailyMed for evaluations related to this dissertation work. This table illustrates the evolving nature of knowledge contained in FDA drug labels. Namely, the last date of revision for 28 drug labels evaluated in this work occurred following the original evaluation performed in September 2009 (which was one of the stimuli for updating the analysis for all 71 drugs). There are also more instances where the drug label containing the latest revision was available on the DailyMed website but not on the Drugs@FDA website (e.g. protriptyline, quinidine, and thioridazine), then the other way around (e.g. telaprevir). This further justifies the decision to focus on drug labels provided on the DailyMed website.

Table 9. *FDA drug labels and associated biomarkers investigated (Note: this table is also on the next two pages)*

FDA drug labels	Biomarker(s)	Date of last revision at time of most recent evaluation (Source: Drugs@FDA, unless otherwise specified)	Date accessed for most recent evaluation (Source: DailyMed, unless otherwise specified)
Abacavir	HLA-B*5701	12/14/2008	9/2009
Aripiprazole	CYP2D6	12/1/2010	1/24/2011
Arsenic Trioxide	PML/RAR(alpha) translocation	7/23/2010	1/24/2011
Atomoxetine	CYP2D6	6/3/2009	9/2009
Atorvastatin	LDL receptor	6/17/2009	9/2009
Azathioprine	TPMT	7/9/2008	9/2009
Busulfan	Philadelphia chromosome	12/24/2003	9/2009
Capecitabine	DPD	2/4/2011	2/9/2011
Carbamazepine	HLA-B*1502	4/3/2009	9/2009
Carvedilol	CYP2D6	1/6/2011	1/24/2011
Celecoxib	CYP2C9	12/31/2008	9/2009
Cetuximab (1)	EGFR	7/22/2009	9/2009
Cetuximab (2)	KRAS	7/22/2009	1/24/2011
Cevimeline	CYP2D6	12/8/2006	1/24/2011
Chloroquine	G6PD	6/12/2009 (06/13/2003 available online)	2/2/2011
Clopidogrel	CYP2C19	2/1/2011	2/9/2011
Clozapine	CYP2D6	12/1/2010	1/24/2011
Codine sulfate	CYP2D6	7/16/2009	9/2009
Dapsone	G6PD	3/26/2009	1/24/2011
Dasatinib	Philadelphia chromosome	5/21/2009	9/2009
Dextromethorphan and Quinidine	CYP2D6	10/29/2010	1/24/2011
Diazepam	CYP2C19	9/15/2005	1/24/2011
Doxepin	CYP2D6	3/17/2010	1/24/2011
Drospirenone and Ethinyl Estradiol	CYP2C19	4/7/2010	2/2/2011
Erlotinib	EGFR	4/27/2009	9/2009
Esomeprazole	CYP2C19	9/3/2010	1/24/2011
Fluorouracil	DPD	12/16/2003	7/14/2011
Fluoxetine and Olanzapine	CYP2D6	12/1/2010	2/2/2011
Fluoxetine HCL	CYP2D6	1/30/2009	9/2009
Fulvestrant	Estrogen receptor	5/17/2011	7/14/2011
Gefitinib	EGFR	6/17/2005	2/2/2011
Imatinib (1)	C-KIT	5/27/2009	9/2009
Imatinib (2)	Philadelphia chromosome	5/27/2009	2/2/2011
Imatinib (3)	PDGFR (platelet-derived growth factor receptor) gene re-arrangements	4/1/2011	7/14/2011
Imatinib (4)	FIP1L1-PDGFRα fusion	4/1/2011	7/14/2011
Irinotecan	UGT1A1	5/14/2010	2/9/2011

FDA drug labels	Biomarker(s)	Date of last revision at time of most recent evaluation (Source: Drugs@FDA, unless otherwise specified)	Date accessed for most recent evaluation (Source: DailyMed, unless otherwise specified)
Isosorbide and Hydralazine	NAT1; NAT2	6/23/2005	2/2/2011
Lapatinib	Ner2/neu	1/29/2010	2/2/2011
Lenalidomide	Deletion of Chromosome 5q	2/23/2009	9/2009
Maraviroc	CCR5	8/6/2007	9/2009
Mercaptopurine	TPMT	7/15/2004	2/2/2011
Metoprolol	CYP2D6	3/19/2010	2/2/2011
Nelfinavir	CYP2C19	4/26/2010	2/2/2011
Nilotinib (1)	Philadelphia chromosome	1/14/2011	2/2/2011
Nilotinib (2)	UGT1A1	1/14/2011	2/9/2011
Panitumumab (1)	EGFR	7/17/2009	2/2/2011
Panitumumab (2)	KRAS	7/17/2009	9/2009
Peginterferon alfa-2b	Interferon-lambda-3 (IL-28b)	3/29/2011	7/14/2011
Prasugrel	CYP2C19	7/10/2009	9/2009
Primaquine	G6PD	?	9/2009
Propafenone	CYP2D6	10/29/2010	2/2/2011
Propranolol	CYP2D6	12/14/2010	2/2/2011
Protriptyline	CYP2D6	02/2010 (DailyMed)	2/2/2011
Quinidine	CYP2D6	02/2007 (DailyMed)	2/2/2011
Rabeprazole	CYP2C19	9/3/2010	2/2/2011
Rasburicase	G6PD	9/10/2007	9/2009
Rifampin, isoniazid, and pyrazinamide	NAT	12/18/2008	9/2009
Risperidone	CYP2D6	12/1/2010	2/2/2011
Sodium Phenylacetate and Sodium Benzoate	NAGS; CPS; ASS; OTC; ASL; ARG	2/17/2005	2/2/2011
Sodium Phenylbutyrate	NAGS; CPS; ASS; OTC; ASL; ARG	3/31/2009	2/2/2011
Tamoxifen	Estrogen receptor	3/9/2006	2/2/2011
Telaprevir	Interferon-lambda-3 (IL-28b)	5/23/2011	7/14/2011 (No DailyMed version to download)
Terbinafine	CYP2D6	02/12/2010 (3/17/2000 available online)	2/2/2011
Tetrabenazine	CYP2D6	12/01/2009 (08/15/2008 available online)	2/2/2011
Thioguanine	TPMT	11/15/2004	2/2/2011
Thioridazine	CYP2D6	09/2010 (DailyMed)	2/2/2011
Timolol	CYP2D6	6/8/2007	2/2/2011
Tiotropium	CYP2D6	12/17/2009	2/2/2011
Tolterodine	CYP2D6	4/8/2009	2/2/2011
Tositumomab	CD20 antigen	12/22/2004	7/14/2011
Tramadol and	CYP2D6	9/9/2009	2/2/2011

FDA drug labels	Biomarker(s)	Date of last revision at time of most recent evaluation (Source: Drugs@FDA, unless otherwise specified)	Date accessed for most recent evaluation (Source: DailyMed, unless otherwise specified)
Acetominophen			
Trastuzumab	Her2/neu	1/8/2008	9/2009
Tretinoin	PML/RAR alpha	7/1/2008	9/2009
Valproic acid	UCD Deficiency -> NAGS; CPS; ASS; OTC; ASL; ARG	04/23/2009 (10/13/2006 available online)	2/2/2011
Venlafaxine	CYP2D6	1/6/2010	2/2/2011
Voriconazole	CYP2C19	5/30/2008	9/2009
Warfarin (1)	CYP2C9	1/22/2010	2/9/2011
Warfarin (1)(2)(3)	CYP2C9, Protein C, VKORC1	8/16/2007	9/2009
Warfarin (2)	VKORC1	1/22/2010	7/18/2011

DailyMed contains electronically available knowledge in which drug label sections are tagged (See *Figure 1* on the next page), but data and knowledge are still in free text (See *Figure 2* on the next page). *Figure 1* shows a screenshot of the Mercaptopurine drug label from DailyMed with tagging for drug label sections circled. The arrow within the figure highlights the "Precautions" tab, which when clicked the page jumps to that portion of the drug label (See *Figure 2*). *Figure 1* and *Figure 2* illustrate functionalities facilitated by tagging knowledge for particular sections of the drug label. Specifically, tagging knowledge supports the ability to jump to particular portions of the drug label within a webpage. Given that the FDA" Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2009) now lists the label sections with PGx information, tagged knowledge might also be used to automate the inclusion of specific drug label sections in a CDS system.

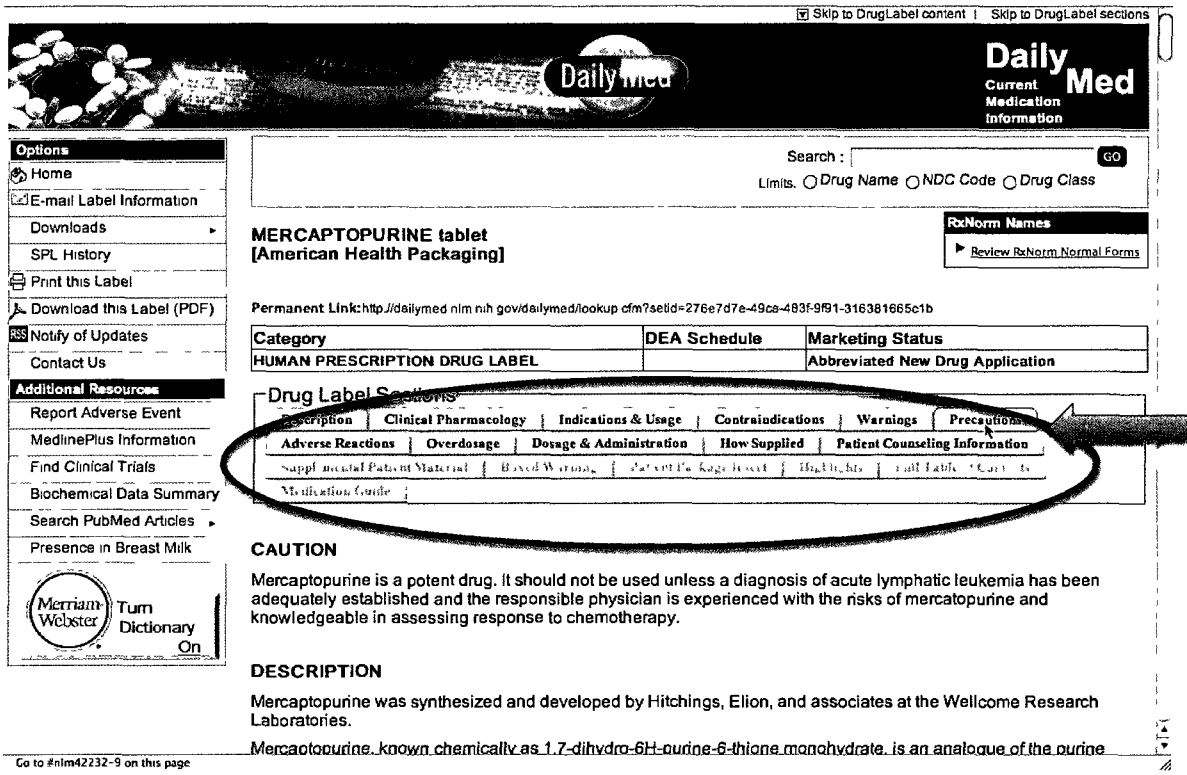


Figure 1. *Screen shot of the Mercaptopurine drug label accessed from DailyMed (http://dailymed.nlm.nih.gov). The tagged drug label sections are shown in the blue circle callout. The blue arrow points to the "Precaution" drug label section. When clicked, this website navigates to the "Precaution" section of the drug label (See* ***Figure 2****).*

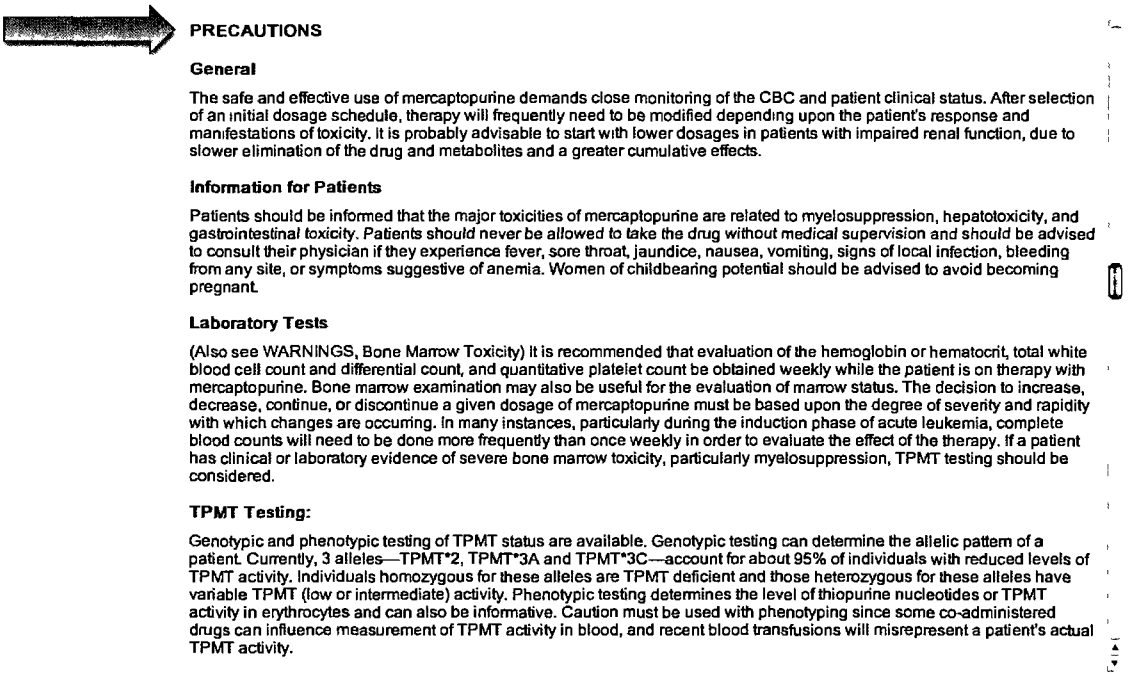


Figure 2. *Screen shot the "Precautions" section of the Mercaptopurine drug label accessed from DailyMed (http://dailymed.nlm.nih.gov).*

In addition to DailyMed drug sections, PharmGKB provides encoded knowledge relevant to drugs that could provide a useful source of PGx knowledge for drug therapy individualization. *Table 10* displays types of knowledge available for the drugs of interest in this work (updated 7/2011). The first column lists the drug names and the following columns are categories of evidence including: drug pathway, annotated PGx gene, important variants, important haplotypes, genotype data, phenotype data, and clinical PGx section.

Table 10. *Types of knowledge in PharmGKB. "x" indicates the inclusion of a particular category of evidence (columns 2 – 6) for a particular medication (column 1) in PharmGKB. "Drug specific" and "Biomarker specific" indicate the focus of the initial keyword search within PharmGKB (e.g. A search for curated pathway evidence involves performing a keyword search for the drug of interest, then filtering for pathways). The super-script (i.e. "x[a]") indicates that the drug (for biomarker-specific searches) and at least one biomarker (for drug-specific searches) are associated with a particular category of evidence (e.g. if there is drug-specific curated pathway evidence involving the biomarker of interest "x[a]" is shown, if not "x" is shown). Other limitations are indicated in parentheses. "External link only" specifies that PharmGKB has not provided the evidence internally, but does provide a link out to another resource containing the indicated category of evidence. A medication name is specified in parentheses if particular categories of evidence are available for a part of a combined drug regimen (e.g. qunidine for dextromethorphan and quinidine). Note: table is on next two pages.*

Drug, biomarker	drug pathway (drug specific)	annotated PGx genes (biomarker specific)	important variants (biomarker specific)	important haplotype information (biomarker specific)	genotype data (drug specific)	phenotype data (drug specific)	clinical PGx section (drug specific)
Abacavir, HLA*5701							x[a]
Aripiprazole, CYP2D6		x	x	x			
Arsenic Trioxide, PML/RARα	x				x	x	
Atomoxetine, CYP2D6		x[a]	x[a]	x[a]			
Atorvastatin, LDL receptor	x						x[a]
Azathioprine, TPMT	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]
Busulfan, Philadelphia Chromoxome							x[a]
Capecitabine, DPD	x[a]	x[a]	x[a]				x[a]
Carbamazepine, HLA*1502	x						x[a]
Carvedilol, CYP2D6	x	x[a]	x[a]	x[a]			
Celecoxib, CYP2C9	x[a]	x[a]	x[a]	x[a]			x[a]
Cetuximab, EGFR; KRAS	x[a]						x[a]
Cevimeline, CYP2D6		x	x	x			
Chloroquine, G6PD	x (external link only)						x[a]
Clopidogrel, CYP2C19	x[a]	x[a]	x[a]	x[a]			x[a]
Clozapine, CYP2D6		x[a]	x[a]	x[a]			
Codeine, CYP2D6	x[a]	x[a]	x[a]	x[a]			

Drug, biomarker	drug pathway (drug specific)	annotated PGx genes (biomarker specific)	important variants (biomarker specific)	important haplotype information (biomarker specific)	genotype data (drug specific)	phenotype data (drug specific)	clinical PGx section (drug specific)
Dapsone, G6PD					x	x	x[a]
Dasatinib, Philadelphia chromosome							x[a]
Dextromethorphan and Quinidine, CYP2D6		x[a]	x[a]	x[a]	x (Quinidine)	x (Quinidine)	
Diazepam, CYP2C19	x[a]	x	X	x			
Doxepin, CYP2D6		x[a]	x[a]	x[a]			
Drospirenone and Ethinyl Estradiol, CYP2C19	X (external link only, Ethinyl Estradiol)	x	X	x			x[a]
Erlotinib, EGFR	x[a]						x[a]
Esomeprazole, CYP2C19		x	X	x			x[a]
Fluorouracil, DPD	x[a]	x[a]	x[a]		x	x	x[a]
Fluoxetine and Olanzapine, CYP2D6	x[a] (Fluoxetine)	x[a]	x[a]	x[a]		x (Fluoxetine)	x[a]
Fluoxetine HCL, CYP2D6	x[a]	x[a]	x[a]	x[a]		x	
***Fulvestrant*, Estrogen receptor**							x[a]
Gefitinib, EGFR	x[a]						x[a]
Imatinib, c-KIT; Philadelphia chromosome; PDGFR; FIP1L1-PDGFRα fusion	x[a]	x					x[a]
Irinotecan, UGT1A1	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]
Isosorbide and Hydralazine, NAT1; NAT2							
Lapatinib, Her2/neu	X						x[a]
Lenalidomide, Deletion of Chromosome 5q							x[a]
Maraviroc, CCR5							x[a]
Mercaptopurine, TPMT	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]
Metoprolol, CYP2D6	X	x[a]	x[a]	x[a]			
Nelfinavir, CYP2C19		x[a]	x[a]	x[a]			x[a]
Nilotinib, Philadelphia chromosome; UGT1A1		x (UGT1A1)	x (UGT1A1)	x (UGT1A1)			x[a]
Panitumumab, EGFR; KRAS							x[a]
Peginterferon alfa-2b, IL-28b							
Prasugrel, CYP2C19		x	X	x			
Primaquine, G6PD							
Propafenone, CYP2D6	x	x[a]	x[a]	x[a]			x[a]
Propranolol, CYP2D6	x	x	X	x			x[a]

Drug, biomarker	drug pathway (drug specific)	annotated PGx genes (biomarker specific)	important variants (biomarker specific)	important haplotype information (biomarker specific)	genotype data (drug specific)	phenotype data (drug specific)	clinical PGx section (drug specific)
Protriptyline, CYP2D6		x	x	x			
Quinidine, CYP2D6	x	x	x	x	x	x	x[a]
Rabeprazole, CYP2C19		x[a]	x[a]	x[a]			x[a]
Rasburicase, G6PD							x[a]
***Rifampin*, isoniazid, and pyrazinamide, NAT**	x				x	x	
Rifampin, *isoniazid*, and pyrazinamide, NAT	x (external link only)						
Rifampin, isoniazid, and *pyrazinamide*, NAT							
Risperidone, CYP2D6		x[a]	x[a]	x[a]			x[a]
Sodium Phenylacetate and Sodium Benzoate, NAGS; CPS; ASS; OTC; ASL; ARG							x[a]
Sodium Phenylbutyrate, NAGS; CPS; ASS; OTC; ASL; ARG							x[a]
Tamoxifen, Estrogen receptor	x[a]				x[a]	x[a]	x[a]
Telaprevir, IL-28b							
Terbinafine, CYP2D6		x	x	x			x[a]
Tetrabenazine, CYP2D6		x	x	x	x	x	x[a]
Thioguanine, TPMT	x[a]	x[a]	x[a]	x[a]			x[a]
Thioridazine, CYP2D6	x	x[a]	x[a]	x[a]		x	x[a]
Timolol, CYP2D6		x[a]	x[a]	x[a]			x[a]
Tiotropium, CYP2D6		x	x	x			x[a]
Tolterodine, CYP2D6		x[a]	x[a]	x[a]			x[a]
Tositumomab, CD20 antigen							x[a]
Tramadol and Acetaminophen, CYP2D6	x[a] (Acetaminophen)	x	x	x			x[a]
Trastuzumab, Her2/neu							x[a]
Tretinoin, PML/RARα	x (external link only)						x[a]
Valproic acid, NAGS; CPS; ASS; OTC; ASL; ARG							x[a]
Venlafaxine, CYP2D6		x	x	x			x[a]
Voriconazole, CYP2C19		x	x	x			x[a]
Warfarin, CYP2C9, VKORC1	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]

The categories of evidence described in *Table 10* include encoded knowledge of gene-drug-disease relationships curated via literature review (See *Figure 3* on the next page). However, with the exception of genotype and phenotype data, evidence is provided in the form of textual summaries. Drug pathway summaries include descriptions of drug targets and mechanism of action or pharmacodynamics (Eichelbaum, Altman, Ratain, & Klein, 2009). Annotated PGx gene, important variants, and important haplotype summaries are available for genes designated by PharmGKB as "Very Important Phamracogenes" (VIP genes) (Eichelbaum et al., 2009). These are genes that have proven to be important contributors in the response to one or more drugs. Variants in VIP genes have also been shown to impact drug response phenotypes. Annotated PGx gene, important variant and important haplotype summaries provide descriptions about the significance of the gene, gene variants and gene haplotypes (respectively), as well as provide links to the literature and lists of relevant drugs, diseases, and side effects (See *Figure 3*).

PharmGKB also provides an infrastructure for handling whole genome data (Hernandez-Boussard et al., 2008). Phenotype datasets that are identified as high-impact (typically published in peer-review journals) are associated with genotype data, include curated annotations, and are downloadable (See *Figure 4* on the next page). Other phenotype datasets receive minimal oversight at PharmGKB. The clinical PGx section evidence for a drug includes a summary of PGx information in the context of the FDA-approved drug label (e.g. whether FDA provides information, recommends or requires genetic testing), and provides links to related PhamrGKB resource (e.g. drug information, variants listed in the drug label, allele frequency information, etc.).

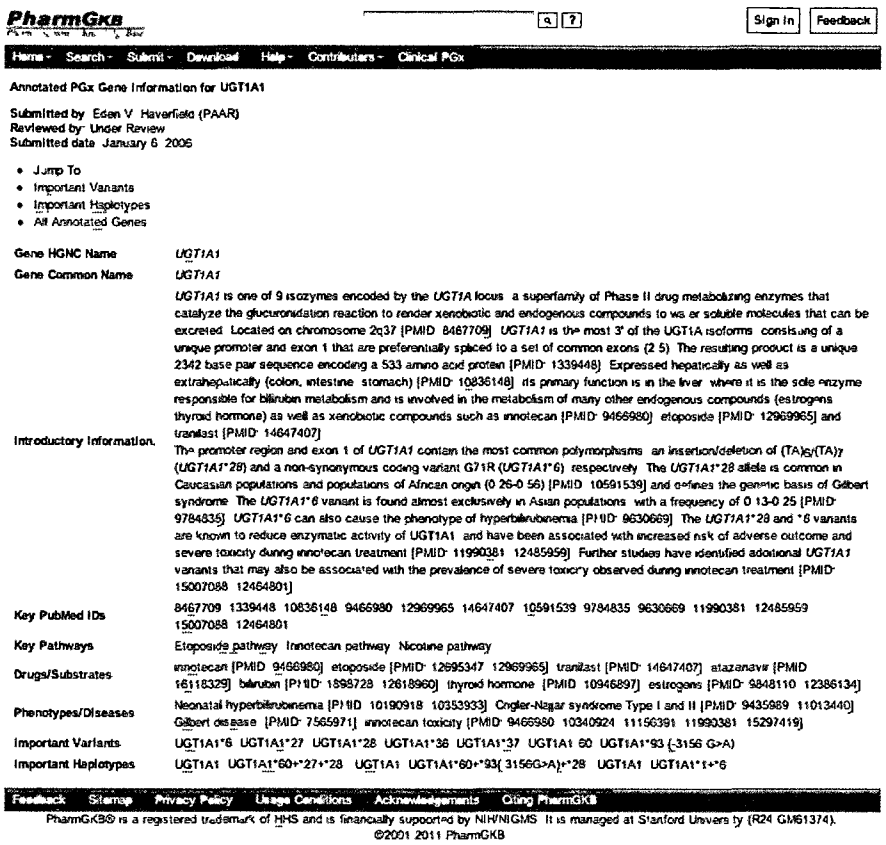


Figure 3. *Screen shot of the PharmGKB annotated PGx Gene summary for UGT1A1 Links to relevant publications, pathways, drugs, phenotypes, variants and haplotypes highlight the forms of encoded knowledge captured in PharmGKB The "introductory information" section provides a primarily free-text summary of the UGT1A1 gene*

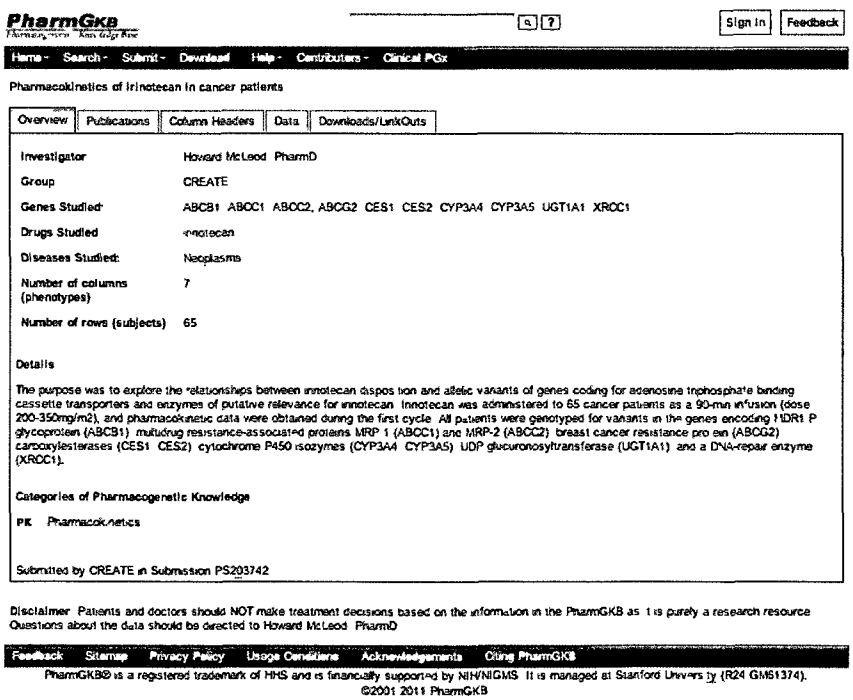
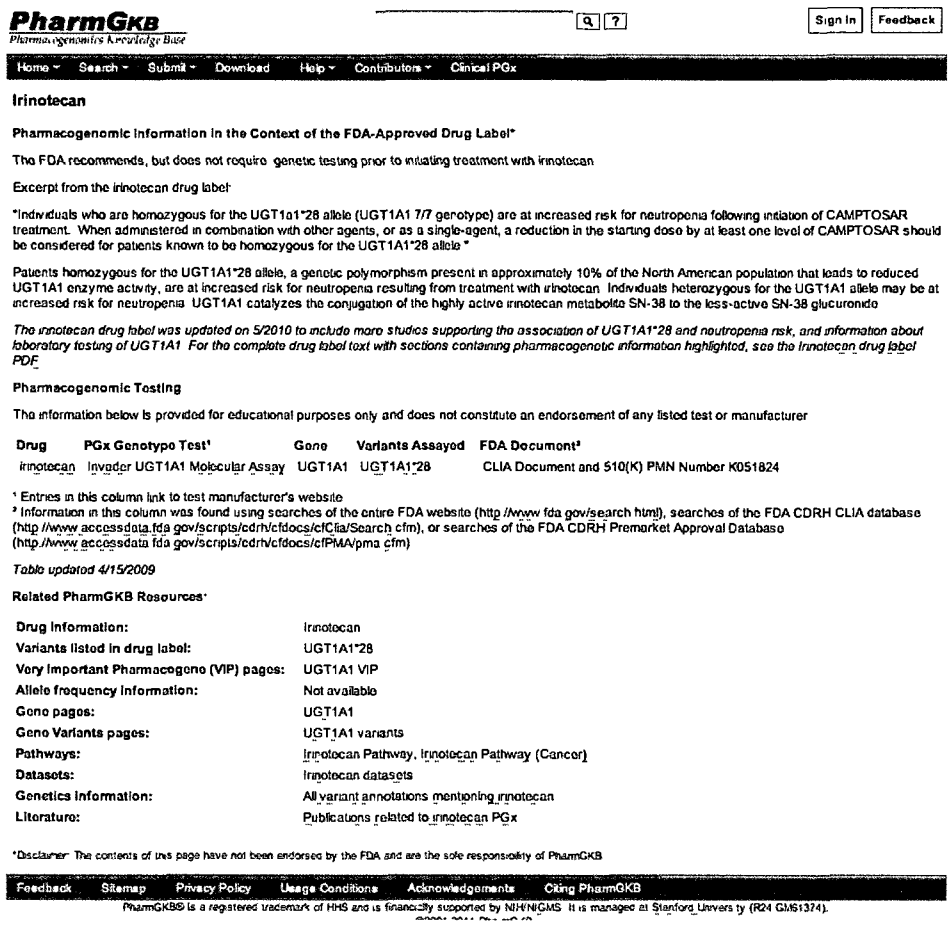


Figure 4. *Screenshot of a high impact dataset to support Ref* (Mathijssen et al , 2003)

Of the 25 validated biomarkers for FDA drug-biomarker pairs explored in this work, six are "annotated PGx genes" within PharmGKB. While this is only 24% of all genes considered in this work, these genes (CYP2D6, CYP2C19, CYP2C9, DPD, TPMT and VKORC1) are validated biomarkers for majority of the drugs explored in this work (60%, 43/71). With a focus on PharmGKB curations that provide evidence of drug-gene associations, only 60% (26/43) of these drugs are indicated as associated with the genes designated as validated biomarkers by the FDA within "annotated PGx gene" summaries. Similarly, of the 34 drugs (48%) that have pathway evidence within PharmGKB, only 56% (19/34) of these pathways involve the validated biomarker identified by the FDA. Also, there are only twelve drugs (21%) for which both genotype and phenotype data are available within PharmGKB, five (42%, 5/12) provide data about genetic variants of genes designated as validated biomarkers by the FDA. There is, however, better coverage of drug-gene association knowledge within the "clinical PGx section" that summarizes PGx biomarker information for 73% (52/71) of FDA drug labels explored in this work (See *Figure 5* on the next page). Given these findings, the information that would likely be most useful for drug therapy individualization would be the "clinical PGx section" within PharmGKB. PharmGKB VIP gene-related resources (i.e. annotated PGx gene, important variant, and important haplotype summaries) and drug pathways that provide evidence of drug-gene relationships are likely to be a good source to supplement FDA approved drug label contents.

Overall, PharmGKB includes both encoded knowledge and knowledge in the form of textual summaries. The "clinical PGx section" summaries that provide the best coverage of drug-gene association knowledge, are among the knowledge made available in PharmGKB that would be most useful for drug therapy individualization. While summaries provided by PharmGKB could be valuable, this knowledge is primarily captured as free-text and is not currently in a computable format. Similarly, FDA drug label content of interest is primarily captured as free-text. The ability to represent PGx knowledge in a format suitable to code within an EHR framework are explored in Section 4.4.2.



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Irinotecan

Pharmacogenomic Information in the Context of the FDA-Approved Drug Label*

The FDA recommends, but does not require genetic testing prior to initiating treatment with irinotecan

Excerpt from the irinotecan drug label:

"Individuals who are homozygous for the UGT1a1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele."

Patients homozygous for the UGT1A1*28 allele, a genetic polymorphism present in approximately 10% of the North American population that leads to reduced UGT1A1 enzyme activity, are at increased risk for neutropenia resulting from treatment with irinotecan. Individuals heterozygous for the UGT1A1 allele may be at increased risk for neutropenia. UGT1A1 catalyzes the conjugation of the highly active irinotecan metabolite SN-38 to the less-active SN-38 glucuronide.

*The irinotecan drug label was updated on 5/2010 to include more studies supporting the association of UGT1A1*28 and neutropenia risk, and information about laboratory testing of UGT1A1. For the complete drug label text with sections containing pharmacogenetic information highlighted, see the Irinotecan drug label PDF.*

Pharmacogenomic Testing

The information below is provided for educational purposes only and does not constitute an endorsement of any listed test or manufacturer.

Drug	PGx Genotype Test[1]	Gene	Variants Assayed	FDA Document[2]
irinotecan	Invader UGT1A1 Molecular Assay	UGT1A1	UGT1A1*28	CLIA Document and 510(K) PMN Number K051824

[1] Entries in this column link to test manufacturer's website
[2] Information in this column was found using searches of the entire FDA website (http://www.fda.gov/search.html), searches of the FDA CDRH CLIA database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm), or searches of the FDA CDRH Premarket Approval Database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm)

Table updated 4/15/2009

Related PharmGKB Resources*

Drug Information:	Irinotecan
Variants listed in drug label:	UGT1A1*28
Very Important Pharmacogene (VIP) pages:	UGT1A1 VIP
Allele frequency information:	Not available
Gene pages:	UGT1A1
Gene Variants pages:	UGT1A1 variants
Pathways:	Irinotecan Pathway, Irinotecan Pathway (Cancer)
Datasets:	Irinotecan datasets
Genetics Information:	All variant annotations mentioning irinotecan
Literature:	Publications related to irinotecan PGx

*Disclaimer: The contents of this page have not been endorsed by the FDA and are the sole responsibility of PharmGKB.

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Figure 5. *Screenshot of a PharmGKB "clinical PGx section" summary for Irinotecan. Illustrates the types of drug-gene association knowledge included in these summaries. Links provided under "Pharmacogenomics Testing" and "Related PharmGKB Resources" sections highlight forms of encoded knowledge captured. The "Pharmacogenomic Information in the Context of FDA-Approved Drug Label" section provides a primarily free-text summary of the knowledge contained in the Irinotecan FDA drug label.*

4.4.2. Aim 1.2: Translation of pharmacogenomics knowledge into a rule-based representation

In the original evaluation 28 drug labels and 79 passages containing PGx knowledge to support drug therapy individualization were identified. Updated methods were applied to the labeling of five drugs for which major updates were made to the labeling since the original evaluation (capecitabine – DPD, irinotecan – UGT1A1, nilotinib – UGT1A1, warfarin – CYP2C9 & VKORC1, and clopidogrel – CYP2C19), and 43 passages were identified. The labeling of 43 additional drugs available on the FDA" Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2009) as of May 2011 were also reviewed. 341 passages were identified from these drug labels. Across all

passages containing PGx knowledge, 565 if-then rules to support PGx clinical decisions were defined (See Appendix 1). The distribution of if-then rules by 25 validated biomarkers identified across 71 FDA biomarker-drug pairs (US Food and Drug Administration, 2011) are shown in ***Figure 6***. Results show that 55% the rules involve genes that encode cytochrome P450 drug metabolizing enzymes (CYP2D6, CYP2C19, CYP2C9). This finding is similar to what would be expected given that these genes are identified by the FDA as being validated biomarkers for ~46% of the drugs evaluated in this work (See Dissertation Chapter 3, Table 1). Validated biomarkers that are drug metabolizing genes other than cytochrome P450's (i.e. DPYD, G6PD, NAT, TPMT and UGT1A1) are associated with 12 (or ~17%) of the drugs evaluated in this work. ***Figure 6*** shows that 15% of the rules are defined for these other drug metabolizing genes, also similar to what would be expected.

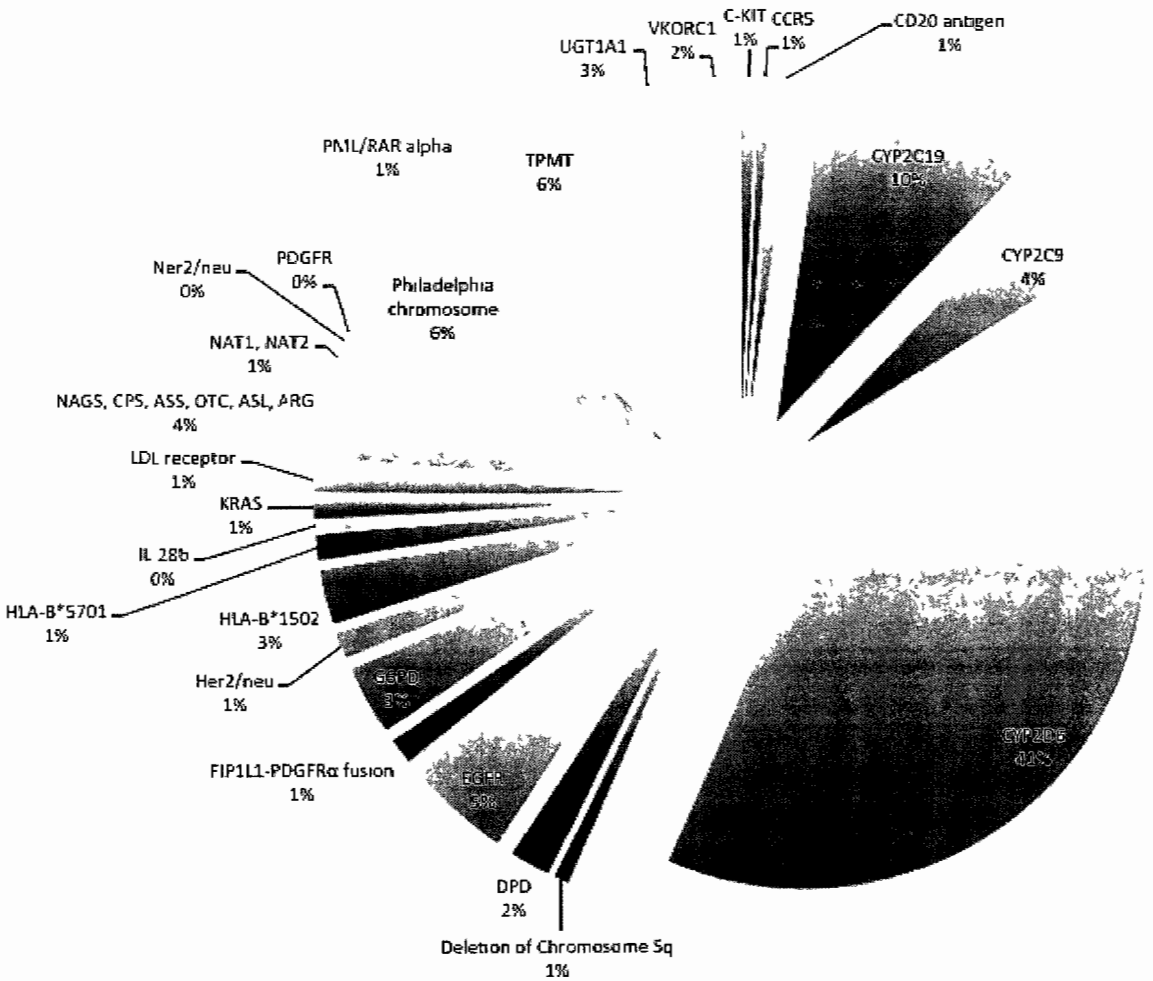

Figure 6. *Distribution of biomarkers covered by 565 decision support rules extracted from 71 FDA drug labels.*

The distribution of decision support rules extracted from 71 FDA drug labels are shown in *Figure 7* (on the next page). Rules extracted from the drug labels of Oncology medications (arsenic trioxide, busulfan, capecitabine, cetuximab, dasatinib, erlotinib, gefitinib, imatinib, irinotecan, lapatinib, mercaptopurine, nilotinib, panitumumab, rasburicase, tamoxifen, thioguanine, tositumomab, and trastuzumab), and Cardiology medications (carvedilol, clopidogrel, isosobide and hydralazine, lenalidomide, metorolol, prasugrel, propafenone, propranolol, and warfarin) account for the majority of all rules defined in this work. In total, there are 239 if-then rules (or ~42% of all rules) defined for oncology and cardiology medications. The drug for which the most rules are defined is Imatinib, with 28 rules. Interestingly, Imatinib also has the most validated biomarkers associated with this drug when compared to other drugs (four biomarkers: C-KIT, philadelphia chromosome, PDGFR and FIP1L1-PDGFRα fusion). Conversely, there were no rules defined for three medications: peginterferon alpha-2b, erlotinib, and azathioprine. This occurrence can be explained for erlotinib and azathioprine given that the biomarkers of interest are included in passages that provide details about their involvement in drug mechanisms (e.g. drug metabolism). In the initial evaluation of drug labels (performed 9/2009) rules that included study results and knowledge about drug mechanism were excluded. In addition, updates were made to the drug labels of erlotinib and azathioprine since the initial evaluation where labels from 4/27/2009 and 7/9/2008 (respectively) were evaluated (See *Table 9*). There are now updated labels that include biomarker information for erlotinib (04/16/2010, Source: Drugs@FDA) and azathioprine (5/24/2011, Source: Drugs@FDA). The peginterferon alpha-2b drug label (03/29/2011 most recent revision date) was evaluated on 7/11/2011 (See *Table 9*). Given that this drug was recently added to the FDA table (as of May 2011), the drug label may not yet be updated to include information about the associated biomarker (i.e. IL28B).

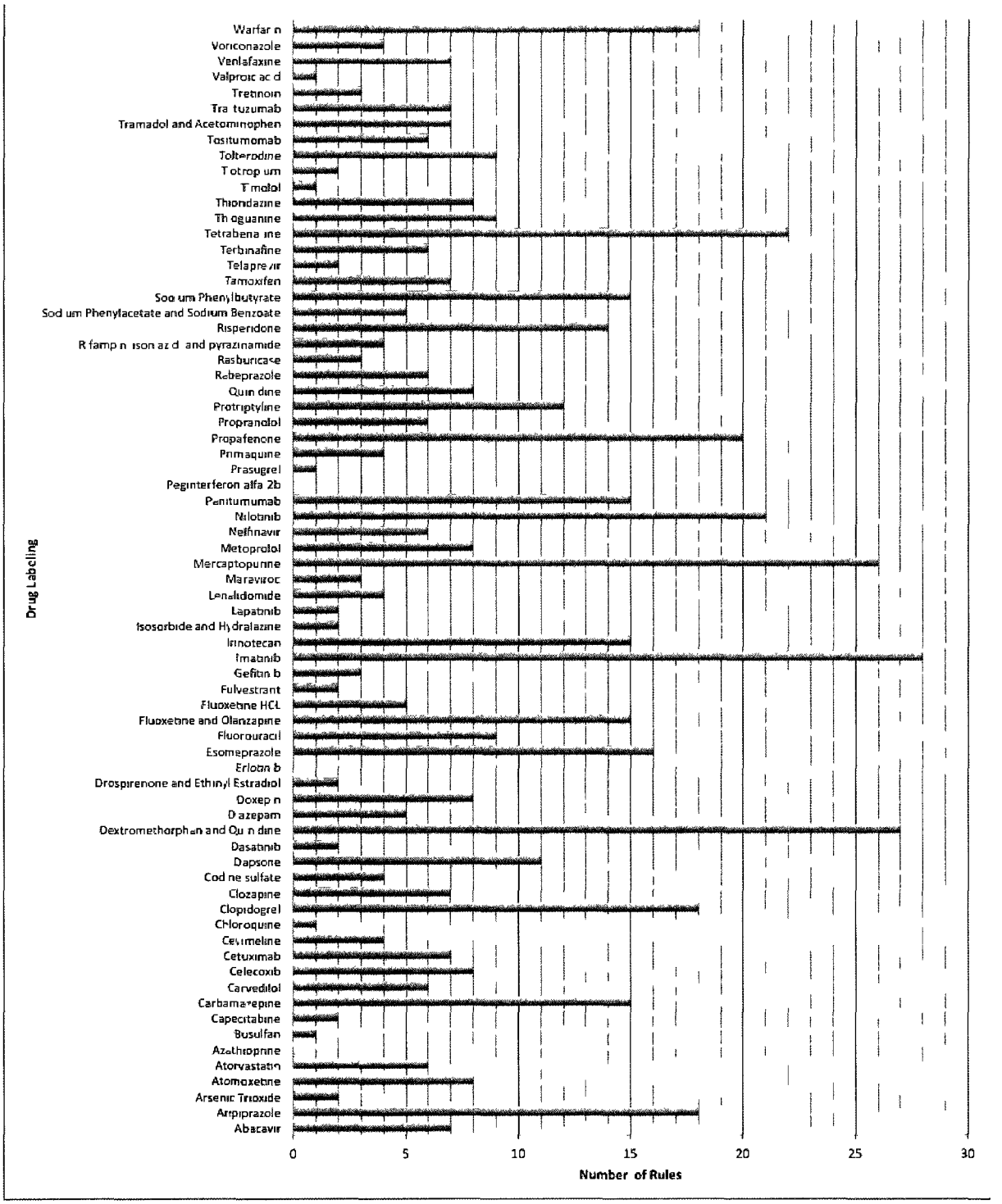

Figure 7. *Distribution of 565 decision support rules extracted from 71 FDA drug labels*

In further evaluation, general categories of support provided by each of the 565 if-then rules were determined. Categories of support provided by approximate decision support rules derived from drug labels included "Considerations before initiating therapy" (41%),

"Treatment protocol" (16%); "What or how are genes/enzymes involved in a drugs' mechanism of action?" (13%); "Who will or will not benefit from treatment?" (11%); "Advice related to testing" (9%); "What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?" (6%); "What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?" (3%); and "Information related to treatment to relay to the patient" (1%) (See *Figure 8*, on the next page). Some categories of support are relevant for the different analytic phases of genetic testing (pre-analytic, analytic or post-analytic phases described in Dissertation Chapter 2, Section 2.3.1). For example, about 68% of approximate decision support rules fall into categories that most clearly provide support for the post-analytic phase of genetic testing including: "Considerations before initiating treatment"; "Treatment protocol"; and "Who will or will not benefit for treatment?" About 22% of approximate decision support rules are included in categories that most clearly provide support for the pre-analytic (and, for some rules, the analytic) phase of genetic testing including: "What or how are genes/enzymes involved in a drugs' mechanism of action?"; "What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?"; and "What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?" The "Advice related to testing" category was too broad to designate as providing support for a particular phase of genetic testing and was therefore investigated further and divided into subcategories (See *Figure 9*, on the next page). Within this category, 25% of the rules fall into the sub-category "How to interpret test results?" that is relevant to the post-analytic phase of genetic testing. Relevant to the pre-analytic phase of genetic testing, 75% of rules fall into sub-categories "What testing is available prior to drug administration?" and "Who should be screened prior to drug administration?" Overall, taking rules defined under the category "Advice related to testing" into consideration along with the other categories discussed, 70% of approximate decision support rules are relevant to the post-analytic phase of genetic testing, and 29% are relevant to the pre-analytic phase. The remaining 1% of approximate decision support rules were categorized as "Information related to treatment to relay to the patient," which does not clearly fall into any phase of genetic testing.

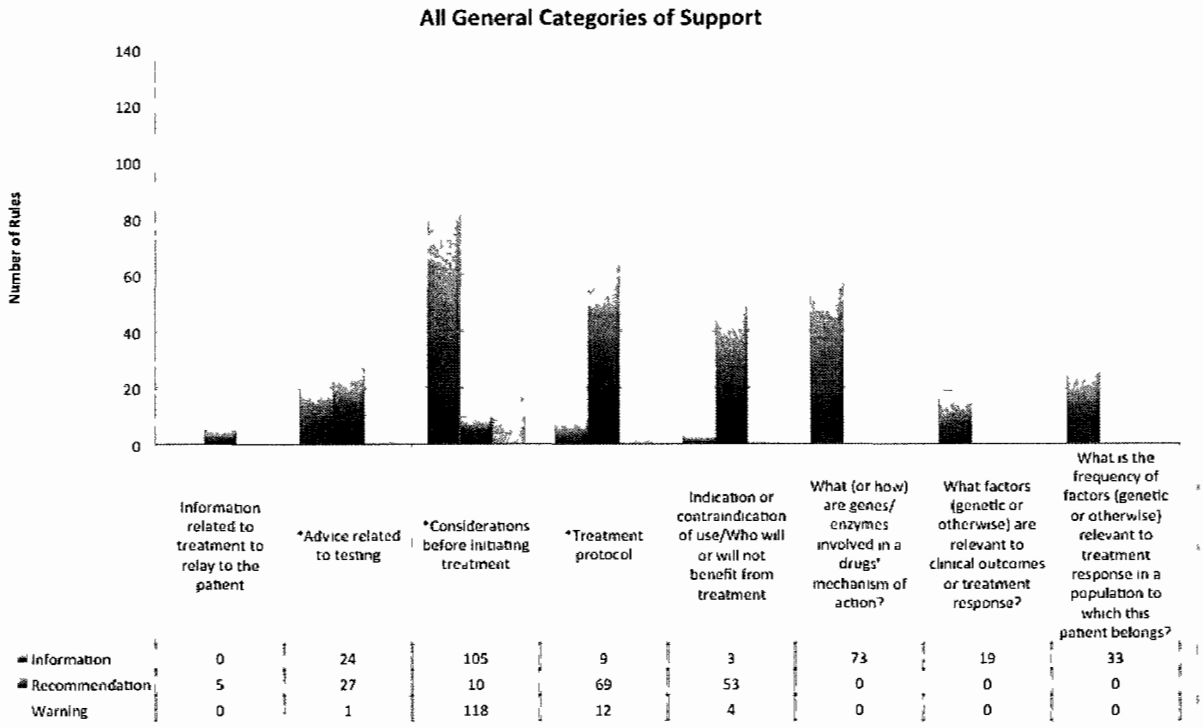

Figure 8. *All General Categories of Support. General categories of support provided by 565 approximate decision support rules derived from 71 FDA drug labels are shown on the x-axis. The number of rules is on the y-axis. For each general category, a blue bar indicates the number of rules designated as "information" only, red bar indicates the number of "recommendations" and green bar indicates the number of "warning" messages.*

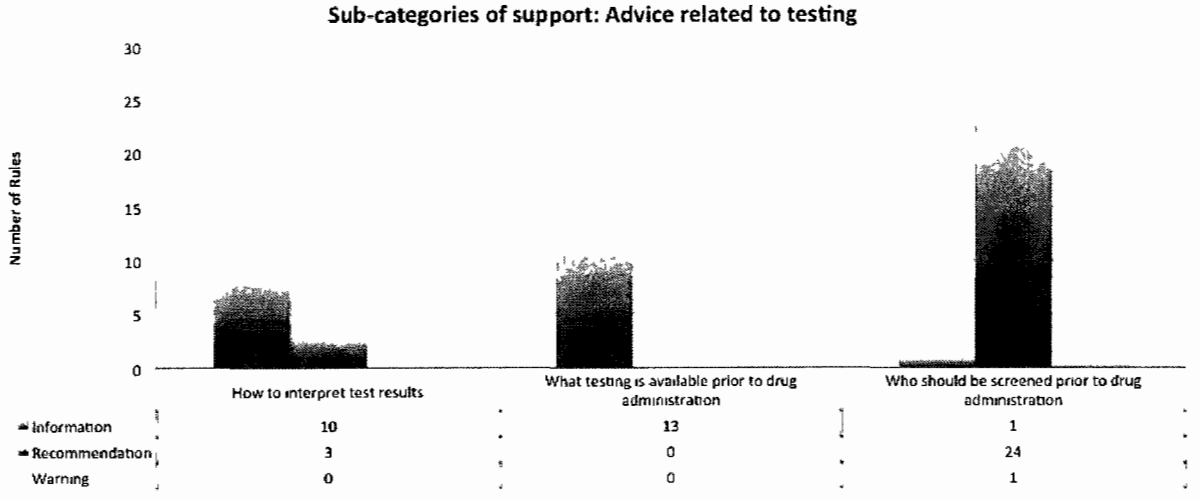

Figure 9. *Subcategories of support from the "Advice related to testing" category shown in* ***Figure 8.***

In addition, the two largest categories of support ("Considerations before initiating therapy" and "Treatment protocol") were investigated further and divided into subcategories to better understand forms of support provided (See *Figure 10* below and *Figure 11* on the next page). Of particular note, rules that suggest treatment indications and contraindications are excluded from the "Considerations before initiating therapy" category and are instead categorized as "Who will or will not benefit from treatment?" Within this category, 45% of the rules fall into the sub-category "Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family history?" and 51% of the rules fall into the sub-category "Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs?" (where coadministered drugs generally involve a similar mechanism of action). This finding shows that, given the keyword search approach taken to identify passages containing the validated biomarker of interest within drug labels, the rules defined are often related to drug-drug interactions rather than patient constitutional or tumor genetics. Within the "Treatment protocol" category, the majority of rules provide "Advice about drug dose," accounting for 82% of the rules. The remaining 18% of rules within this category provide advice about "Appropriate patient monitoring requirements," or some "Other treatment protocol."

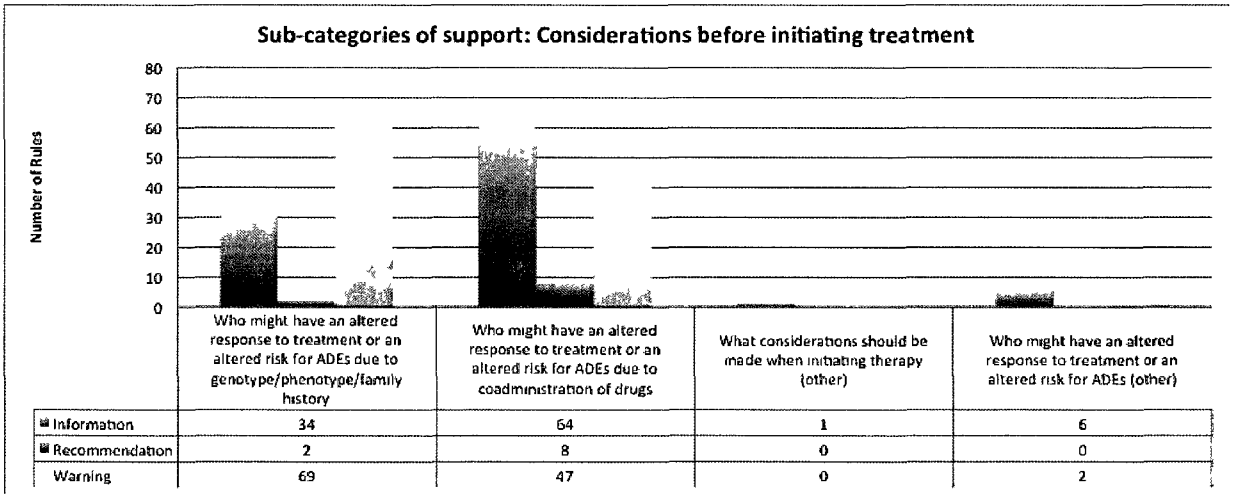

Figure 10. *Subcategories of support from the "Considerations before initiating treatment" category shown in* ***Figure 8****.*

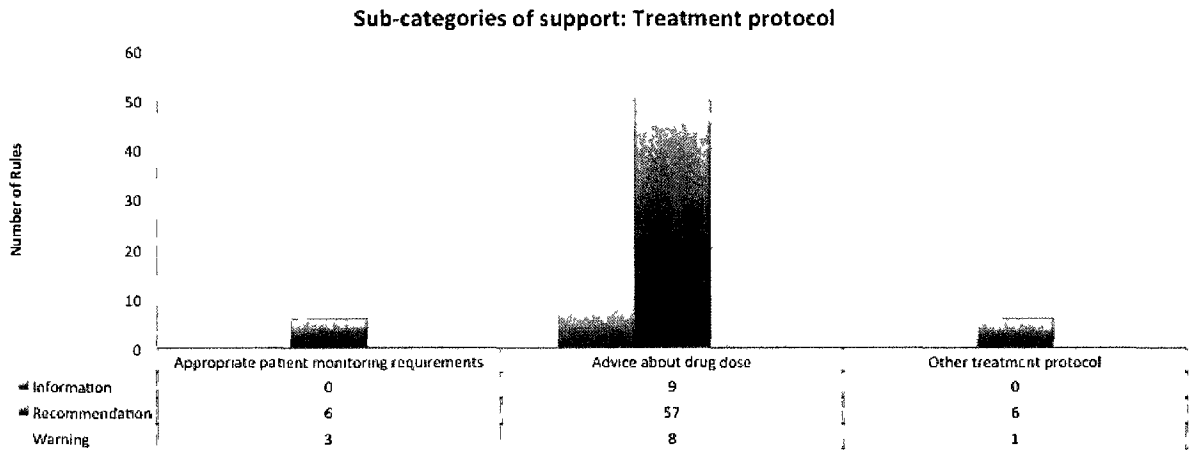

Figure 11. *Sub-categories of support from the "Treatment protocol" category shown in* ***Figure 8***

Categories were also applied to the pre- condition (IF statement) and post- condition (THEN statement) of each rule (See ***Figure 12*** on the next page, Appendix 2 for a legend of identified pre-/post- conditions, and Appendix 3 for designations of each decision support rule). The pre-conditions are shown on the Z-axis, the post-conditions are on the X-axis, and the numbers of rules for each pre- & post- condition combination are shown on the Y-axis. This figure shows that the majority of rules are represented within a small number of pre- & post- condition combinations. The eight combinations that account for the majority of rule patterns are shown in *Table 11* (two pages forward), and accounted for 65% of all approximate decision support rules. Each row includes the pre-condition (column 1), post-condition (column 2) and an example rule designated as having the pre- & post- condition combination (column 3). Pre- and post- conditions rule designations are used to determine data requirements for executing CDS in the following chapter (Dissertation Chapter 5).

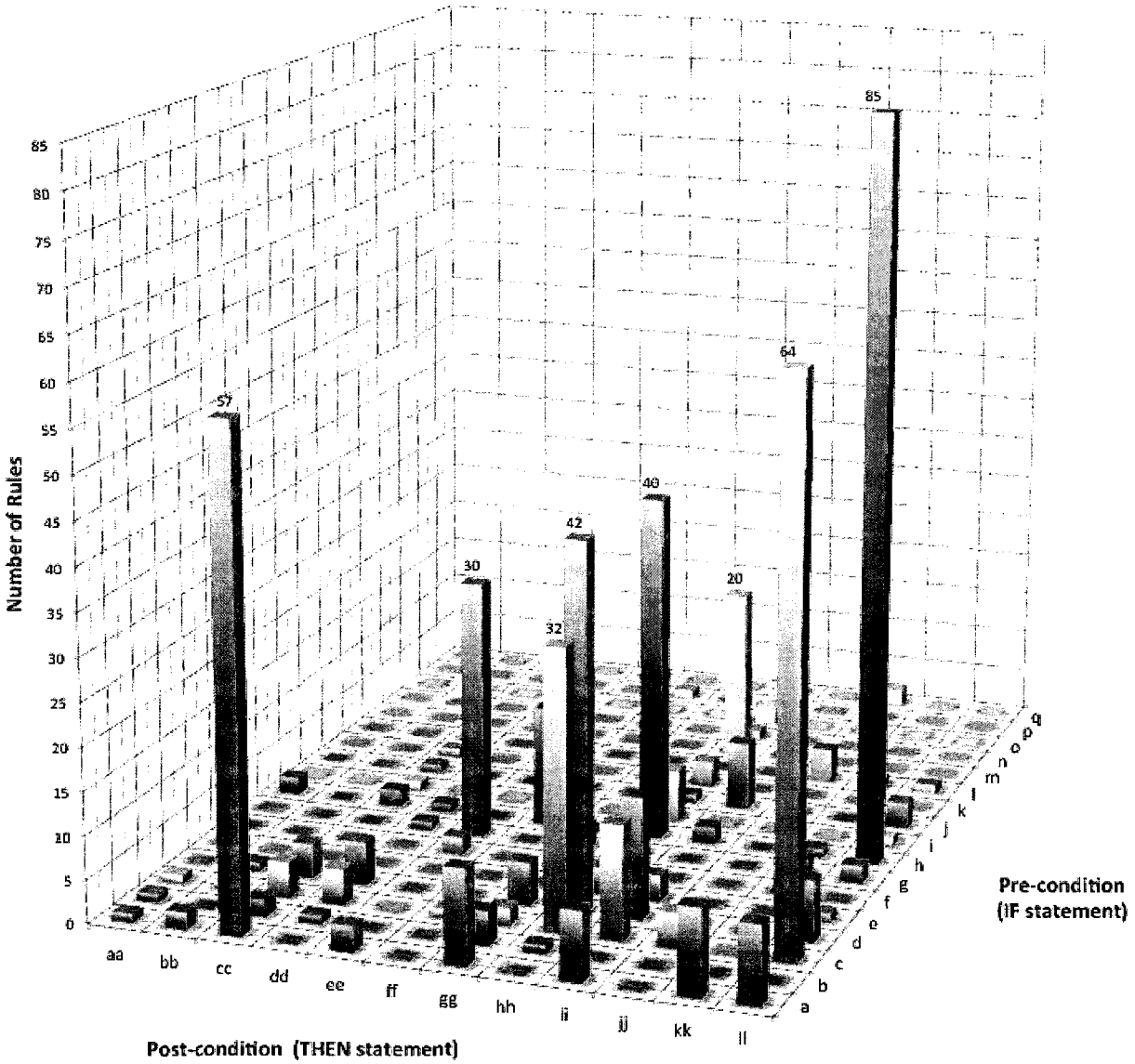

Figure 12. *Distribution and overlap of Pre- and Post- condition categorizations across 565 decision support rules from 71 FDA drug labels. Pre-conditions are represented by a single letter code, and post-conditions are represented by a two-letter code. The number of approximate decision support rules is shown for the top eight IF-THEN rule patterns. Some rule patterns are discussed in Table 11. See Appendix 2 for the legend for this figure.*

Table 11 *Top eight IF-THEN rule patterns seen for 565 approximate decision support rules extracted from 71 FDA drug labels References to pre- and post-condition rule patterns described in Figure 12 are provided*

IF statement	THEN statement	Example approximate decision support rule
drug (label "a" in *Figure 12*)	pharmacological_activity_with_involvement_of_gene/protein (label "cc" in ***Figure 12***)	IF patient is [being considered for] taking Esomeprazole THEN Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4
drug + genotype/phenotype/family_history (label "c" in *Figure 12*)	recommended_treatment_protocol (label "hh" in ***Figure 12***)	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolizm THEN Celecoxib should be administered to the patient with caution
drug + genotype/phenotype/family_history (label "c" in *Figure 12*)	toxicity/complications/change_in_pharmacological_activity (label "ll" in ***Figure 12***)	IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine, and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy
drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds (label "d" in *Figure 12*)	recommended_treatment_protocol (label "hh" in ***Figure 12***)	IF patient is [being considered for] taking ACZONE AND (patient is glucose 6-phosphate dehydrogenase deficient OR patient has a history of anemia) THEN patient is at risk, and routine follow-up for complete blood count and reticulocyte count should be implemented
drug + population (label "g" in *Figure 12*)	probability/frequency_of_having_variants_in_population (label "dd" in ***Figure 12***)	IF the patient is taking Carbamazepine AND patient is Asian AND patient is from Taiwan THEN About 10% of the population is reported positive (for HLA-B*1502) in Taiwan
drug1 + drug2/current_med_list (label "h" in *Figure 12*)	recommended_treatment_protocol (label "hh" in ***Figure 12***)	IF patient is [currently] taking NUEDEXTA AND (patient is [being considered for] taking medications that are primarily metabolized by CYP2D6 AND medications have a relatively narrow therapeutic index) THEN medications should be initiated at a low dose
drug1 + drug2/current_med_list (label "h" in *Figure 12*)	toxicity/complications/change_in_pharmacological_activity (label "ll" in ***Figure 12***)	IF patient is [being considered for] taking clozapine AND patient is taking certain drugs that are metabolized by P450 2D6 including antidepressants THEN drugs metaboized by P450 2D6 may inhibit the activity of P450 2D6 and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction
genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds (label "m" in *Figure 12*)	recommended_treatment_protocol (label "hh" in ***Figure 12***)	IF the patient is an adult AND the patient is infected with an HIV virus that is CCR5-tropic AND the virus is resistant to multiple antiretrovirals AND the patient has evidence of viral replication, THEN treat the patient with SELZENTRY

In addition, the UI presentation that would be appropriate for each rule was determined. Overall 47% should be presented as *information only*; 29% should be presented as a *recommendation*; and 24% should be presented as a *warning* (See *Table 12* on the next page for examples). Rule IDs 50.2, 17.4 and 16.4 provide examples of rules for which a resolution was made (according to preferences described in Section 4.3.2) when multiple UI types were identified. For example Rule IDs 50.2 and 16.4 were classified as both "information only" and "warning," but were both resolved to be "warning." Rule ID 17.4 was classified as both "warning" and "recommendation," but were resolved to be "warning." For each example, in addition to UI types (column 4), *Table 12* also provides examples of designated general categories of support (column 3), and provides rule ids used in this research (column 4). Rule IDs were utilized to uniquely identify rules when applying methods from Aim 1 (this chapter) and Aim 2 (Dissertation Chapter 5).

Table 12 *Example rules with designated category of support and user interface (UI) presentation type*

Rule ID	Example	Category of support	Resolved UI type
22.3	IF patient is [being considered for] taking Esomeprazole THEN Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only
50.2	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolism THEN Celecoxib should be administered to the patient with caution	Treatment protocol Appropriate patient monitoring requirements	Warning (resolved from Warning and Information only)
2.1	IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine, and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history?	Warning
17.4	IF patient is [being considered for] taking ACZONE AND (patient is glucose 6-phosphate dehydrogenase deficient OR patient has a history of anemia) THEN patient is at risk, and routine follow-up for complete blood count and reticulocyte count should be implemented	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history?	Warning (resolved from Recommendation and Warning)
49.7	IF the patient is taking Carbamazepine AND patient is Asian AND patient is from Taiwan THEN About 10% of the population is reported positive (for HLA-B*1502) in Taiwan	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only
18.11	IF patient is [currently] taking NUEDEXTA AND (patient is [being considered for] taking medications that are primarily metabolized by CYP2D6 AND medications have a relatively narrow therapeutic index) THEN medications should be initiated at a low dose	Treatment protocol Advice about drug dose	Recommendation
16.4	IF patient is [being considered for] taking clozapine AND patient is taking certain drugs that are metabolized by P450 2D6 including antidepressants THEN drugs metabolized by P450 2D6 may inhibit the activity of P450 2D6 and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to co-administration of drugs	Warning (resolved from Warning and Information only)
58.2	IF the patient is an adult AND the patient is infected with an HIV virus that is CCR5-tropic AND the virus is resistant to multiple antiretrovirals AND the patient has evidence of viral replication, THEN treat the patient with SELZENTRY	Who will or will not benefit from treatment?	Recommendation

It is evident from *Table 12* that some categories of support may be more or less likely to have a designated UI type. For example, rules that provide advice about drug dose (e.g. Rule 18.11) may be most likely to have a "recommendation" UI type designation when compared to other UI types. In further investigation, this suspicion was confirmed (See *Figure 8*). Rules categorized as "Information related to treatment to relay to the patient," "Advice related to

testing," "Treatment protocol," or "Who will or will not benefit from treatment?" appear to be most likely to have "recommendation" UI types. Rules categorized as "Considerations before initiating treatment" appear to be most likely to be "warning" UI types. Rules categorized as "What (or how) are genes/enzymes involved in a drugs' mechanism of action?" "What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?" or "What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs" appear to be most likely to be "information only" UI types. Interestingly, the categories most likely to be "information only" are categories that best provide support for the pre-analytic phase of genetic testing. Also, the majority of categories most likely to be "recommendations" are also most likely to provide support for the post-analytic phase of genetic testing. This indicates that there may be more actionable information (i.e. recommendations) available in the context of post-analytic phase of genetic testing when compared to the pre-analytic phase of genetic testing.

4.5. Summary & Discussion

This chapter provides details on an evaluation of pharmacogenomics resources, focusing on PharmGKB and the labeling of drugs from the FDA "Table of valid genomic biomarkers in the context of approved drug labels" (FDA biomarker-drug pairs) (US Food and Drug Administration, 2009). Specifically, the current representation of knowledge within these resources was characterized (Aim 1.1) and the feasibility of translating pharmacogenomics knowledge into a computable form was assessed (Aim 1.2). Additionally, this chapter provides some insight into the clinical relevance of pharmacogenomics knowledge captured within FDA drug labels and PharmGKB (with a focus on the 71 drugs and their associated biomarkers evaluated in this work).

To summarize findings from Aim 1.1, there was little overlap of evidence cited for FDA biomarker-drug pairs and the evidence for the same biomarker-drug associations cited within PharmGKB. This lack of overlap also suggested that PharmGKB might be a good source to supplement evidence the FDA already considers for pharmacogenomics knowledge in FDA drug labeling. Further investigation indicated that the lack of overlap might in part be due to the more gene-centric approach PharmGKB takes to curating gene-drug relationships. Therefore the clinical relevance of evidence within PharmGKB should be taken into account.

Publication "evidence categories" might be useful to determine the relevance of publication contents to drug therapy individualization and its potential to enhance knowledge contained in FDA drug labels. For example, articles curated for both "GN" (genotype information) and "CO" (clinical outcomes) may be most promising to consider. Non-publication specific "categories of evidence" provided by PharmGKB were also investigated. In addition to publications, PharmGKB VIP gene-related resources (i.e. annotated PGx gene, important variant, and important haplotype summaries) and drug pathways that provide evidence of drug-gene relationships is another possible good source to supplement FDA approved drug label contents. The category of evidence within PharmGKB most likely to be useful for drug therapy individualization is the "clinical PGx section" that includes a summary of pharmacogenomics information in the context of the FDA-approved drug label. While much knowledge is captured as "encoded knowledge" within PharmGKB (e.g. gene-drug associations), results indicated that the pharmacogenomics knowledge of most value for drug therapy individualization is captured as textual summaries. Similarly, while FDA drug labels are tagged for particular sections within DailyMed, content is primarily captured as free-text. The ability to represent pharmacogenomics knowledge in a format suitable to code within an electronic health record framework was explored in Aim 1.2.

To summarize findings from Aim 1.2, 565 approximate decision support rules were derived from the labels of 71 drugs identified by the FDA as containing information about validated biomarkers (US Food and Drug Administration, 2011). A production rules representation was used because it is a format commonly supported and implemented within electronic health record decision support frameworks. Results showed that 55% of all rules involve genes that encode cytochrome P450 drug metabolizing genes, which was expected given that P450s are identified by the FDA as being validated biomarkers for about 46% of the 71 drugs evaluated in this work. Also, about 42% of all rules were defined for oncology and cardiology medications. Oncology and cardiology drugs are therefore the focus of the Aim 4 (Dissertation Chapter 7) evaluations of the utility of a pharmacogenomics clinical decision support implementation with physicians.

To further investigate the clinical context in which the approximate decision support rules derived in this work would be most appropriate, rules were each associated with a general category of support. 70% of rules were associated with categories relevant to the post-

analytic phase of genetic testing, and 29% were relevant to the pre-analytic phase. The remaining 1% did not clearly fall into any phase of genetic testing. Moreover, some categories of support were found to be more or less likely to have different designations for user interface type ("information only," "recommendation," or "warning"). Of particular note were indications that there may be more actionable information (i.e. recommendations) available in the context of the post-analytic phase of genetic testing when compared to the pre-analytic phase of genetic testing. In further evaluation, the pre-condition (IF statement) and post- condition (THEN statement) were categorized for each rule. Findings showed that the majority of rules were represented within a small number of pre- & post- condition combinations, which might be useful for prioritizing EHR decision support framework requirements. This chapter augments work done by others working towards delivering genomics knowledge (described in Dissertation Chapters 2). Previous efforts have focused primary on delivering knowledge developed internally, where as in this aim, a scheme for translating existing knowledge into a computable form is applied. Translating pharmacogenomics knowledge highlighted characteristics of pharmacogenomics knowledge that could influence our ability to incorporate pharmacogenomics knowledge in clinical practice. Findings augment characteristics identified in previous work described in Dissertation Chapter 3 (e.g. the increasing prevalence of biomarker-drug associations, the evolving maturity of pharmacogenomics knowledge, and the varying clinical applicability of pharmacogenomics knowledge between resources). Additional characteristics of pharmacogenomics knowledge identified in this aim that might impact the ability to incorporate knowledge into a clinical context were: findings that majority of knowledge in drug labels support the post-analytic phase of genetic testing indicating a possible need for more knowledge to support other phases of genetic testing; the applicability of pharmacogenomics knowledge to clinical practice within individual resources may vary, indicating another level of investigation required to identify knowledge that is useful in a clinical context; and findings that the knowledge of most value within electronically available resources were captured as free-text requiring additional processing to be made computer interpretable. University of Washington electronic health record decision support framework capabilities and requirements are explored in more detail in the following chapter

(Dissertation Chapter 5), and a prototype system implementation is described in Dissertation Chapter 6.

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5. CHAPTER 5: DETERMINING CAPABILITIES OF CURRENT CLINICAL DECISION SUPPORT SYSTEMS (AIM 2)

5.1. INTRODUCTION

In the previous chapter, results from a formal evaluation of the characteristics and the value of current pharmacogenomics knowledge in the clinical context were presented. As an outcome of that work, 565 decision support rules containing pharmacogenomics knowledge were derived from the FDA labeling of 71 drugs. In addition, the clinical context in which the decision support rules would be most appropriate were investigated. Building on that work, categories of support provided by approximate decision support rules determined in the previous chapter are used to determine functional requirements for providing pharmacogenomics knowledge in the context of clinical decision support embedded in an electronic health record. The details and results from the evaluation are presented in this chapter. The research question addressed in this chapter is: How do current clinical decision support system frameworks align with requirements of characterized pharmacogenomics knowledge in computable form? Answering this research question improves our understanding of the feasibility of electronic health records to provide clinical data and clinical decision support capabilities to execute the pharmacogenomics decision support rules defined in the previous chapter. Related to the overarching aim of this research, the requirements for incorporating pharmacogenomics knowledge into an EHR will be determined in this chapter. In the next chapter (Dissertation Chapter 6), a prototype system implementation based on the capabilities of a local electronic health record system and the clinical decision support requirements for pharmacogenomics knowledge were described. Quoted sections in this dissertation chapter are primarily borrowed from the publications titled "Feasibility of incorporating genomic knowledge into electronic medical records for pharmacogenomic clinical decision support,"(Overby, Tarczy-Hornoch, Hoath, Kalet, & Veenstra, 2010) and "An Evaluation of Functional and User Interface Requirements for Pharmacogenomic Clinical Decision Support" (Overby et al., 2011) with permission from the publishers.

5.2. Related work & Significance

University of Washington (UW) clinical systems provide a good testbed for investigating the provision of clinical decision support (CDS) for drug therapy individualization (Dissertation Chapter 2, Section 2.5). Specifically, the ability of UW clinical systems to provide (a) the clinical data (Aim 2.1), and (b) the functional capabilities (Aim 2.2) required for pharmacogenomics (PGx) CDS are investigated in this chapter.

Related to Aim 2.1 work, data requirements for personalized healthcare information exchange have previously been defined as part of the AHIC Personalized Healthcare Use Case (Dissertation Chapter 2, Section 2.3.1). Specifically, general data elements were mapped to data categories (or data requirements, DRs) (Dissertation Chapter 2, Table 1) and data categories were mapped to information exchange requirements (IERs). For example, "Send/receive genomic information" IER is mapped with "Demographic data," "Clinical History," and "Personal genetic/genomic data" DRs. Rather than evaluating general data requirements, as was done with the Personalized Healthcare Use Case, a formal evaluation of the availability of data elements (e.g. lab values, disease definitions, etc.) needed for implementing approximate decision support rules containing pharmacaogenomics knowledge are investigated in this work. This work provides a general scheme for evaluating the availability of computable data needed for PGx CDS that is applied in a local setting and forms the foundation for the approach to Aim 2.1.

Related to Aim 2.2 work, "the need to design and evaluate clinical decision support architectures and systems has resulted in the development of a taxonomy that characterizes functional requirements of decision support (Wright, Goldberg, Hongsermeier, & Middleton, 2007). A taxonomy proposed in 2007 covers clinical decision support functional capabilities including: *triggers* (events that cause a decision support rule to be invoked e.g. order entered); *data elements* (used by a rule to make inferences e.g. laboratory result); *interventions* (actions a decision support module can take e.g. show guidelines); and *offered choices* (e.g. cancel current order). Since the development of the taxonomy, it has been used to evaluate various clinical decision support architectures (Wright & Sittig, 2008) and clinical information systems (Wright et al., 2009)."(Overby et al., 2011). The taxonomy is utilized in this work (and expanded upon where needed) to evaluate electronic health record (EHR) support provided by UW clinical systems to execute PGx CDS rules. As an outcome

of this work, the decision support capabilities of UW clinical systems and their alignment with the requirements for PGx CDS are determined using an adaptation of this taxonomy for Aim 2.2.

5.3. METHODS

5.3.1. Aim 2.1: Feasibility of electronic health records to provide computable forms of clinical data

The ability of UW clinical systems to provide in computable form (not free text) clinical data needed for PGx CDS was evaluated. Specifically, data available within UW clinical data repositories, including laboratory systems (pathology and microbiology), were investigated. For approximate decision support rules containing PGx knowledge (See Dissertation Chapter 4), the following steps were performed: 1) the types of clinical data needed in combination with PGx knowledge to provide CDS were determined; 2) it was determined whether or not different types of data are already captured as discrete data in UW clinical data repositories; and, 3) for clinical data that are not currently captured, the feasibility of capturing these data were determined by expert opinion. An example approximate decision support rule is as follows:

- "IF patient is taking Warfarin AND patient has CYP2C9*2 or CYP2C9*3 variants, THEN there will be a decrease in S-warfarin clearance AND there is an increased bleeding risk"

The data requirements for the above rule "would be the inclusion (or considering the inclusion) of Warfarin on a patients' medication list; and, CYP2C9 variant status. In some cases, our ability to utilize clinical data might depend on the existence of supporting knowledge. For example, with the statement 'the patient is a poor metabolizer of CYP2C9,' supporting knowledge must define the CYP2C9 genotype that would classify a patient as a poor metabolizer of CYP2C9, (e.g. IF patient has genotype CYP2C9*2/*3 THEN the patient is a poor metabolizer)." (Overby et al., 2010). Using the same example, it would then be determined whether "warfarin" in a patients' medication list and CYP2C9 test results can be captured within UW clinical data repositories. A required data element was labeled as 'not captured' if it was not available within the Medical Information Network Database (MIND)

and Online Record of Clinical Activity (ORCA) UW clinical data repositories, or if it was captured as free-text that is not easily parsed (i.e. requires full natural language processing (NLP)). MIND and ORCA data repositories were of particular focus in this work because the local UW homegrown and commercial EHR systems interface with MIND and ORCA (respectively). This evaluation was primarily performed through conducting informal interviews with Mr. Jim Hoath (UW Medicine IT Services) and Dr. Peter Tarczy-Hornoch (UW Medical Education and Biomedical Informatics).

The feasibility of capturing data elements that were "not captured' within MIND and ORCA at the time of this evaluation was determined by expert opinion. The feasible data types to incorporate included: disease status definitions, data fields captured in pathology and microbiology laboratory systems, and pathology or microbiology laboratory values that exist in free text and can be parsed without use of full NLP methods. Note that only a subset of pathology and microbiology laboratory values were captured in MIND and ORCA.

Finally, the ability for PGx rules to be executed in the UW clinical care environment was evaluated by determining the proportion of rules that, within the UW clinical care environment (a) would have all data requirements satisfied; (b) with the addition of supportive knowledge, would have all data requirements satisfied; and (c) with the addition of data types that are feasible to incorporate, would have all data requirements satisfied.

This Aim 2.1 evaluation was originally performed in September 2009 with 106 rules derived from the FDA labeling of the 28 drugs that were listed on the "Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2009) at that time. The results of that evaluation are included in a publication titled "Feasibility of incorporating genomic knowledge into electronic medical records for pharmacogenomic clinical decision support,"(Overby et al., 2010). Since then, the evaluation was updated to include rules derived from the FDA labeling of 71 drugs listed on the "Table of valid genomic biomarkers in the context of approved drug labels" as of May 2011 (US Food and Drug Administration, 2011). The evaluation of data requirements for PGx CDS is therefore performed with the use of 565 PGx CDS rules in Aim 2.1. Similarly, functional requirements for PGx CDS rules are also determined based on the requirements for these 565 rules in the following Aim 2.2.

5.3.2. *Aim 2.2: Feasibility of UW clinical systems to support pharmacogenomics clinical decision support functional requirements*

The ability for UW clinical systems to implement PGx CDS given their current CDS functional capabilities were investigated by performing the following steps: (1) analyzed the functional requirements for PGx CDS; (2) analyzed the functional capabilities of UW clinical systems; and (3) determined how well functional requirements for PGx CDS align with the capabilities of UW clinical systems. The taxonomy of rule-based decision support content (Wright et al., 2007) was applied to analyze the functional requirements for PGx CDS and capabilities of UW clinical systems. Taxonomy elements included nine *triggers* (events that cause a decision support rule to be invoked e.g. order entered), seven *interventions* (actions a decision support module can take e.g. show guidelines), fourteen *offered choices* (e.g. cancel current order), and eighteen *data elements* (used by a rule to make inferences e.g. laboratory result).

The functional requirements for PGx CDS were determined by associating pre- condition (IF statement) and post- condition (THEN statement) rule classifications (See Dissertation Chapter 4, Section 4.4.2) with taxonomy values. For example, *Table 13* (on the next page) provides assigned taxonomy elements, by category, for the following approximate decision support rule. The generic form of the rule and the pre- and post- condition classifications are also shown for the following example rule.

- Approximate decision support rule: "IF patient is taking clopidogrel AND patient is a CYP2C19 poor metabolizer THEN clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in the patient"
- Generic rule: IF [drug] AND [genotype/phenotype/family_history] THEN [toxicity/complications/change_in_pharmacological_activity]
- Pre-condition classification: "drug + genotype/ phenotype/family_history"
- Post-condition classification: "toxicity/complications/change_in_pharmacological_activity"

Table 13. *Functional requirements for an example pre-/post- condition classification. Taxonomy categories are shown in the first column. In the second column, taxonomy elements are listed for each taxonomy category for an example pre-/post- condition rule classification.*

Taxonomy category	Taxonomy elements for an example pre-/post- condition rule classification Pre-condition: drug + genotype/phenotype/family_history Post-condition: toxicity/complications/change_in_pharmacological_activity
Triggers	Order entered, Lab result stored
Interventions	Notify
Offered choice	Override rule/keep order, Cancel existing order, Cancel current order, Edit current order, Write letter, Write note
Data elements	Lab result/observation, Drug list

The functional requirements for PGx CDS were defined as the set of triggers, interventions, offered choices & data elements required across all of the pre- and post-condition combinations represented within the set of 565 rules derived from FDA drug labels.

Next, the CDS capabilities of UW clinical systems were evaluated by completing informal interviews with individuals that are knowledgeable of UW clinical systems. Specifically, Dr. Joe W. Smith (Pharmacy Informatics, UW Medicine) was interviewed to determine the capabilities of applications that interface with ORCA, and Mr. James Hoath (UW Medicine IT Services) was interviewed to determine the capabilities of applications that interface with MIND or Microsoft Amalga. The terminology shown in *Table 14* (on the next page) was used to describe the extent to which UW clinical systems provide various CDS functional capabilities (it is possible that other implementations and configurations might result in different functionality). Applications for ORCA are based on the Cerner Millennium application suite that includes Powerchart® (the inpatient EHR application) and PharmNet® (the inpatient pharmacy application). Applications for MIND include MINDscape (a web-based, predominantly view only, EHR application), Healthreach (a patient portal), and ULink (a referring healthcare provider portal). Applications for Microsoft Amalga include over 300 applications and reports supporting quality improvement, clinical care and operational aspects across UW Medicine.

Table 14. *Terminology used to describe the existence of clinical system functional support elements (as defined in the taxonomy of rule-based decision support content* (Wright et al., 2007)*). Applications that interface with UW clinical data repositories were evaluated by assigning a value from this table for each taxonomy element.*

Y – supported and currently implemented in at least one application
Y* – supported but not currently implemented in any of the applications
Y – not currently supported, but can be supported with minimal system expansion/configuration (defined as ≤ 6 hours of labor)**
N – not currently supported

Finally, to determine how well functional requirements of PGx knowledge align with the capabilities of UW clinical systems the following assignments were made for taxonomy categories for each UW clinical data repository. "Y" was assigned to a taxonomy category for a UW clinical data system if the needs for executing all PGx decision support rules within that category are currently satisfied (i.e. all "Y's"). "Y*" was assigned if there were no "Y**" or "N" values, and there was at least one "Y*" across all PGx decision support rules within a category (indicating that the support for at least one required feature exists but is not currently implemented in the clinical system). "Y**" was assigned if there were no "N" values, and there was at lease one "Y**" across all PGx decision support rules within a category (indicating that at least one required feature is not currently supported by the clinical system, but can be supported with minimal system expansion/configuration). "N" is assigned if there were any "N's" across all PGx decision support rules within a category (indicating that at least one required feature is not currently supported).

This Aim 2.2 evaluation was originally performed in June 2011 with a subset of the 565 rules derived from the FDA labeling of the 71 drugs that were listed on the "Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2011). Specifically, focusing on two domains of practice (oncology and cardiology), this evaluation was performed with 110 approximate decision support rules derived from the drug labels of ten medications (five oncology and five cardiology medications). The results of that evaluation are included in a publication titled "An Evaluation of Functional and User Interface Requirements for Pharmacogenomic CDS" (Overby et al., 2011). Since then, the evaluation was updated to include the full set of 565 rules derived from the FDA labeling of 71 drugs (Summer 2011).

5.4. RESULTS

5.4.1. Aim 2.1: Clinical data access within UW electronic health records

In the initial evaluation of 106 rules derived from 28 drugs listed on the "Table of valid genomic biomarkers in the context of approved drug labels" (US Food and Drug Administration, 2009), "32% of our 106 if then rules could be expressed without additional supporting knowledge or information contained in clinical notes. The addition of supporting knowledge would raise the percentage of rules with sufficient clinical data access to 50%. It was also determined, by expert opinion, the feasibility of expanding the current UW EMR system to incorporate data fields that allow for the execution of PGx CDS rules. Feasible expansion was considered to be the addition of disease status definitions (11%); the addition of data entry fields in pathology laboratory systems (<1%); the addition of data fields in microbiology laboratory systems (20%); and, the ability to parse (not by full NLP) pathology or microbiology laboratory values that exist in free text (7%). Percentages designate instances within the full set of if-then rules for which lack of access to these definitions/fields would inhibit our ability to execute rules. With feasible expansion to the current EMR system, sufficient clinical data access for our if-then rules would increase to 89%." (Overby et al., 2010). This evaluation was updated to assess the feasibility of representing PGx knowledge in EHRs based on 565 rules derived from the FDA labeling of 71 drugs listed on the "Table of valid genomic biomarkers in the context of approved drug labels," as of May 2011(US Food and Drug Administration, 2011). See Appendix 1 for the full list of rules.

Data element categories including medications (i.e. drug names, therapeutic classes, chemical classes, and metabolic classes), conditions (e.g. diseases and side effects), laboratory values (e.g. CYP2D6 variant status), demographics (e.g. age, race), and procedures (e.g. resection) were assessed in this sub-aim. In the original evaluation, 35 data elements categorized as medications, 19 conditions, 20 laboratory values, and one procedure were investigated. In the updated evaluation, 172 medications, 68 conditions, 37 laboratory values, 39 demographics, and four procedures were investigated (See *Figure 13* on the next page). The full set of data elements evaluated in this work is also shown in Appendix 4.

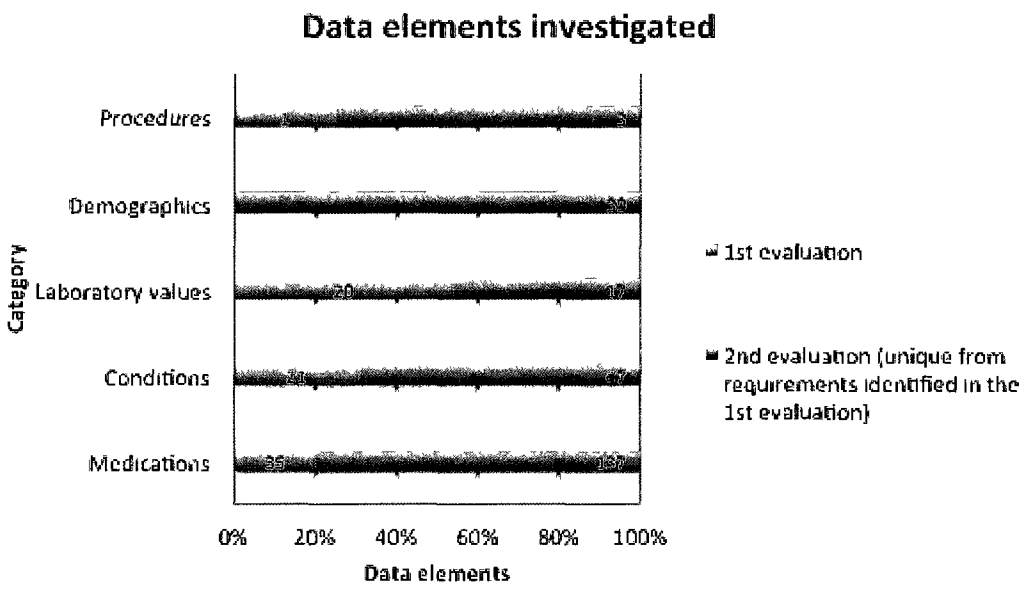

Figure 13. *The number of data elements investigated by category This figure also shows the percentage of all data elements that were investigated during the first evaluation (Fall 2009) compared to the second evaluation (Summer 2011)*

Data elements were investigated individually, and the number of PGx decision support rules that could be implemented given current data availability in local EHRs was determined. Through performing informal interviews it became evident that there were cases where minor to major derivation would be required in order to make a data element available within UW clinical data repositories. Classification criteria were therefore refined so that a data element was labeled "captured" if (a) no additional derivation was required, or (b) if simple derivation was required. A data element was labeled "not captured" if (a) complex derivation was required, or (b) the data element was not available and could not be derived.

This evaluation was performed primarily through performing informal interviews, however, some data elements required further investigation. Further investigation was based on the assumption that if a data element was assigned a code within the UW clinical environment then it could potentially be utilized to trigger CDS. Coding systems incorporated into UW clinical systems that were particularly useful for this evaluation included the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification (I-CD9) coding system, the National Drug Code (NDC) coding system, and the internal coding system used by the Department of Laboratory Medicine. ICD-9 and ICD-10 are the official systems in the United States for assigning

codes to diagnoses and procedures associated with hospital utilization. It was primarily utilized to confirm the availability of condition and procedure data elements. The Food and Drug Administration (FDA) developed the NDC coding system for drug package labeling of medications administered in healthcare settings. Medication data elements investigated in this work, however, often lacked the precise drug product information captured by NDC codes. For example, most approximate decision support rules specified drug names, but not strength or dosage. Also, in many cases therapeutic or chemical classes of medications were the data elements under investigation, which were not identifiable at the granularity of NDCs. Instead a proprietary drug knowledge base, Multum Lexicon (Cerner Multum, Inc., Denver CO), was utilized to confirm the existence of individual and classes of medications. The Multum Lexicon includes drug category codes associated with the NDC code on each prescription service, and it incorporates a therapeutic chemical classification scheme that groups drugs according to their therapeutic and chemical characteristics. The Department of Laboratory Medicine assigns mnemonic codes to all of the laboratory tests that can be ordered within the UW. A searchable online laboratory test guide (UW Department of Laboratory Medicine) was utilized to confirm the availability of laboratory value data elements. In some cases, the availability of data elements were confirmed by personal contacts within UW Laboratory Medicine or UW Medicine Pharmacy Informatics.

Coding systems also helped with distinguishing whether a data element required simple or complex derivation. For example, medication generic and brand names would not require any derivation given that NDC codes exist for the majority of medication names. In addition, therapeutic (disease) classes did not require additional derivation because classes were assigned Multum drug category codes UW clinical systems. Simple derivation, however, would be required for medication data elements that were chemical classes (e.g. aminosalicylate derivatives) and metabolic classes (e.g. CYP2D6 inducer) in many cases. With chemical classes in particular, there were many cases where either broader or more specific codes existed in Multum. For example, "aminosalicylate derivatives" does not exist as a discrete data element, but there are 277 discrete data elements for 5-aminosalicylates. Therefore, this data element could be defined by multiple Multum codes. Simple derivation would also be required for all metabolic classes. While no codes were identified for metabolic classes in Multum, data elements could be defined by multiple individual NDC

codes. Resources such as the P450 Drug interaction: Abbreviated "Clinically Relevant" Table that describes drugs that appear to be metabolized via specified cytochrome P450 isoforms (Flockhart, 2007) could be utilized to define metabolic classes. A an important note, while this work classifies metabolic classes as simple derivation given that NDC codes exist for medications listed on resources identifying P450 drug interactions, defining metabolic classes may not be an area of priority for vender products such as Multum.

Medication data elements requiring complex derivation were categorized as "not captured." These included "drugs that have a narrow therapeutic index," "drugs that prolong QT interval," "drugs that prolong QTc interval," and "major drug metabolizing CYP enzyme substrates." Drugs with a narrow therapeutic index (NTI drugs) pose concerns about potential over or under-dosing with use of a standard dosing regimen. Information regarding testing for particular genetic polymorphisms is included in the product labeling of some NTI drugs for which genotyping might improve drug choice/dosing and consequent patient outcomes. Identifying NTI drugs requires complex derivation because calculating the dose ratio in dose-response curves or calculating the effect-plasma concentration relationship would ideally identify a NTI drug. Current frameworks for representing knowledge in UW clinical environments do not support such calculations. In addition, there would need to be some internal agreement on an operational definition for NTI drugs. Similarly, complex derivation would be required to identify drugs that prolong QT interval, prolong QTc interval, or are major drug metabolizing CYP enzyme substrates given that an operational definition is needed. To provide some background on QT interval and corrected QT (cQT) interval, it is a measure of the time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart. It is important to identify drugs that might prolong the QT or cQT interval because prolonging the QT interval is a risk factor for sudden death.

Several condition data elements were investigated further to determine whether relevant I-CD9 codes existed. Data elements for which no ICD-9 code was identified either required some form of derivation or were unable to be derived. There were nine condition data elements that could be made available with complex derivation. For example, an ICD-9 code did not exist for "bone marrow suppression," but with an internal operational definition could be defined by multiple codes. If a condition data element could be defined by multiple codes and an internal operational definition was not needed (e.g. cardiovascular disease), then it

was considered "captured" but would require simple derivation (e.g. IF patient has acute pulmonary heart disease THEN patient has cardiovascular disease).

There were no demographics data elements that could be made available with complex derivation. Demographics data elements labeled as "not captured" were primarily countries or regions of origin (e.g. Taiwan, Middle East). Demographics requiring simple derivation included data elements such as "child" that could be defined easily with supportive knowledge (e.g. IF age ≤18 THEN patient is a "child"). Demographics data elements that were "captured" without need for derivation were race and ethnicity (e.g. Caucasian) or gender (e.g. Female) categories.

All laboratory value data elements with a UW Laboratory medicine mnemonic code were assumed to require simple derivation. Approximate decision support rules that specify a genetic laboratory value generally included some interpretation of the laboratory values (e.g. CYP2D6 extensive metabolizer, CYP2D6 poor metabolizer). The current coding scheme does not include interpretations given that it is primarily used for ordering purposes. Therefore, such interpretations require some additional knowledge. Laboratory data elements without a UW Laboratory medicine mnemonic were classified as "not captured" and unable to be derived.

All together, 78% (251/320) of the data elements investigated in this work were captured in UW clinical data repositories. Within each data category, 97% (167/172) of the medications, 57% (39/68) of the conditions, 51% (19/37) of the laboratory values, 59% (23/39) of the demographics, and 75% (3/4) of the procedures were captured. These results are further summarized in *Figure 14* (on the next page). Data element categories are listed on the x-axis and the number of data elements on the y-axis. The number of data elements that are captured (no derivation required), captured (simple derivation required), not captured (complex derivation required), and not captured (unable to be derived) are indicated for each category of data elements. 91% (63/69) of the data elements categorized as "not captured" were within the conditions, laboratory values or demographics categories (42%,26% and 23%, respectively). In addition, of the 69 data elements categorized as "not captured," the majority (81%, 56/69) could not be captured with complex derivation. Therefore, new data fields and definitions needed to be added to UW clinical data repositories for the majority of

the data elements that were not captured to be made available.

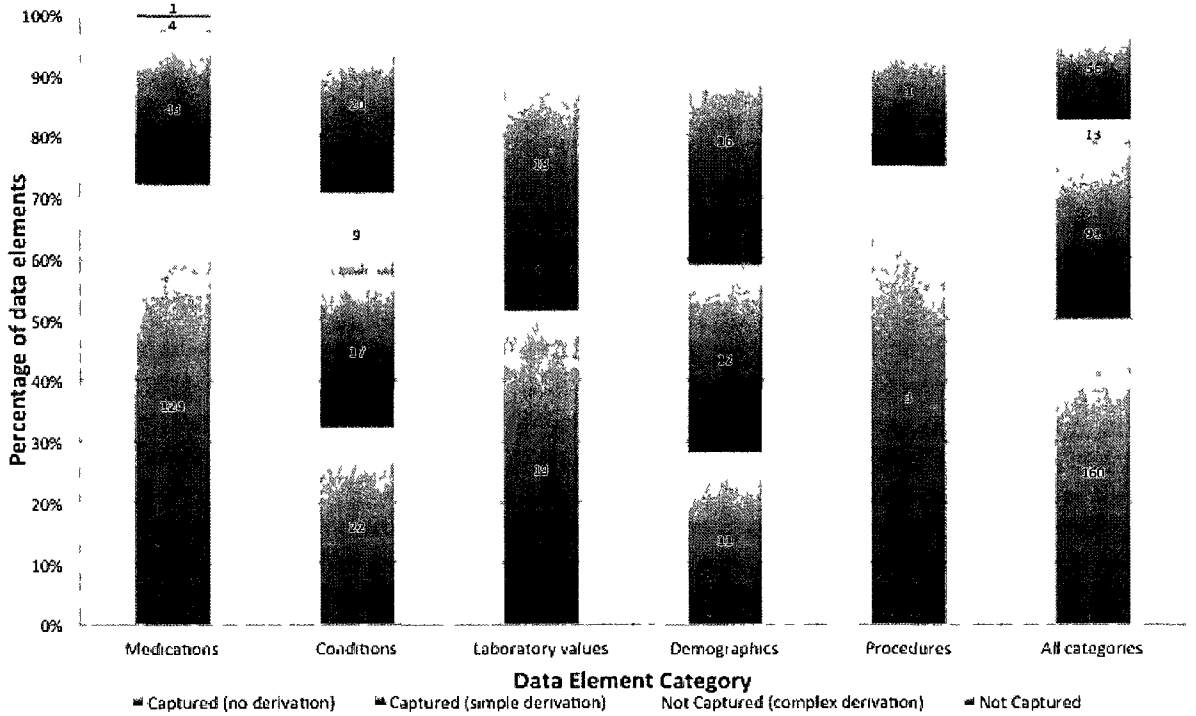

Figure 14. *Availability of data elements by category. Data element categories are listed on the x-axis. The last category, "All categories" indicates values across all data element categories. The y-axis is the percentage of data elements that are: captured (no derivation required), captured (simple derivation required), not captured (complex derivation required), and not captured (unable to be derived) for each category.*

Disease status definitions, data fields captured in pathology and microbiology laboratory systems, and pathology or microbiology laboratory values that exist in free text and can be parsed without use of full NLP methods were identified as feasible data types to incorporate into MIND and ORCA by expert opinion. In the updated evaluation (Summer 2011), the existence of laboratory value data elements in pathology and microbiology laboratory systems were not investigated with the assistance of UW Laboratory Medicine colleagues as they were in the initial evaluation (Fall 2009). Instead, the evaluation was performed based on the assumption that all laboratory values with UW Laboratory Medicine mnemonic code were considered "captured" and requiring simple derivation. Given this assumption, feasible data types were refined to be (a) disease status definitions, and (b) laboratory value data fields. Of the two, adding laboratory value data fields would be more difficult because it requires customizing the laboratory system, updating outbound interfaces with clinical data repositories, and customizing use of the new field for functions such as CDS.

The availability of data elements (requiring no or simple derivation) with and without feasible expansion of UW clinical systems is shown in *Figure 15*. The first bar indicates that 78% (251/320) of the data elements could be available within the current EHR with no or little additional knowledge required. The second bar indicates that the availability of data elements within the EHR could increase to 90% (289/320) with feasible expansion. With feasible expansion, twenty conditions and eighteen laboratory value data elements that were "not captured" and unable to be derived could be made available.

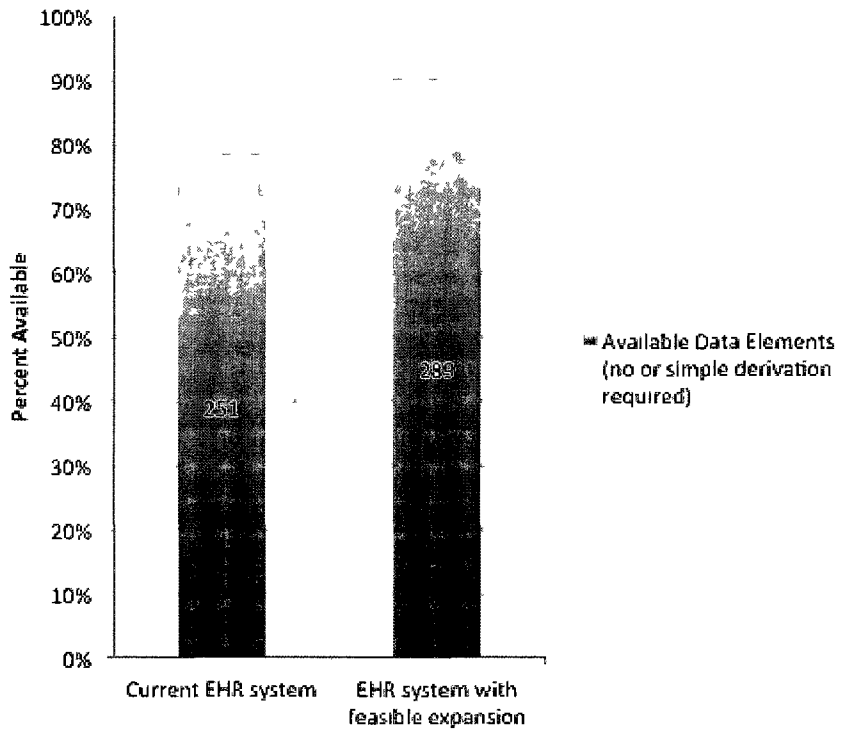

Figure 15. *Availability of data elements within the current EHR system with and without feasible expansion of the UW EHR system.*

Subsequent evaluation based on capabilities of the current EHR indicated that data were available to support executing 29% (165/565) of the 565 approximate PGx CDS rules within the UW clinical environment given current clinical data access. With the addition of knowledge for simple or complex derivation of data elements, the support for decision support rules would increase to 80% (449/565). *Figure 16* (on the next page) illustrates the proportions of rules that could be executed without any derivation, with simple derivation, and with complex derivation. It is evident that around 50% (284/565) of PGx decision rules

evaluated in this work would require at least some additional knowledge (as indicated by the requirement of simple or complex derivation). It is estimated that these numbers would increase even further given access to data elements made available with feasible expansion of the current EHR. In Appendix 5, the clinical data access support provided by UW clinical systems are summarized for each FDA drug-biomarker pair (US Food and Drug Administration, 2011).

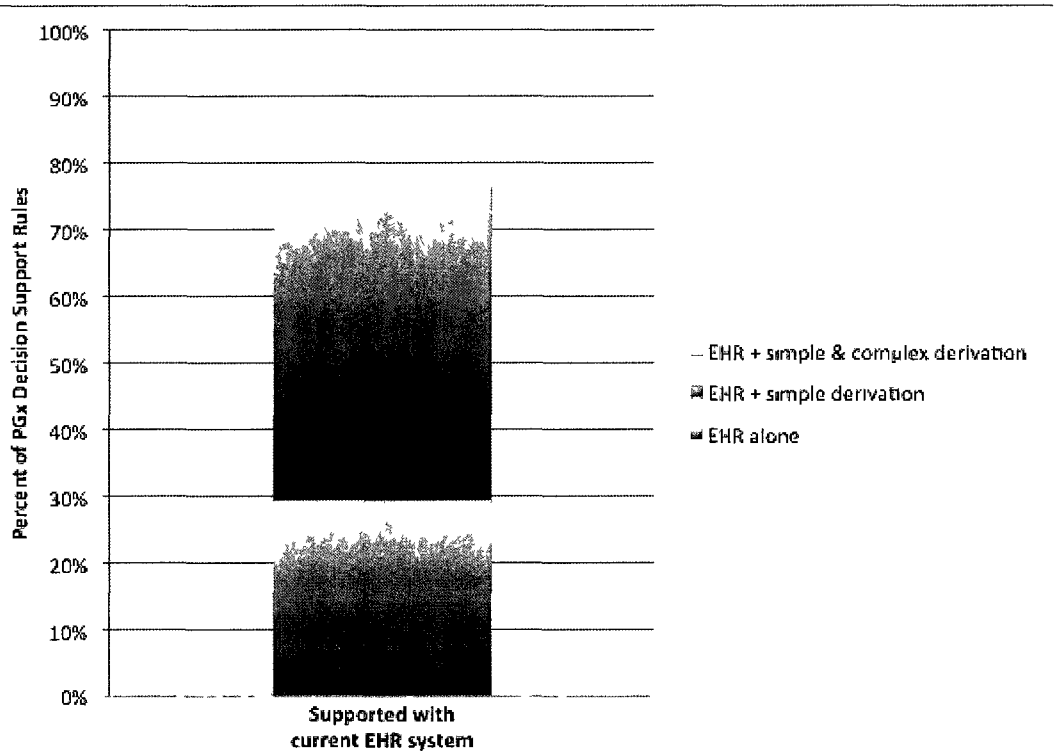

Figure 16. *Clinical data access for approximate pharmacogenomics decision support rule execution*

Clinical data access for executing approximate PGx decision support rules was explored in a more granular fashion to evaluate the CDS functionalities provided by UW clinical systems.

5.4.2. Aim 2.2: UW clinical system support for providing pharmacogenomics clinical decision support

5.4.2.1. UW clinical system clinical decision support functional capabilities

The results of evaluating the CDS capabilities of UW clinical systems are summarized in *Table 15*. Findings showed that across all systems (4/9, 44%) of triggers, (3/7, 43%) of interventions, (0/14, 0%) of offered choices, and (14/18, 78%) discrete data elements are supported. A capability is "supported" if it is assigned a value of Y or Y* (See *Table 14* on the next page). Only one UW clinical system, ORCA, supported all triggers and interventions investigated in this work. Only one UW clinical system, Amalga, provided support for all data elements invested in this work. The UW clinical system that best provided support for offered choices investigated in this work was ORCA (supported thirteen out of fourteen offered choices). Next, the requirements for PGx CDS were evaluated. Following, the alignment of these requirements with the current capabilities of UW clinical systems was determined.

Table 15. *UW Clinical system clinical decision support functional capabilities (Ref* (Overby et al , 2011)*)*

	MIND	ORCA	Amalga
Triggers			
Order entered	Y**	Y	Y
Lab result stored	Y	Y*	Y
Outpatient encounter	Y*	Y*	Y*
User request	Y	Y	Y**
Time	Y	Y*	Y
Admission	Y*	Y	Y
Problem entered	Y	Y*	Y**
Enter allergies	N	Y	Y*
Enter weight	N	Y	Y*
Interventions			
Notify	Y	Y*	Y
Log	Y**	Y*	Y
Provide defaults/picklists	N	Y*	Y**
Show Guidelines	Y	Y*	Y*
Collect free text	Y	Y*	Y**
Get approval	N	Y	N
Show data entry template	Y*	Y	Y*
Offered choice			
Write order	N	Y*	N
Defer warning	Y**	Y*	Y**
Override rule/ keep order	N	Y	N
Cancel existing order	N	Y*	N
Cancel current order	N	Y	N
Edit current order	N	Y	N
Edit existing order	N	Y*	N
Set allergies	N	Y	N
Write letter	Y	Y*	Y**
Write note	Y	Y	Y**
Edit problem list	Y	Y	Y**
*Enter weight	Y**	Y	Y**
*Enter height	Y**	Y	Y**
*Enter lab value status	Y*	N	N
Structured/discrete data element			
Lab result/ observation *A single genomic marker from a single gene test result	Y	Y	Y
Drug list	Y	Y	Y
Hospital Unit	Y	Y	Y
Diagnosis	Y	Y*	Y
Problem	Y	Y	Y
Age	Y	Y	Y
Non-drug orders	N	Y	Y
Gender	Y	Y	Y
Family history	Y	Y**	Y
Allergy list	Y	Y	Y
Weight	Y	Y	Y
Surgical history	Y	Y**	Y
Reason for admission	Y	Y	Y
Prior visit types	Y	Y*	Y
Race	Y	Y	Y
Patient medical history	Y	Y**	Y
Language	Y	Y	Y
Place of birth	Y	Y*	Y

5.4.2.2. *Pharmacogenomics clinical decision support functional requirements*

The initial evaluation of the functional requirements for PGx CDS, completed Summer 2011, was performed with 110 approximate decision support rules derived from the drug labels of ten medications (five oncology and five cardiology medications). Findings showed that, for this subset of approximate decision support rules, 6/9 of the triggers, 4/7 of the interventions, 9/14 of the offered choices, and 6/18 of the discrete data elements evaluated in this work were required across all decision support rules. The updated evaluation, performed Summer 2011, investigated the CDS functional requirements for all 565 approximate decision support rules derived from the FDA labeling of 71 drugs. Similar to the previous findings, 6/9 of the triggers, 4/7 of the interventions and 9/14 of the offered choices were required across all decision support rules. However, the discrete data element requirements increased from 6/18 (when 110 rules were evaluated) to 13/18 discrete data elements required (when 556 rules are evaluated). *Figure 17* illustrates the number and percentage of all functional requirement categories that were investigated during the first and second evaluations.

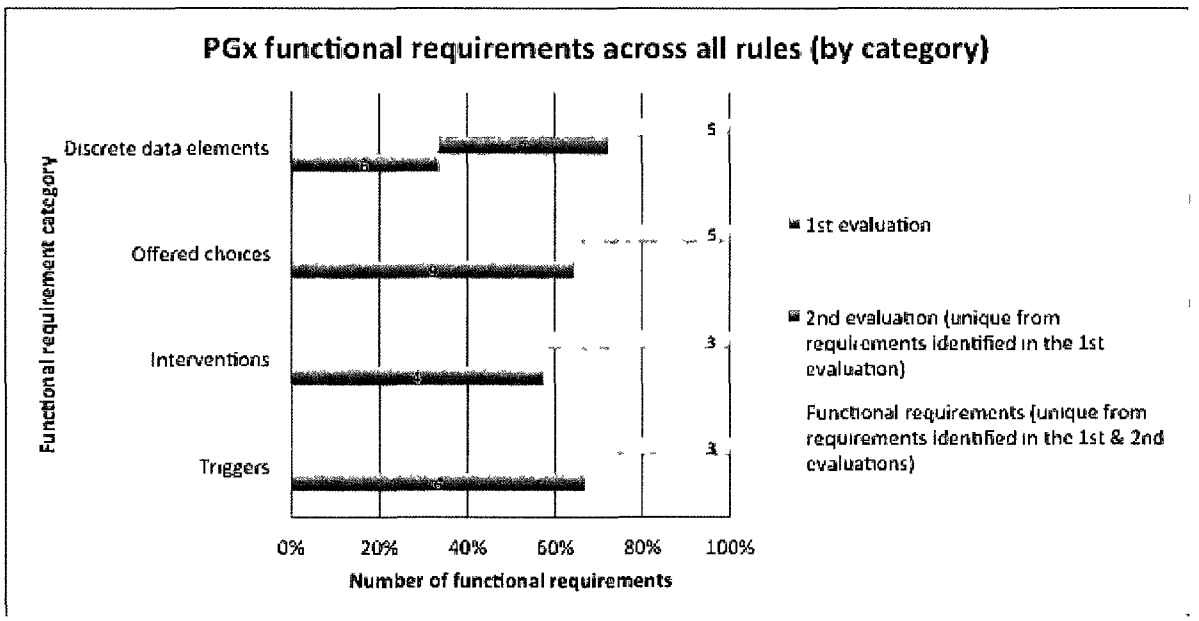

Figure 17. *The number of requirements for pharmacogenomics clinical decision support by functional requirement category. This figure also shows the percentage of all functional requirement categories that were investigated during the first (Fall 2009) and second (Summer 2011) evaluations.*

While several of the data element requirements were the same for the two evaluations, as expected, the number of rules (or in this case, rule pattern categories) for a given requirement increased substantially. Rule pattern categories were assigned to rules according to their pre-condition (IF statement) and post-condition (THEN statement). The top eight IF-THEN rule pattern categories are described in detail in Dissertation Chapter 4, Section 4.4.1.2. ***Figure 18*** (on the next page) illustrates the number of rules that fell into each rule pattern category. In total, there were 61 unique rule pattern categories identified. Nineteen out of 61 rule pattern categories were identified in the original evaluation. Also, seven of the top eight IF-THEN rule pattern categories were represented in the initial evaluation. These results suggest that the original investigation (using rules derived from oncology and cardiology drugs) was representative of the full set of PGx decision support rules reported in this chapter. The legend describing details for each for the 61 rule pattern categories is available in Appendix 6. Details and examples for the eight most frequent rule patterns (patterns 3, 20, 23, 28, 35, 43, 46 and 59 from ***Figure 18***) are shown in *Table 11*. For example, pattern 20 represents *pre-condition*: drug + genotype/phenotype/family_history & *post-condition*: recommended_treatment_protocol. An example rule of this pattern would be "IF patient is [bing considered for] taking mercaptopurine AND patient is heterozygous TPMT deficient THEN most patients with heterozygous TPMT deficiency tolerated recommended mercaptopurine doses, but some require dose reduction." Also related, the distribution and overlap of pre- and post- condition categories are shown in ***Figure 12***.

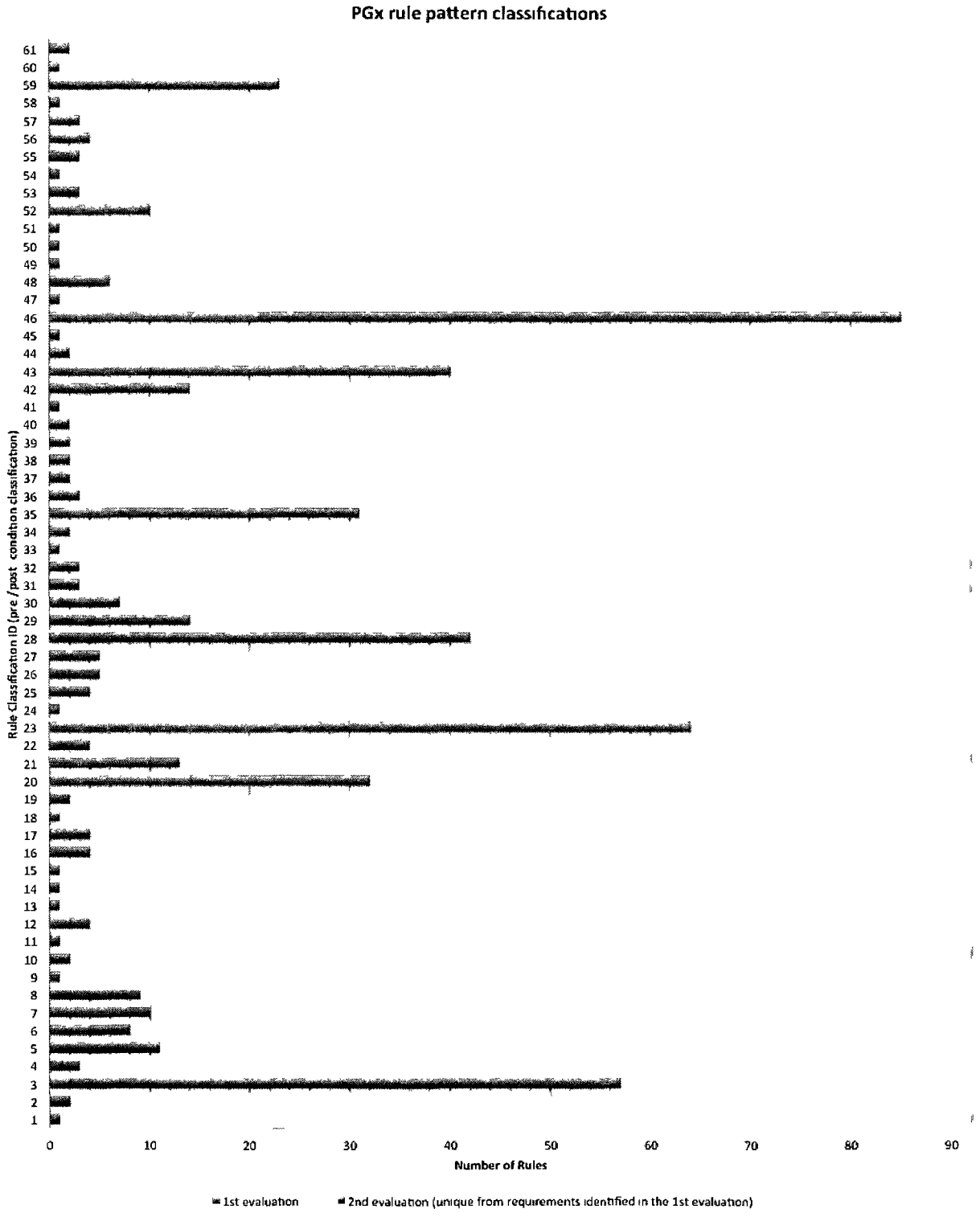

Figure 18. *The number of pharmacogenomics clinical decision support rules by rule pattern classification (classification by pre-/post- condition) This figure also shows the number of rules that were investigated during the first (Summer 2011) and second (Summer 2011) evaluation The legend describing the details for each of the 61 decision support rule pattern categories is available in Appendix 6*

The functional requirements for PGx CDS were determined by evaluating the requirements for each rule pattern individually. Many rule patterns had multiple functional requirements. The distribution of functional requirements for PGx CDS are described in *Figure 20* (discrete data element functional requirements), *Figure 19* (trigger functional requirements), *Figure 21* (intervention functional requirements) and *Figure 22* (offered choice functional requirements). The maximum number of rule classifications that require a given functional capability is 61, given that 61 unique rule patterns were identified in this work (See ***Figure 18***).

The triggers required for the majority of the approximate decision support rule patterns included *order entered*, *lab result stored* and *user request* (See *Figure 19* on the next page). Rule patterns designated as requiring *order entered* triggers were all those with "drug" in the pre-condition (55 rule patterns). This accounted for rule conditions that would fire when a new order (specifically, a medication order) is entered. Two additional rules for ordering laboratory tests were also included in the set of rule patterns requiring *order entered* triggers, both categories involved considerations to be made prior to ordering a test (e.g. "IF patient is [being considered for] phenotypic testing to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes AND patient has recently had a blood transfusion THEN Caution must be used with phenotyping since recent blood transfusions will misrepresent a patient's actual TPMT activity"). Rule patterns requiring *lab result stored* triggers were those with "genotype/phenotype" in the pre-condition (32 rule patterns). This accounted for rule conditions that would fire when a previously ordered laboratory result is stored. The primary difference between *order entered* and *lab result stored* is that one would present decision support in a synchronous manner (i.e. during the ordering process) and the other in an asynchronous manner (e.g. a reminder message appears next time the patient record is viewed, indicating that lab results are available). Rule patterns requiring *user request* triggers were rules with post-conditions that do not include "recommend" (e.g. recommended_treatment_protocol) or "interpretation" (e.g. test_interpretation) (42 rule patterns). Since a *user request* trigger is not an automatic trigger, but instead must be deliberately requested, the more "actionable" categories of rules (i.e. recommendations & interpretations) were excluded from the full set of rule patterns. After decision support is

triggered by a clinical event (e.g. prescribing a medication), discrete data elements (e.g. laboratory results) are used by decision support rules to make inferences.

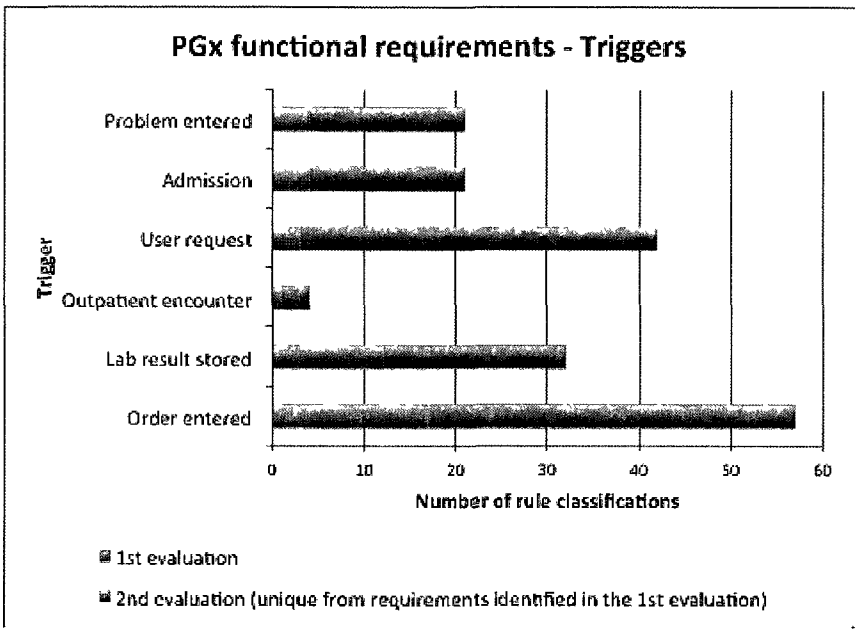

Figure 19. *The number of pharmacogenomics clinical decision support rule pattern classifications that require trigger functional capabilities evaluated in this work. Six trigger functional capabilities that are required for at least one rule pattern classification are included in this figure. This figure also shows the number of rule pattern classifications that were investigated during the first (Summer 2011) and second (Summer 2011) evaluation.*

An inference engine can identify and use discrete data elements to perform rule-based reasoning. The discrete data elements required for the majority of the PGx approximate decision support rule patterns included: *drug list*, *family history*, and *laboratory result/observation* (See *Figure 20* on the next page). Rule patterns designated as requiring *drug list* discrete data elements were all those with "drug" in the pre-condition (55 rule patterns). In this evaluation, the distinction was not made between the pre-conditions of approximate decision support rules where the patient is "being considered for" or "currently taking" a drug. Therefore, conservatively designating *drug list* as a discrete data element requirement for these rule patterns accounted for the "currently taking drug X" pre-condition. Rule patterns designated as requiring *family history* discrete data elements were all those with "family history" in the pre-condition (32 rule patterns). Rule patterns designated as requiring *laboratory result/observation* discrete data elements were all those with "genotype" or "phenotype" in the pre-condition (32 rule patterns). The same 32 rule patterns are

associated with *family history* and *laboratory result/observation* discrete data elements because "family history", "genotype" and "phenotype" pre-conditions were grouped together in this evaluation. The justification for this grouping was that family history is often used in the clinical setting to infer genetic inheritance, and like genotypic and phenotypic laboratory testing, is often used to make clinical predictions (e.g. risk predictions).

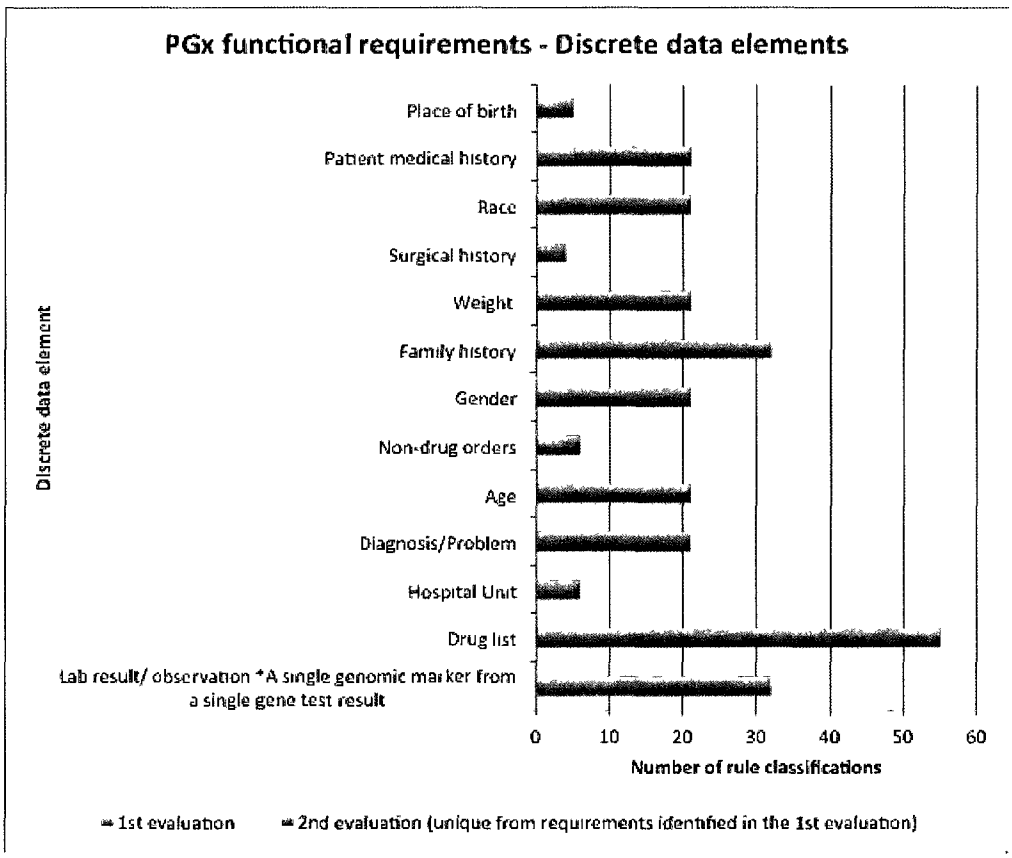

Figure 20. *The number of pharmacogenomics clinical decision support rule pattern classifications that require evaluated discrete data element functional capabilities. Thirteen discrete data element functional capabilities that are required for at least one rule pattern classification are included in this figure. This figure also shows the number of rule pattern classifications that were investigated during the first (Summer 2011) and second evaluation (Summer 2011).*

Here is an example where the same set of rule patterns ("drug" in the pre-condition) were designated as requiring the *order entered* trigger and *drug list* discrete data elements. An example rule with drug in the pre-condition is "IF patient is [being considered for] taking clopidogrel AND patient is identified as a CYP2C19 poor metabolizer THEN consider alternative treatment or treatment strategies". This rule has the pre-condition "drug + genotype/phenotype/family_history" and the post-condition

"recommended_treatment_protocol" (or rule pattern 20). In this case, when a physician tries to order clopidogrel for a patient, decision support could be triggered (i.e. *order entered* trigger). The inference engine would then initiate rule-based reasoning involving, in this case, the medication being ordered (i.e. *drug list* data element) and genetic laboratory results (*laboratory result/observation* data element). After reasoning concludes, if the conditions being investigated were satisfied (i.e. the patient is being prescribed cloplidogrel and is a poor metabolizer of CYP2C19) the inference engine might generate an output. There are several possible interventions that can be presented as output. Interventions are made visible to a clinical user once reasoning (that is triggered in response to the clinical event) concludes.

The *notify* intervention was required for all of the approximate decision support rule patterns (61 rule patterns) (See *Figure 21* on the next page). All rule patterns had this requirement because the notify (or notification) intervention involves any communication of information to a clinical user. Rule patterns requiring the *collect free text* and *show guideline* interventions were the same. Specifically, rule patterns with "recommended_testing" or "recommended_treatment_protocol" in the THEN statement (15 rule patterns) were assigned these intervention requirements. The *collect free text* intervention was considered an appropriate requirement for rules that provide recommendations for treatment protocols or for testing because if a physician decides to override an alert with a recommendation, a reason for overriding the alert should be requested. The *show guideline* intervention was considered an appropriate requirement for these rules because guidelines for acting on a given recommendation should be made available. Rule patterns requiring the *provide defaults/pick lists* intervention included "recommended_testing," "recommended_treatment_protocol," or testing_is_available" in the post-condition (18 rule patterns). In the case that a recommendation is provided in an alert message, a default method of acting on the recommendation could save the physician time. If the physician is alerted of laboratory tests they should consider ordering for a patient, then a pick list of testing alternatives could be appropriate. Considering the same example rule from the previous paragraph ("IF patient is [being considered for] taking clopidogrel AND patient is identified as a CYP2C19 poor metabolizer THEN consider alternative treatment or treatment strategies"), the post-condition is "recommended_treatment_protocol" but a specific treatment protocol is not suggested. In its current state, a *notification* intervention could be

implemented, but *guideline* or *defaults/pick lists* interventions would be inappropriate options for this rule (even though all three of these interventions are indicated as requirements for rules with recommendations in the post-condition). Even so, these requirements indicate a need to supplement the post-condition of the decision support rule with richer information so that all of the interventions could be implemented. Therefore, the associated intervention requirements for this rule helped identify how additional information could be specified within the approximate decision support rule (e.g. providing access to a specific guideline). Offered choices are particular types of *notification* interventions that can be presented to clinical users.

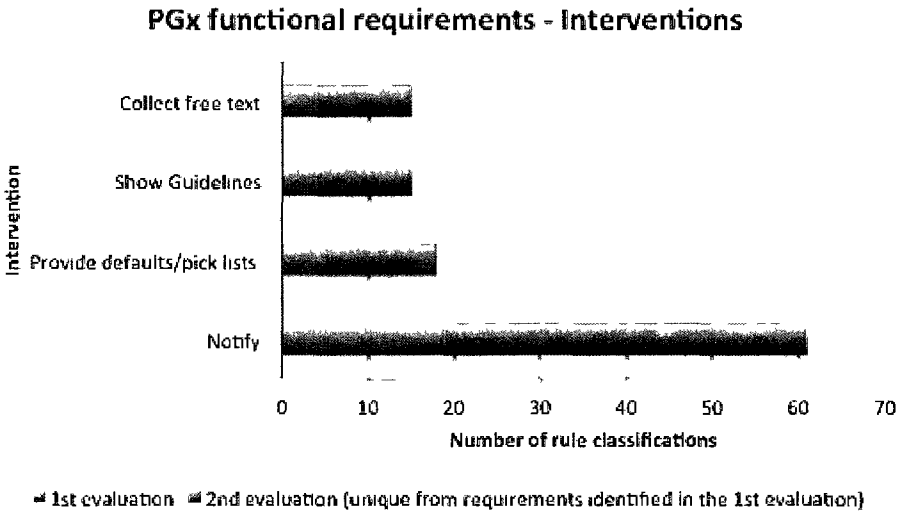

Figure 21. *The number of pharmacogenomics clinical decision support rule pattern classifications that require evaluated intervention functional capabilities. Four intervention functional capabilities that are required for at least one rule pattern classification are included in this figure. This figure also shows the number of rule pattern classifications that were investigated during the first (Summer 2011) and second (Summer 2011) evaluation.*

The offered choices category is considered a child of the notify intervention. The offered choices required for the majority of the approximate decision support rule patterns included: *edit existing order*, *edit current order*, *cancel existing order*, *cancel current order*, and *override rule/keep order* (See *Figure 22* on the next page). Rule patterns requiring these offered choices are most appropriate in the context of medication order entry where, given an alert message, the clinical user might be provided the option of canceling or editing the new drug order or the existing order. The *override rule/keep order* offered choice would allow

the clinical user to dismiss a notification (and is generally followed by a prompt to provide an override reason). Rule patterns requiring *edit current order*, *cancel current order*, or *override rule/keep order* were those with "drug" in the pre-condition (55 rule patterns), plus two additional rule patterns that included considerations to be made prior to ordering a laboratory test in the post-condition. Rule patterns requiring *edit existing order* or *cancel existing order* did not include the two rule patterns for ordering a laboratory test because unlike medication orders that are continued for a period of time, laboratory tests are either ordered or not ordered (results exist or do not exist).

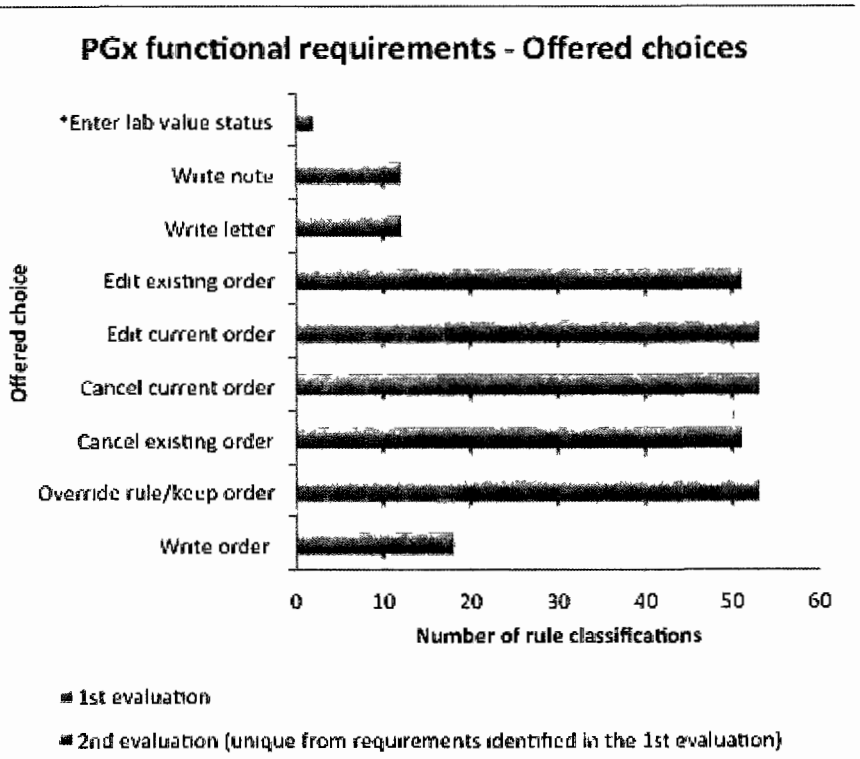

Figure 22. *The number of pharmacogenomics clinical decision support rule pattern classifications that require evaluated offered choice functional capabilities. Nine offered choice functional capabilities that are required for at least one rule pattern classification are included in this figure. This figure also shows the number of rule pattern classifications that were investigated during the first (Summer 2011) and second (Summer 2011) evaluation*

These five offered choices were considered required for the example rule "IF patient is [being considered for] taking clopidogrel AND patient is identified as a CYP2C19 poor metabolizer THEN consider alternative treatment or treatment strategies". The *edit existing order* and *cancel existing order* offered choices would be appropriate if, for example, the

patient was currently taking clopidogrel and the results of a laboratory test indicating the patient was a CYP2C19 poor metabolizer were made available in the system (*lab result stored* trigger). Triggers such as the *lab result stored* trigger are "asynchronous" because there is a delay between when the lab was ordered and when the lab result was stored. An asynchronous implementation of this rule might lead to an email being sent to the physician indicating the *edit existing order* and *cancel current order* offered choices for editing or canceling a clopidogrel order for the patient. If the example rule were implemented in a synchronous manner, the *edit current order*, *cancel current order*, and *override rule/keep order* offered choices would be appropriate options to present. For example, if the rule were triggered by ordering clopidogrel for a patient already identified as being a CYP2C19 metabolizer (*order entered* trigger), then the a notify intervention could occur during the ordering process. Accordingly, the *edit current order*, *cancel current order*, and *override rule/keep order* offered choices could be presented within an alert message prior to completing the order. This example highlights that there are often multiple ways to implement a decision support rule. Depending on implementation choices, it may be appropriate to incorporate only a subset of the functional requirements for a given rule.

In summary, the process of determining functional requirements for 61 CDS rule pattern classifications was described. An example rule was considered to illustrate that individual rule patterns span multiple functional requirements. For the majority of the rule classifications (like with the example rule), there were requirements for at least one taxonomy element of each taxonomy category (triggers, data elements, interventions, and offered choices). There may be several implementations for the same rule, with each implementation incorporating a different subset of the functional requirements for that rule. There are also situations where there are no implementations of a rule where a particular functional requirement is appropriate. Consequently, these situations can highlight the need to provide richer information within those approximate decision support rules. All rule classification functional requirements are summarized in Appendix 7.

5.4.2.3. *Alignment of pharmacogenomics clinical decision support functional requirements with UW clinical system functional capabilities*

After determining the functional capabilities of UW clinical systems and the functional requirements for PGx CDS, the ability of UW clinical systems to support the functional requirements for PGx CDS was investigated. *Table 16* summarizes the alignment of UW CDS functional capabilities with PGx CDS requirements. Currently, triggers required for PGx CDS are only supported by ORCA. However, with some minimal system configuration, MIND and Amalga could also support the triggers. The interventions required for PGx CDS are also currently supported only by ORCA. With minimal system configuration, Amalga could also support interventions, and considerable system configuration is needed for MIND to support required interventions. None of the systems evaluated in this work supported all of the offered choices required for PGx CDS without considerable system configuration. Finally, discrete data elements required for PGx CDS were supported by Amalga, and with minimal system configuration, could also be supported by ORCA. Considerable system configuration is needed for MIND to support the required discrete data elements.

Table 16. *Functional capabilities for pharmacogenomics clinical decision support by UW clinical system. The functional capability categories of support provided by each UW clinical system are shown. Support values (Y,Y*,Y**, N) were assigned to each UW clinical system (MIND, ORCA, Amalga) according to methods described in Section 5.3.2. Y/Y*/Y**/N counts are shown in parentheses.*

	MIND	ORCA	Amalga
Triggers	Y** (3/2/1/0)	Y* (3/3/0/0)	Y** (3/1/2/0)
Interventions	N (3/0/0/1)	Y* (0/4/0/0)	Y** (1/1/2/0)
Offered choices	N (2/1/0/6)	N (4/4/0/1)	N (0/0/2/7)
Discrete data element	N (12/0/0/1)	Y** (9/1/3/0)	Y (13/0/0/0)

To better understand which UW clinical system best supports the requirements for PGx CDS, the percentage of requirements that were and were not supported by each system were investigated and compared. See *Figure 23* for support provided by MIND, *Figure 24* for support provided by ORCA, and *Figure 25* for support provided by Amalga (figures on the next page). A PGx CDS requirement is considered "supported" by a system if it is assigned the value of Y or Y*, and "not supported" if assigned Y** or N.

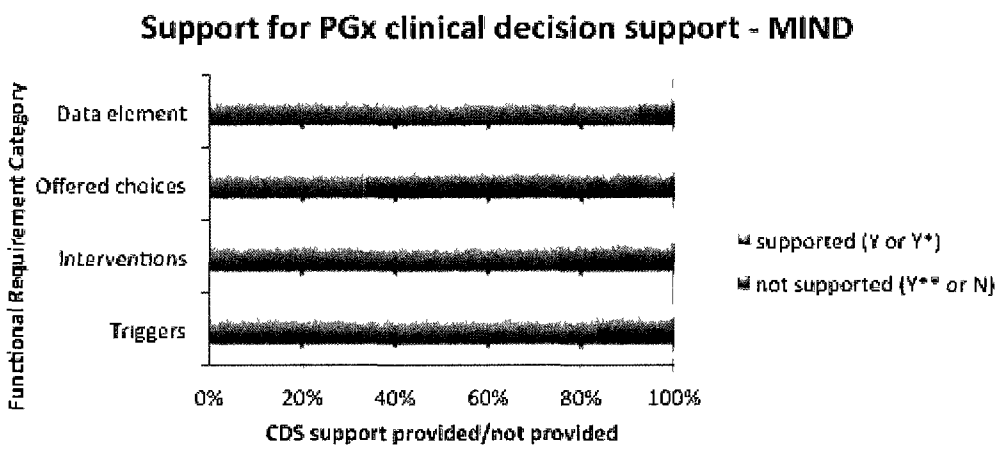

Figure 23. *Percentage of pharmacogenomics clinical decision support requirements supported and not supported by MIND (by functional requirement category).*

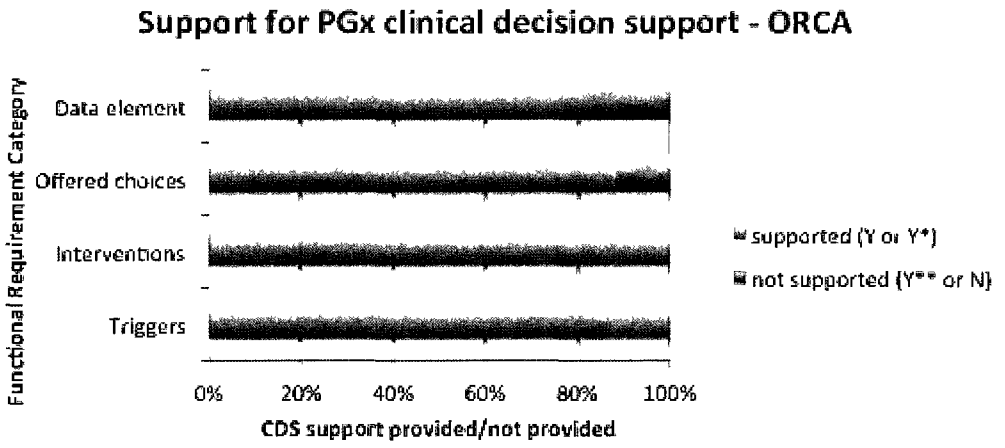

Figure 24. *Percentage of pharmacogenomics clinical decision support requirements supported and not supported by ORCA (by functional requirement category)*

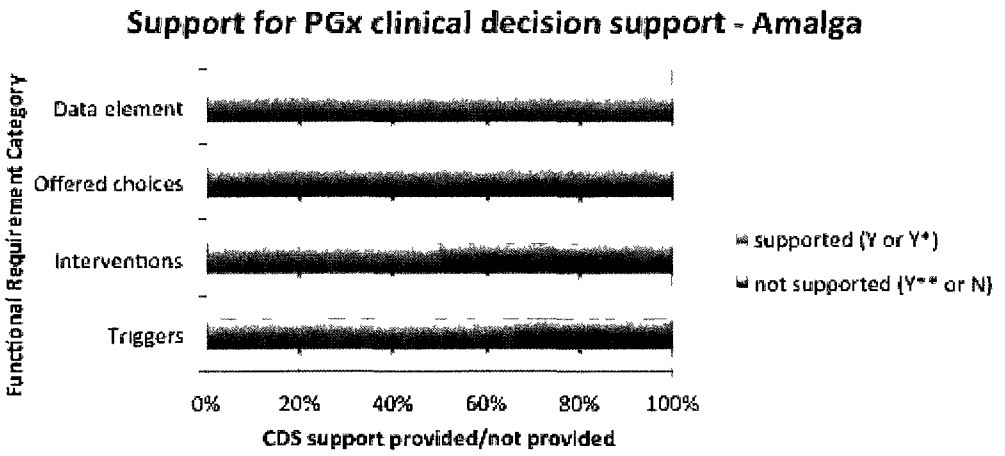

Figure 25. *Percentage of pharmacogenomics clinical decision support requirements supported and not supported by Amalga (by functional requirement category).*

Results showed that across the three UW clinical systems, ORCA currently best supports PGx CDS implementation with 77% of discrete data elements, 89% of offered choice, 100% of intervention and 100% of trigger CDS functional requirements supported. The following chapter (Dissertation Chapter 6) describes the implementation of approximate decision support rules electronically in ORCA.

5.5. Summary & Discussion

This chapter provides details from an evaluation of the ability of University of Washington clinical systems to (a) provide the data needed for pharmacogenomics clinical decision support, and (b) support the functional requirements for pharmacogenomics clinical decision support. To summarize findings from Aim 2.1 the feasibility of University of Washington clinical systems to provide computable data was determined. Specifically, 29% of the pharmacogenomics approximate decision support rules explored in this work could be executed within the University of Washington electronic health record environment given the current availability of clinical data. With the addition of supporting knowledge (simple or complex derivation) this number goes up to 80%.

One potential limitation to this evaluation is that there were around 30 data elements excluded from this evaluation (See Appendix 8 for "other data elements"). This subset of data elements were excluded primarily because they would likely require investigating whether or not they were captured as free-text in a form that can be easily parsed. Investigating the availability of data elements as free-text values within the University of Washington clinical systems was considered out of scope in the updated analysis performed Summer 2011. In addition, the priorities of venders were not considered in designating simple and complex derivation. For example, from the vender point of view, providing support for therapeutic classes might be of a higher priority when compared to providing support for chemical classes and metabolic classes. As such, there may be additional barriers to defining chemical and metabolic class data elements for pharmacogenomics clinical decision support. This is an area that requires further investigation to fully understand the impact of vendor priorities on what can be accomplished at individual institutions.

Overall, while results from Aim 2.1 analyses may differ between institutions, methods provided in this chapter can be used by other institutions interested in evaluating their

electronic health record environment, "we believe our methods are generalizable and can be used to evaluate the availability of clinical data to support pharmacogenomics clinical decision support within any EHR framework." (Overby et al., 2010).

Also, "it has been shown that different representations of pharmacogenomics test results (e.g. gene single nucleotide polymorphisms, gene alleles) with automated interpretation (e.g. ' homozygous normal' , ' heterozygous affected') can be used effectively within the electronic health record without impacting reaction times in responding to alert messages (Deshmukh, Hoffman, Arnoldi, Bray, & Mitchell, 2009)." (Overby et al., 2010). Therefore, the methods used in this research should be applicable independent of pharmacogenomics data representation.

To summarize findings from Aim 2.2, the feasibility of University of Washington clinical systems to support the functional requirements for pharmacogenomics clinical decision support was determined. First, to determine the functional capabilities of MIND, ORCA, and Amalga informal interviews were performed with individuals that are knowledgeable of UW clinical systems. Overall, the clinical decision support functional capabilities vary across University of Washington clinical systems. ORCA was the only University of Washington clinical system that supported all triggers and interventions investigated in this work. Also, Amalga was the only one University of Washington clinical system that provided support for all data elements invested in this work. While no system supported all of the offered choices investigating in this work, ORCA provided the best support when compared to the other systems. Next, pharmacogenomics clinical decision support functional requirements were determined. Across all pharmacogenomics approximate clinical decision support rules, 6/9 of the triggers, 4/7 of the interventions, 9/14 of the offered choices and 13/18 discrete data elements investigated in this work were required. Lastly, the alignment of current UW clinical system capabilities with the requirements for pharmacogenomics clinical decision support was determined. Of the three clinical systems investigated in this work, ORCA best supported the implementation of PGx clinical decision support.

Similar to the Aim 2.1 evaluation of the availability of clinical data in University of Washington clinical systems, results from the work discussed in Aim 2.2 may differ between institutions. It is possible that other implementations and configurations might result in different functionality. Even so, a range of clinical systems were evaluated in this work, two

of which are based on broadly used commercially available clinical data repositories. Therefore, findings from this work are likely generalizable to other environments.

The following chapter (Dissertation Chapter 6) reports findings from work building on the results presented in this chapter. Namely, approximate decision support rules are implemented electronically in ORCA given that (of the systems evaluated in this work) it best supports pharmacogenomics clinical decision support implementation.

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6. CHAPTER 6: DEVELOPING A PROTOTYPE IMPLEMENTATION OF A MODEL FOR PHARMACOGENOMICS CLINICAL DECISION SUPPORT (AIM 3)

6.1. INTRODUCTION

In Chapter 4 of this dissertation, 565 decision support rules containing pharmacogenomics knowledge were derived from the FDA labeling of 71 drugs. Categories of support provided by approximate decision support rules determined in that chapter were used in the previous chapter (Dissertation Chapter 5) to determine clinical data requirements and clinical decision support functional requirements for providing pharmacogenomics knowledge in the context of clinical decision support embedded in an EHR. To further determine the requirements for pharmacogenomics clinical decision support, in this chapter, the user interface requirements for providing pharmacogenomics clinical decision support were predicted. In addition, based on findings from Dissertation Chapter 5 and predicted user interface requirements, a prototype implementation of a University of Washington clinical system was developed and is presented in this chapter. This prototype version of the University of Washington clinical system was designed to have the best potential to support pharmacogenomics clinical decision support (according to previous evaluations) was established.

The primary research question addressed in this chapter is: How can patient genetic test results and just-in-time pharmacogenomics knowledge be presented to users with electronic health record clinical data so that it aligns with requirements of pharmacogenomics knowledge? Answering this research question improves our understanding of what user interface features are needed to appropriately implement pharmacogenomics clinical decision support rules explored in the previous two chapters. Related to the overarching aim of this research, the requirements for incorporating pharmacogenomics knowledge into an EHR are further determined (predicted user interface requirements). Also, implementing a prototype system further provides insight into the technical requirements and barriers to incorporating pharmacogenomics knowledge into an EHR. The utility of the implemented model for pharmacogenomics clinical decision support presented in this chapter is evaluated in the following chapter (Dissertation Chapter 7). Quoted sections in this dissertation chapter are

primarily borrowed from the publication titled "An Evaluation of Functional and User Interface Requirements for Pharmacogenomic Clinical Decision Support" (Overby et al., 2011) with permission from the publishers.

6.2. Related work & Significance

In this work, scenarios were used to evaluate possible designs for pharmacogenomics (PGx) clinical decision support (CDS). Scenarios incorporating characteristics of PGx knowledge and CDS features in the context of computerized order entry system (CPOE) were constructed (Aim 3.1). For each scenario, claims were then generated about positive and negative effects of varying maturity of PGx knowledge and different system feature configurations (Aim 3.2).

6.2.1. Use of scenarios for engineering design requirements

Scenarios are used in a variety of engineering settings to assist with design progression. To give a brief definition, "scenarios are stories about people and their activities, and are a means to improve communication between developers and system users (Carroll, 2000). Motivations for using scenarios as a design tool differ; therefore there are several methodologies. For example, Scenario-based Design methods (Carroll, 1995), (Hertzum, 2003) are commonly used in Human Computer Interaction (HCI) research to manage the flow of design activity wherein user tasks and artifacts are characterized to inform design (Carroll, 2000). However, there are several other uses for scenarios in technology design and development. Three categories of scenario content include: system context, system interaction, and internal system (Weidenhaupt, Pohl, Jarke, & Haumer, 1998). Scenario-based Design methods focus primarily on system context (descriptions of the broader environment in which the system sits) and system interaction (how the system interacts with the environment). In this work, we are also interested in the internal system (the internal interactions among system components)." (Overby et al., 2011). Similar to the work presented in this dissertation, the Personalized Health Care Initiative and the American Health Information Community's Personalized Health Care (AHIC PHC) Workgroup (US Department of Health and Human Services & Office of the National Coordinator for Health Information, 2008) used scenarios focused on describing the internal system of EHRs.

6.2.2. *Use of scenarios for genetic test results in the electronic health record*

Scenarios for presenting genetic test results in the EHR were utilized both in the work completed as part of this dissertation, and in work completed by the AHIC PHC Workgroup. In this dissertation, scenarios were specifically used to evaluate how well CDS interface design features fit PGx knowledge characteristics. The scenarios constructed in this work were therefore scenarios for just-in-time CDS incorporating various forms of PGx knowledge. User interface (UI) presentation requirements are predicted for each scenario, and the technical implementation to support the scenarios is proposed based on the requirements. The internal system investigated in this work is the implementation of just-in-time CDS in the context of personalized healthcare delivery. The internal system investigated by the AHIC PHC Workgroup, on the other hand, involved the interactions and exchange of information between perspectives (i.e. clinician, testing laboratory, or consumer) in the context of a personalized healthcare workflow (i.e. pre-analytic, analytic, or post-analytic phases of genetic testing). In contrast, the work presented in this dissertation focused specifically on the perspective of the clinician participating in post-analytic phase workflows.

6.2.3. *Use of scenarios in the evaluation process*

A prototype implementation of a UW clinical system that incorporated PGx CDS was established in this work. Scenarios constructed in this work served as a tool to evaluate possible designs before they were implemented. For example, "scenarios may be used as a tool to provide contextual information for evaluating early system designs (Carroll & Rosson, 1992). In this work, we employed the Claims Analysis method (Carroll, 1995) to assess task and proposed new functionalities." (Overby et al., 2011) Tasks (or use scenarios) are constructed for the purpose of exploring UI presentation requirements for different forms of PGx knowledge. The claims analysis process involves generating statements about what has happened or what is expected to happen as a result of engaging in a task (or use scenario). It is a method by which designers or evaluators can consider the trade-offs of system support (provided by particular system features) for a given use scenario. Traditionally, claims analysis was applied as a user-centered evaluation approach that does not generally take the functional capabilities of existing systems into consideration. This work took a more participatory development approach to applying claims analysis, rather

then the user-centered evaluation approach. A participatory approach to performing claims analysis was also applied in a case study where investigators worked with the developers of a corporate digital library interested in incorporating a novel design features (Blandford, Keith, & Fields, 2006). In that work, the investigators were able to adopt and adapt the claims analysis technique to bridge evaluation of an existing system and redesign of that system. Some aspects of their codification scheme for performing claims analysis was incorporated into this work (See Aim 3.2, Section 6.3.2), such as the reverse process of generating scenarios based on functions the system developers were concerned about. Similar to the case study work, scenarios were not constructed based on empirical studies of how users work (as in the work discussed by Carroll and Rosson). Instead, scenarios in the case study work were constructed by reflecting on how users intend to work under new interaction possibilities. Claims analysis techniques were then applied to explore the positive and negative effects of adding new features to the digital library from the user perspective. Several features of the library, such as the keyword browser (a search tool that analyzed index terms used to categorize documents), were considered. Scenarios in this work, in contrast, described new interaction possibilities. The interaction possibilities of interest were based on characteristics of PGx knowledge in the context of CDS embedded in the EHR. For each scenario, claims analysis techniques were then applied to explore the positive and negative effects of select system feature configurations. Features for semi-active and active CDS within one UW clinical system were considered in this evaluation.

Another unique aspect of the approach to performing claims analysis that was explored in this work, is that multiple system state models were considered. The process of generating claims involves investigating various aspects of how a system user performs a task e.g. establishes a goal, specifies an action sequence, etc. (See Section 6.3.2.2 for more detail). During this process the system state is generally considered something that can change as a result of performing a task. In this work, however, system state models based on the maturity of PGx knowledge are determined as a preliminary step to that investigation.

6.2.4. Significance

The significance of this work included an evaluation of potential UI requirements for presenting PGx in EHRs with use scenarios. In addition, claims analysis techniques were

applied in a novel way to perform the evaluation. Moreover, as an outcome of this work a conceptual model for PGx CDS in the EHR was proposed and incorporated into a prototype system implementation. The technical limitations to establishing a prototype system implementation are described.

6.3. METHODS

6.3.1. Aim 3.1: Constructing scenarios and defining clinical decision support system features

In applying claims analysis techniques, claims are generated in the context of scenarios. *Problem initiation scenarios*, *usage scenarios*, and *projected scenarios* are three forms of scenarios used with claims analysis that have been described previously (Sutcliffe & Carroll, 1999). *Problem initiation scenarios* describe the original situation motivating the redesign of a system, *usage scenarios* describe a sequence of user-system interaction to illustrate a problem in a current design, and *projected usage* describes anticipated interaction with a system that has been redesigned.

Three usage scenarios were constructed describing possible new interactions of a user with PGx knowledge (See *Table 17* on the next page). Characteristics of PGx knowledge differ between scenarios by how actionable it would be in a clinical context. Specifically, the terms *information only*, *recommendation*, and *warning* were used to characterize the maturity of PGx knowledge available in each usage scenario. In Dissertation Chapter 4, these terms were referred to as *user interface (UI) presentation types* and the definitions for each type are summarized in *Table 18* (on the next page).

In addition, the results of the evaluation presented in Dissertation Chapter 5 indicated that computerized provider order entry (CPOE) support was often required for PGx CDS. Therefore, all usage scenarios were described in the context of CPOE. In addition, the presentation of knowledge through one of three CDS features common in CPOE systems were considered. Scenarios describing possible new interactions with three CDS features are described in *Table 19* (on the next page).

Table 17. Usage scenarios describing interactions with pharmacogenomics knowledge

Scenario number and title	Scenario description
Scenario 1 – CPOE & recommendation	Using CPOE, the clinician is prescribing a medication for which there are recommendations in the FDA drug label about its' use given the patients' genetic test results
Scenario 2 – CPOE & warning	Using CPOE, the clinician is prescribing a medication for which there are warnings in the FDA drug label about its' use given the patients' genetic test results
Scenario 3 – CPOE & information only	Using CPOE, the clinician is prescribing a medication for which there is information only in the FDA drug label about its' use given the patients' genetic test results

Table 18. Descriptions of user interface presentation types (descriptions used in Dissertation Chapter 4).

User interface presentation type	Description
Information only	A statement is classified as *information only* if no direct action is specified within the statement, or actions are specified using language with a low degree of certainty (i.e. might, may, could).
Recommendation	A statement is classified as a *recommendation* if a clear action is specified using language with a medium to high degree of certainty (i.e. should, will, are, is, must, was, do).
Warning	A statement is classified as a *warning* if potential consequences are specified (language may be of any degree of certainty).

Table 19. Usage scenarios describing interactions with system clinical decision support features

Feature number and title	Feature description
Feature 1 – PGx link to e-resources (semi-active CDS feature)	• The clinician selects the medication they wish to prescribe and a context-specific link to PGx e-resources appears. • A context-specific link to PGx e-resources appears next to the genetic test results of interest.
Feature 2 – Alert message (active CDS feature)	• The clinician enters prescribing information consistent with empirical therapy, clicks the "prescribe" button, and an alert message pops up providing a message relevant to the patients' genetic test results and the medication being ordered.
Feature 3 – PGx link to e-resources within an alert message (semi-active CDS feature that follows active CDS)	• A context-specific link to PGx e-resources appears within an alert message relevant to the patients' genetic test results and the medication being ordered.

Active and semi-active CDS features that either currently exist or have the potential to be incorporated into the current UW clinical system infrastructures were considered. Properties of alert messages (Features 2 and 3 in *Table 19*) are assumed to include: title, text message, alert action, and an optional link to an external website that displays PGx e-resource (Features 1 and 3 in *Table 19*). "The text message is for indicating the event that is being performed (e.g. you have ordered Warfarin); incorporates substitution values (e.g. order

name, patient specific test results), and is used to describe relevant information, a warning, or a recommendation The alert action includes options to cancel (allows the order that was just entered to be canceled), override (allows for the text message to be ignored and overrides the alert), and modify (allows for the order that was just entered to be modified)." (Overby et al , 2011). Previous work revealed that for context-sensitive links to e-resources, incorporating "topics" lead clinicians to content subsections that are more closely related to the clinicans' question Therefore, several sections are defined for context-specific PGx links to e-resources (Features 1 and 3 in *Table 19*). Categories of evidence considered for inclusion in PGx resource websites are described in *Table 20*

Table 20. *List of PGx resource categories of evidence*

Category of evidence	Description
FDA Information on Genomic Biomarkers	Resources that allow for quick location of relevant label content and sections (e g Boxed Warning, Contraindications, Warning and Precautions, etc)
Evidence Based Synopses	Evidence summaries that allow clinicians to quickly assess scientific justifications
Guidelines	Guidelines that include authoritative recommendations about what actions to take
Systematic Reviews	Systematic review of the relevant primary literature
Metabolism and Pharmacogenetics	Evidence of the influence of genetics in the drug elimination process
Primary literature	Primary literature describing relevant studies

In summary, two sets of usage scenarios were constructed in this work. One set of scenarios conveys new interaction possibilities based on current maturity of PGx knowledge (PGx knowledge usage scenarios, see *Table 17*). The other set of usage scenarios were constructed to suggest new interaction possibilities in the context of various implementations of CDS embedded in the EHR (CDS feature usage scenarios, see *Table 19*). Claims analysis was performed as a method for considering the positive and negative effects of the new interaction possibilities described in the scenarios The general approach taken to perform claims analysis involving these scenarios can be summarized in five steps (See Section 6.3 2).

6.3.2. *Aim 3.2: Claims analysis for user interface presentation needs assessment*

The general approach developed to apply claims analysis is described in the following steps (also see *Figure 26* on the next page):

1. Design features of interest that can be presented (in this case, CDS UI properties) or configured (in this case, CDS features) within the current system are described.
2. Scenarios to evaluate design features are proposed. The primary sources for scenarios included results from evaluating the maturity of PGx knowledge in FDA drug labeling in Dissertation Chapter 4 (PGx knowledge usage scenarios), and knowledge of user-feature interaction tasks (CDS feature usage scenarios).
3. System state models to support usage scenarios are characterized. The primary source for specifying system state models are the results from evaluating the maturity of PGx knowledge (PGx knowledge usage scenarios) and CDS UI properties (e.g. alert message properties and categories of evidence available to include in resource websites).
4. Claims are generated by looking, in detail, at user-feature interactions within various system state models. During this process the following are considered: what actions the user would perform, how the actions are executed within the system, how the system state is perceived by the user, and how the system state is interpreted by the user.
5. The positive and negative claims are considered to make system presentation and configuration decisions.

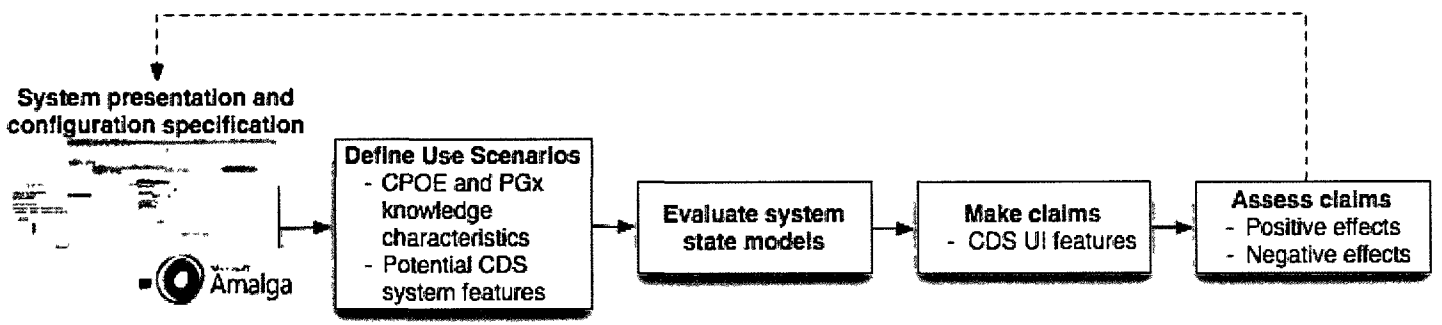

Figure 26. *Process model of claims analysis*

6.3.2.1. *Defining system state models for pharmacogenomics knowledge presentation*

System state models were defined by predicting CDS UI properties (i.e. alert message and e-resource website properties) given the maturity of PGx knowledge covered in the PGx knowledge usage scenarios (i.e. recommendations, warnings, information only). A pairwise assessment between PGx knowledge usage scenarios and CDS UI properties was performed. Each pair was assigned the value "always," "often," "sometimes," or "rarely" to indicate the frequency a UI property appears for a given PGx knowledge usage scenario. For example, the frequency for having the "Guidelines" topic subsection within an e-resource website would be "often" when there are recommendations, "sometimes" when there are warnings, and "rarely" when there is information only. The frequencies of a set of UI properties for a PGx knowledge usage scenario represents the system state model for that scenario. Following, claims were generated for user-feature interaction tasks (CDS feature usage scenarios).

6.3.2.2. *Generating and evaluating claims*

Guidance on how to apply claims analysis techniques, including nineteen questions to ask to generate claims, was presented in a previous publication (Carroll & Rosson, 1992). Questions were organized according to Norman's seven stages of action (Norman, 1986): establishing a goal, forming an intention, specifying the action sequence, executing the action, perceiving the system state, interpreting the state, and evaluating the system state with respect to the goals and intentions.

The approach to generating claims in this work was refined to include consideration of what actions the user would perform, how the actions are executed within the system, how the system state is perceived by the user, how the system state is interpreted by the user and how the system state is evaluated with respect to the goals and intentions. Goal and intention formation were excluded from the evaluation because all of the PGx knowledge usage scenarios already described a clinician make a prescribing decision (goal) and ordering a medication using CPOE (intention). PGx knowledge usage scenarios (See *Table 17*) were used to define system state models (See Section 6.3.2.1), however, claims were primarily

generated in the context of 3 CDS feature usage scenarios (See *Table 19*). The relevant PGx knowledge usage scenarios are indicated for the claims resulting from reflections on how the system state is perceived by the user, how the system state is interpreted by the user, and how the system state is evaluated with respect to the goals and intentions. For example, the claim "sources for alert messages/resources are provided so that the clinician can decide whether they trust the information displayed" is a reflection on how the system state would be perceived and interpreted by the user. In this situation, while the sources being evaluated under each PGx knowledge usage scenario would differ (i.e. different system state models), the claim would be relevant for all scenarios (providing recommendations, warnings or information only).

Some claims were applicable to multiple CDS feature usage scenarios as well, given there was some overlap with CDS UI properties. For example, both features 1 and 3 incorporate e-resources websites (See *Table 19*). Therefore, for each claim, each CDS feature usage scenario is assigned the value "Y" or "N" (indicating a claim is applicable or not applicable, respectively). In addition, each claim is either positive (+) or negative (-), indicating a positive or negative effect in the context of CDS feature usage scenarios. As a result of performing the claims analysis, UI presentation requirements to support PGx knowledge usages scenarios were determined.

Findings from determining UI presentation requirements to support PGx knowledge usage scenarios were not incorporated in the design of the prototype system. Rather, UI presentation requirements provided insight into what new interaction possibilities described the scenarios might look like in reality. The proposed UI presentation requirements were investigated in more depth in Dissertation Chapter 7 in a simulated context where physicians were able to interact with a prototype system. The prototype system was designed such that features considered in the CDS feature usage scenarios (*Table 19*) could be implemented.

6.3.3. Aim 3.3: Prototype system design

Prototype system design decisions were made so that the three CDS features described in *Table 19* could be supported. Design decisions were illustrated in a derived conceptual model for PGx CDS. The CDS features considered for the conceptual model implementation required customization in order to be incorporated into the final prototype system.

6.3.3.1. Deriving a conceptual model for pharmacogenomics clinical decision support

Functional requirements for PGx CDS were described in Dissertation Chapter 5 and considered in the context of PGx knowledge usage scenarios to predict UI presentation requirements (Aim 3.2, Section 6.3.2). A conceptual model to support potential requirements is summarized in *Figure 27* (on the next page). Specifically, the model describes EHR application environment and CDS module components to support possible functional and UI requirements explored in this work.

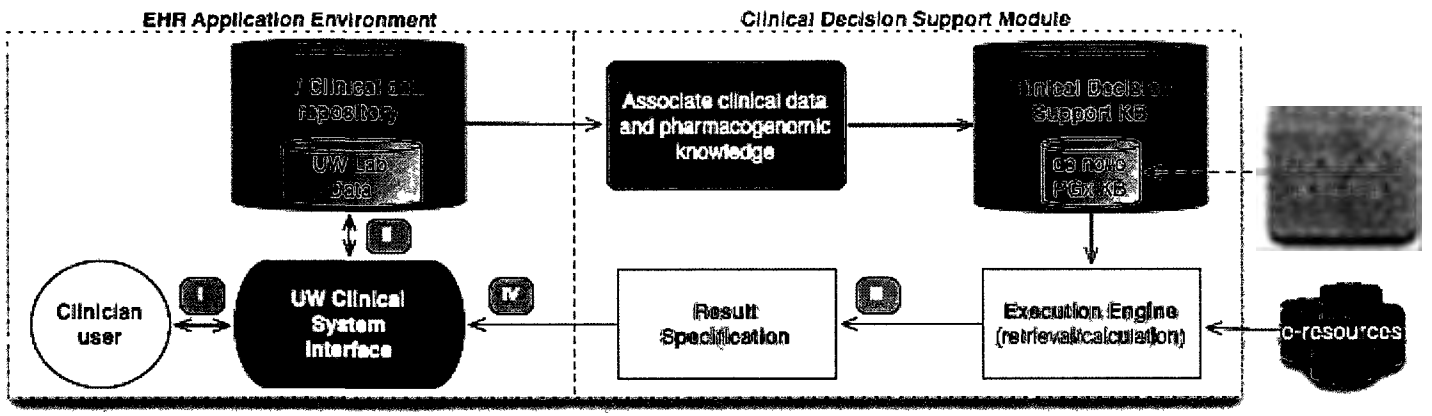

Figure 27. *Conceptual model for pharmacogenomics clinical decision support (borrowed directly from (Overby et al., 2011))*

The EHR application environment and CDS module are introduced in Dissertation Chapter 2, Section 2.2.3. Here, more details about the functional requirements discussed in Dissertation Chapter 5 within the EHR application environment are described. Standard components of the EHR application environment that support functional requirements are the *clinical system interface* and the *clinical data repository*. The functional requirements fall into the following categories: *discrete data elements*, *triggers*, *interventions* and *offered choices*. The clinical user can interact with the clinical system interface to view *discrete data elements* and perform clinical events (e.g. ordering a medication) (*Figure 27*, Step I). Clinical events might then trigger decision support to fire (e.g. in the form of an alert message) (*Figure 27*, Step II). *Triggers* are implemented in the clinical data repository. *Interventions* and *offered choices* are displayed to the clinical user within the clinical system interface (*Figure 27*, Step IV).

The CDS module provides methods for transforming input parameters (e.g. discrete data about genetic test results and the medication being ordered) into a patient specific output (*Figure 27*, Step III). Major components of the CDS module include the *CDS knowledge base* (e.g. containing production rules) and *execution engine* (e.g. performs retrieval or calculation operations). The CDS module can be configured to support different UI presentations for patient specific output (i.e. UI presentations for semi-active or active CDS).

The conceptual model illustrates that the UW clinical data repository within the EHR Application environment subsumes the UW laboratory data repository (includes genetic/genomic laboratory values). The model also illustrates that a de novo PGx knowledge base required for PGx CDS is subsumed by the UW CDS knowledge base. The connection between clinical data and PGx knowledge (Figure *Figure 27*, shown in green), requires the development of new and/or the application of existing standards for the exchange of PGx knowledge. Given that standards needed for this exchange were not supported by UW clinical systems at the time this work was completed, implementation of this step was considered beyond the scope of this dissertation. It was therefore implemented in the prototype system in a simulated manner (See Section 6.4.2.1). While the EHR application environment and CDS module were already part of UW clinical systems explored in this work, customized implementation was required.

6.3.4. *Aim 3.4: Prototype pharmacogenomics clinical decision support model implementation*

The results from the evaluation of functional capabilities and requirements for PGx CDS (Dissertation Chapter 5) indicated that UW clinical systems built on the ORCA data repository provided the best support. Therefore, a prototype implementation of PowerChart (the inpatient EHR clinical system at UW) was established. Active and semi-active CDS aspects of the conceptual model for PGx CDS were implemented in a customized manner using existing tools. Specifically, Discern Expert® (for active CDS) (Cerner Corporation) and OpenInfobutton (for semi-active CDS) (Del Fiol, Kawamoto, & Cimino, 2011; OpenInfobutton project webpage) tools were utilized. The connection between clinical data and PGx knowledge was accomplished with the use of simulated patients and data to trigger Cerner's Discern Expert® rules engine.

6.3.4.1. *Representing pharmacogenomics knowledge for clinical decision support*

PGx knowledge for CDS was represented for a subset of the 71 medications listed on the "Table of valid genomic biomarkers in the context of approved drug labels" as of May 2011 (US Food and Drug Administration, 2011). Oncology and cardiology domains of practice were of particular focus given that the majority of all decision support rules described in Dissertation Chapter 4 were relevant for oncology and cardiology medications (See Dissertation Chapter 4, Section 4.4.2). The 17 oncology medications and nine cardiology medications included on the FDA table was narrowed down to include only commonly used medications (a) with information in their drug labels suggesting that dose modifications may be indicated, and (b) for which the relevant genomic biomarker codes for a drug metabolizing enzyme found in the liver. As a result, PGx knowledge was represented for six oncology drugs (capecitabine, irinotecan, mercaptopurine, nilotinib, tamoxifen, and thioguanine) and five cardiology drugs (carvedilol, clopidogrel, metoprolol, propafenone, and warfarin) using Cerner's Discern Expert® and OpenInfobutton. Discern Expert® was utilized as a tool for implementing active CDS and OpenInfobutton for semi-active CDS. LibGuide (used by UW Libraries to create webpages with information guides, (University of Washington, Health Sciences Library) (Springshare products)) was another tool that was considered for providing access to PGx knowledge resources. There are examples where

LibGuide has been used to educate heath providers (Weaver & Bates, 2011) and used to support their decision making needs in a clinical context (Korinow et al., 2011). OpenInfobutton, however, was utilized instead because it provides an infrastructure capable of being integrated into existing clinical systems, implementation would be more generalizable to other clinical environments, and it supports semi-active CDS (LibGuide would provide passive CDS).

6.3.4.1.1. Configuring OpenInfobutton to generate context-specific websites

To support semi-active CDS, context-specific websites that can be incorporated into EHR frameworks were generated using the OpenInfobutton. The OpenInfobutton (formally "CPRS Decision Support enhanced by Context-Sensitive Infobuttons") project is part of the Veterans Health Administration (VHA) Greenfield Incubation initiative. Infobuttons are context sensitive links embedded within the EHR. Links are implemented through the Infobutton Manager (the "knowledge broker"). When a user clicks on an infobutton link in the EHR, the concept of interest (e.g. "warfarin") and the user context (e.g. Medication Order Entry) are passed to the Infobutton Manager, which then generates a website populated with relevant electronic resources. Specifically, the Infobutton Manager performs two steps when an infobutton is clicked (i.e. receives an infobutton request): resources in the OpenInfobutton knowledge base that are most relevant to the request are identified (the matching process); and a set of links are created - each associated with a content subtopic (the creation process).

The OpenInfobutton testing tool (OpenInfobutton Project Testing Tool) was used to generate context-specific websites. Input parameters for the testing tool were the following:

- Requesting Organization (i.e. Univeristy of Washington) – provides a list of resources the requesting organization wants to access
- Task context (e.g. Medication Order Entry)
- Main search criteria (e.g. RxNorm code for Warfarin)
- Patient characteristics (e.g. Age, Gender)
- Care setting (e.g. Outpatient)
- Performer (e.g. Healthcare provider)
- Information recipient (e.g. Healthcare provider)
- Output (e.g. HTML)

Once the testing tool form is submitted, the Infobutton Manager dynamically builds a URL that links to a website containing resources relevant to the specific input parameters. OpenInfobutton has been implemented in the Portland VA Medical Center, University of Utah, and is planned to be part of Aviva (a Web-based EHR system being developed by the Veterans Affairs Department). It is planned for Aviva to be used at all VA hospitals and the US Department of Defense. While OpenInfobutton has not yet been implemented within Cerner systems, most commercial EHR venders are compliant with the HL7 Infobutton standard. If Cerner systems are also compliant, there is great potential for OpenInfobutton to be integrated into the UW Cerner implementation.

The major steps taken to utilize OpenInfobuttons in this work were to (a) create a customized layout for the generated websites, and (b) configure the OpenInfobutton Knowledge base. This work was pursued in collaboration with Dr. Guilherme Del Fiol (University of Utah). A customized layout was originally specified using HTML (Hypertext Markup Language) and later enhanced using XSLT (Extensible Stylesheet Language Transformations). UW branding requirements (e.g. background and text color requirements) were adhered to in the specified HTML pages. *Figure 28* illustrates what a website generated by the Infobutton Manager looked like.

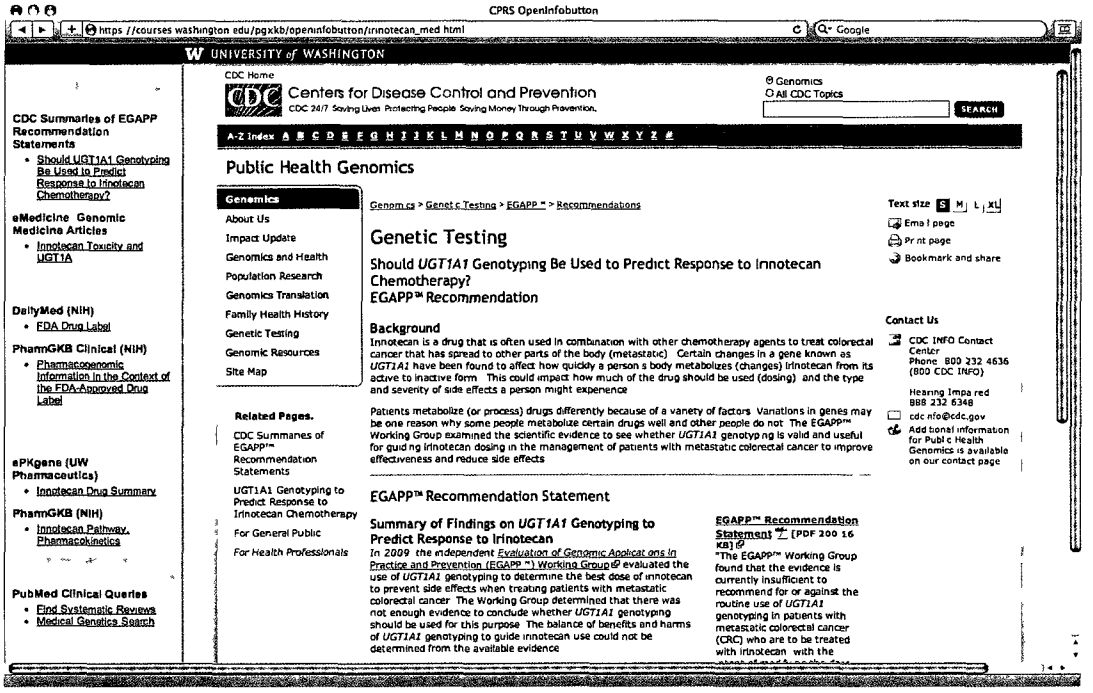

Figure 28. *An example website generated using the OpenInfobutton Knoweldge base configured for this project and a customized HTML layout. (See Appendix 11 for examples of each resource configured for this project)*

The OpenInfobutton knowledge base is composed of XML files called knowledge resource profiles. Profiles were created for each resource that might be included in the websites generated by the Infobutton Manager. The Altova® Authentic® 2011 Desktop Community Edition XML authoring environment was utilized to create profiles for knowledge resources of interest (general process described in Ref. (Del Fiol, 2011)). Details on PGx knowledge resources for which knowledge resource profiles were created are described in ***Table 21*** and ***Table 22*** (two pages forward). Both tables include details about the knowledge resource (column 1) and content subsection (column 2). *Context parameters* are defined within resource profiles and are used for *matching* the resource or *searching* against the resource application program interface (API). All resources considered in this work required configuration of the following context parameters: the *task* (a code representing the task being performed in the EHR e.g. medication order entry), *concept of interest* (the main clinical data of interest in an infobutton request e.g. a medication), and *subtopic* (the specific topic(s) of interest that are associated with the "concept of interest" e.g. a relevant clinical guideline). *Matching* indicates that the context parameter will be used to determine whether the resource is relevant in a particular EHR context. For example, the DailyMed resource was considered a good "match" only for requests from "medication order entry" infobuttons. *Search* indicates that the resource API is able to process the context parameter for searching content. For example, the rxcui (or RxNorm concept unique identifier) concept of interest was used to search the DailyMed resource.

Table 21 provides details about an example PGx knowledge resources configured for the "medication order entry" task context. OpenInfobutton knowledge resources configured for this task are made available via a prototype implementation of the CDS Feature 3 described in *Table 19*. Specifically, the electronic resources made available in an OpenInfobutton website that links from an alert message include a subset or all of the resources configured for the medication order entry task. ***Table 22*** provides details about an example PGx knowledge resource configured for the "laboratory review" task context, and that are also made available within a prototype implementation of the CDS Feature 1 described in *Table 19*. Specifically, the electronic resources made available within an OpenInfobutton website that links from genetic laboratory results includes a subset or all of those configured for the laboratory review task. Knowledge resources provided in both task contexts are made

available to physicians to support their interpretation of patient genetic laboratory values when prescribing a medication.

Information about the API and about the OpenInfobutton configuration is described for example resources in column 1 of ***Table 21*** and ***Table 22*** (on the next page, the full set of resources are described in Appendix 9 and Appendix 10). Specifically, the API *Base URL*; the configured *concepts of interest*, and the configured *subtopics* are described. The Base URL is the URL of the knowledge resource search engine. Across the full set of resources described in Appendix 9 and Appendix 10, only one had an API to support performing a search using a standard medical terminology. Specifically, DailyMed resource uses an RxNorm terminology code specifying a medication name (rxcui) to perform a search. Therefore, rxcui is the concept of interest defined within the DailyMed resource profile. For all other resources (that require matching), medication names and genetic laboratory test results are defined as concepts of interest. The concepts of interest for resources configured for the medication order entry task were primarily RxNorm codes for drug names. LOINC codes for genetic laboratory test names were primarily used for resources configured for the laboratory review task. A *subtopic* is the document or website linked to for a particular concept of interest.

The *content subsection* for example resources are shown in column 2 of ***Table 21*** and ***Table 22*** (See Appendix 9 and Appendix 10 for all resources). Categories were drawn from the website evidence categories described in *Table 20*, and includes "Drug Genomic Biomarker Clinical Evidence," "FDA Drug Label resources," "Metabolism and Pharmacogenetics," "Search for Articles," and "Gene Specific Resources." Resources within evidence categories "Guidelines" and "Evidence based synopses" were included as part of the "Drug Genomic Biomarker Clinical Evidence" content subsection. "FDA Information on Genomic Biomarkers" evidence category resources were part of the "FDA Drug Label resources" content subsection. The evidence categories "Systematic Reviews" and "Primary Literature" were included as part of the "Search for Articles" content subsection. A subset of the resources considered part of the "Metabolism and Pharmacogenetics" evidence category were provided within the "Gene Specific Resources" content subsection defined for resources that provide support for interpreting laboratory values in the laboratory review task context. Other resources categorized as "Metabolism and Pharmacogenetics" were included

as part of the "Metabolism and Pharmacogenetics" content subsection. Content subsections were included within the customized HTML of websites generated by the Infobutton Manager using XSLT.

Table 21. *Example pharmacogenomics knowledge resource included in OpenInfobutton generated websites and configured for the Medication Order Entry context (This is one of nine such examples, see Appendix 9 for details).*

Pharmacogenomics Knowledge Resource Details (Medication order entry context)	Content subsection
Resource: CDC Summaries of EGAPP Recommendation Statements (US Centers for Disease Control and Prevention) **Base URL:** http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/ **Concept of interest:** Irinotecan **Subtopic:** Should UGT1A1 Genotyping Be Used to Predict Response to Irinotecan Chemotherapy? EGAPP Recommendation	Drug Genomic Biomarker Clinical Evidence

Table 22. *Example pharmacogenomics knowledge resource included in OpenInfobutton generated websites and configured for the Laboratory Review context (This is one of three such examples, See Appendix 10 for the full set of resources).*

Pharmacogenomics Knowledge Resource Details (Laboratory review context)	Category of evidence
Resource: ePKgene (University of Washington, Department of Pharmaceutics) **Base URL:** https://courses.washington.edu/pgxkb/images/ *(NOTE: URL was active only for this study)* **Concept of interest:** CYP2C19 **Subtopic:** CYP2C19 Gene Summary **Concept of interest:** CYP2C9 **Subtopic:** CYP2C9 Gene Summary **Concept of interest:** CYP2D6 **Subtopic:** CYP2D6 Gene Summary **Concept of interest:** UGT1A1 **Subtopic:** UGT1A1 Gene Summary	Gene Specific Resources

Configuration files were defined for nine resources relevant to the medication order entry context (details in Appendix 9) and three for the laboratory review context (details in Appendix 10). All files were made publically available for download on the OpenInfobutton project webpage (OpenInfobutton project webpage). Context-specific websites generated using OpenInfobutton facilitated semi-active CDS in a prototype PGx CDS model. The Discern Expert® rules engine was used to facilitate active CDS.

6.3.4.1.2. Representing alert messages using the Discern Expert rules engine

In addition to using OpenInfobutton to facilitate semi-active CDS, Cerner's Discern Expert® tool was used to facilitate active CDS in a prototype PGx CDS model. Two types of alerts, low actionable and high actionable alerts, were defined using Cerner's Discern Expert® tool. Low actionable and high actionable alert messages were defined by performing the following steps: (1) identify decision support rule pattern categories associated with each level of actionability, excluding rule patterns that define multiple drugs in the pre-condition (see *Table 23*); (2) define a simple scenario for each of the eleven medication; (3) for each of eleven scenarios, identify decision support rules categorized as having low or high actionable rule patterns; (4) for each of eleven scenarios, define one low actionable message that combines the post-conditions of the set of rules categorized as having a low actionable rule pattern, and define one high actionable rule that combines the post-conditions of the set of rules categorized as having a high actionable rule pattern.

Table 23. *Decision support rule patterns associated with low and high actionability*

Pre-condition (IF statement)	Post-condition (THEN statement)	Actionability
drug + genotype/phenotype/family_history	toxicity/complications/change_in_ pharmacological_activity	Low
drug + genotype/phenotype/family_history + current_condition/demographic_data/ history_of_condition/ history_of_meds	toxicity/complications/change_in_ pharmacological_activity	Low
drug + genotype/phenotype + current condition/history of condition/history of meds + inpatient/outpatient procedure	toxicity/complications/change_in_ pharmacological_activity	Low
drug + genotype/phenotype/family_history	study_clinical_outcomes	Low
drug + genotype/phenotype/family_history + current_condition/demographic_data/ history_of_condition/history_of_meds	study_clinical_outcomes	Low
drug + genotype/phenotype/family_history + current_condition/demographic_data/ history_of_condition/history_of_meds + inpatient/outpatient_procedure	study_clinical_outcomes	Low
drug + genotype/phenotype/family_history	recommended_treatment_protocol	High
drug + genotype/phenotype/family_history + current_condition/demographic_data/ history_of_condition/ history_of_meds	recommended_treatment_protocol	High
drug + genotype/phenotype/family_history + current_condition/demographic_data/ history_of_condition/history_of_meds + inpatient/outpatient_procedure	recommended_treatment_protocol	High

The post-conditions of low and high actionable rules incorporated into final alert messages for six oncology medications and five cardiology medication are defined in *Table 24* (below) and *Table 25* (on the next page). Example simple scenarios for an oncology medication and a cardiology medication are described in column 1 of described in *Table 24* and *Table 25* (respectively). Decision support rules categorized as having low or high actionable rule patterns are shown for examples in column 3 of *Table 24* and *Table 25*. A low actionable message and a high actionable message that combines post-conditions of the set of rules are defined for each simple scenario in column 2 of *Table 24* and *Table 25*. Simple scenarios and decision support rules are described for all medications in Appendix 12 and Appendix 13.

Table 24. *Example alert messages derived from the post-conditions of approximate decision support rules for Oncology medication scenarios (This is one of six such examples. See Appendix 12 for the full set of alert messages for oncology medications).*

Scenario (Medication & Genomic Information)	Alert messages	Approximate decision support rules
Medication: Capecitabine **Genomic Information:** DPYD*2A (deficient DPD activity)	Low actionable alert message: **Patient has DPD deficiency** This patient has deficiency of dihydropyrimidine dehydrogenase (DPD) activity. Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to DPD deficiency. A link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be excluded. High actionable alert message: **Patient has DPD deficiency** This patient has known dihydropyrimidine dehydrogenase (DPD) deficiency. Capecitabine (XELODA) is contraindicated in this patient	Low actionable rule(s): • Rule 3.2: IF patient is [being considered for] taking capecitabine AND patient has deficiency of dihydropyrimidine dehydrogenase (DPD) activity THEN rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to DPD deficiency AND a link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be excluded High actionable rule(s): • Rule 3.1: IF patient is [being considered for] taking XELODA AND (patient has known hypersensitivity to capecitabine or to any of its components OR patient has a known hypersensitivity to 5-fluorouracil OR patient has known dihydropyrimidine dehydrogenases (DPD) deficiency OR patient has severe renal impairment) THEN XELODA is contraindicated in patient

Table 25. *Example alert message derived from the post-conditions of approximate decision support rules for Cardiology medication scenarios (This is one of five such examples. See Appendix 13 for the full set of alert messages for cardiology medications).*

Scenarios (Medication & Genomic Information)	Alert messages	Approximate decision support rules
Medication: Carvedilol **Genomic Information:** CYP2D6*4/*4 (poor metabolizer (ePKgene, 2010))	Low actionable alert message: **Patient is a CYP2D6 poor metabolizer** This patient is a poor metabolizer of debrisoquin (a marker for cytochrome P450 2D6). Poor metabolizers have 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. Plasma levels of S(-)carvedilol are increased only about 20% to 25% indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. High actionable alert message: • None	Low actionable rule(s): • Rule 4.4: IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin (a marker for cytochrome P450 2D6) THEN 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. • Rule 4.5: IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin THEN plasma levels of S(-)carvedilol are increased only about 20% to 25%, indicating this enantiomer is metabolized to a lesser extent by cytochochrome P450 2D6 than R(+)-carvedilol. High actionable rule(s): • None

Rules with IF-THEN logic were created with Discern Expert® for each alert message described in Appendix 12 (including the example in *Table 24*) and Appendix 13 (including the example in *Table 25*). Discern Expert® acts at three different levels: *Evoke*, *Logic*, and *Action* (See *Figure 29* on the next page for an example rule defined in Discern Expert®, this is one of twelve such logical rules defined in this research). The *Evoke* section defines events that "trigger" the execution of a rule. In this case, all rules are "evoked" when a medication order entry event (ADDTOSCRATCHPAD) that involves ordering a particular drug (EKS_ORDER_E) occurs. The *Logic* section (the "IF" portion of the rule) defines how to evaluate the clinical information that is captured when a rule is triggered. The logic for all of the rules defined in this work involves a check that a particular drug is being ordered (EKS_ORDER_MED_INCOMING_L) for a patient with a particular laboratory value (EKS_CE_RESULT_MOST_RECENT_L). The *Action* section is the "THEN" portion of the rule and defines what action will take place if the rule logic is satisfied. All of the rules

defined in this work involved a Notification action in the form a text alert message presented in a synchronous manner (EKS_ALERT_FLEX_A). The Action section is also the portion of the rule specifying the presentation of alert messages defined in Appendix 12 and Appendix 13, and links from alert message to medication order entry context OpenInfobutton websites (described in Appendix 9).

MAINTENANCE SECTION

TITLE: PGX_CAPECITABINE_ALERT_L
FILE NAME: PGX_CAPECITABINE_ALERT_L
DATE: 3/20/2011
DURATION: 3/20/2011 **TO** 12/31/2100
AUTHORS: C OVERBY
VERSION: 001 011
INSTITUTION: UNIV_WA
SPECIALIST:
VALIDATION: PRODUCTION

LIBRARY SECTION

PURPOSE:

To alert user that patient has DPD deficiency and that rarely, unexpected, severe toxicity associated with 5-fluorouracil has been attributed to DPD deficiency A link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be excluded.

KNOWLEDGE

PRIORITY of Module: 50

EVOKE SECTION

Evoke on ADDTOSCRATCHPAD where,

EKS_ORDER_E

E1 the triggering request contains an order whose primary mnemonic is capecitabine whose ordering physician OPT_QUALIFIER in OPT_ORDDOC

LOGIC SECTION

EKS_STOP_LOGIC_L

L1 the following templates are false, STOP logic evaluation

AND

EKS_ORDER_MED_INCOMING_L

L2 the triggering request contains an order whose primary mnemonic is capecitabine with a dose OPT_EVALUATION OPT_DOSE OPT_DOSE_UNIT and route of OPT_ROUTE whose ordering physician OPT_QUALIFIER in OPT_ORDDOC

AND

EKS_CE_RESULT_MOST_RECENT_L

L3 the most recent result for Creatinine is equal to 1 03 and OPT_VALUE2 for the same encounter as Refer to L2 over the last OPT_TIME_NUM OPT_TIME_UNIT

ACTION SECTION

EKS_ALERT_FLEX_A

A1 Send alert Medication Alert - Capecitabine stating @TEMPLATE [TMP_CAPECITABINE_ALERT_L], Cancel Order, Override Alert, Not applicable, Provider Approved, Modify Order, NONE, OPT_ORDERS, DISABLED, EVIDENCE, https //courses washington edu/pgxkb/openinfobutton/capecitabine html, OK, OPT_FORM, OPT_FORM_BUTTON_NAME, ENABLED, Refer to L2

Figure 29. *Example rule defined using Discern Expert®. This is one of twelve such logical rules defined in this research*

The alert text messages (Appendix 12 and *Table 24*, column 2; Appendix 13 and *Table 25*, column 2) were defined using the Cerner Word Processing Templates Tool that allows for richer formatting options (See *Figure 30*). Templates are referred to within Discern Expert® using the simple @TEMPLATE (see Action section of *Figure 29*). This message is essentially the resulting output from the evocation of the rule.

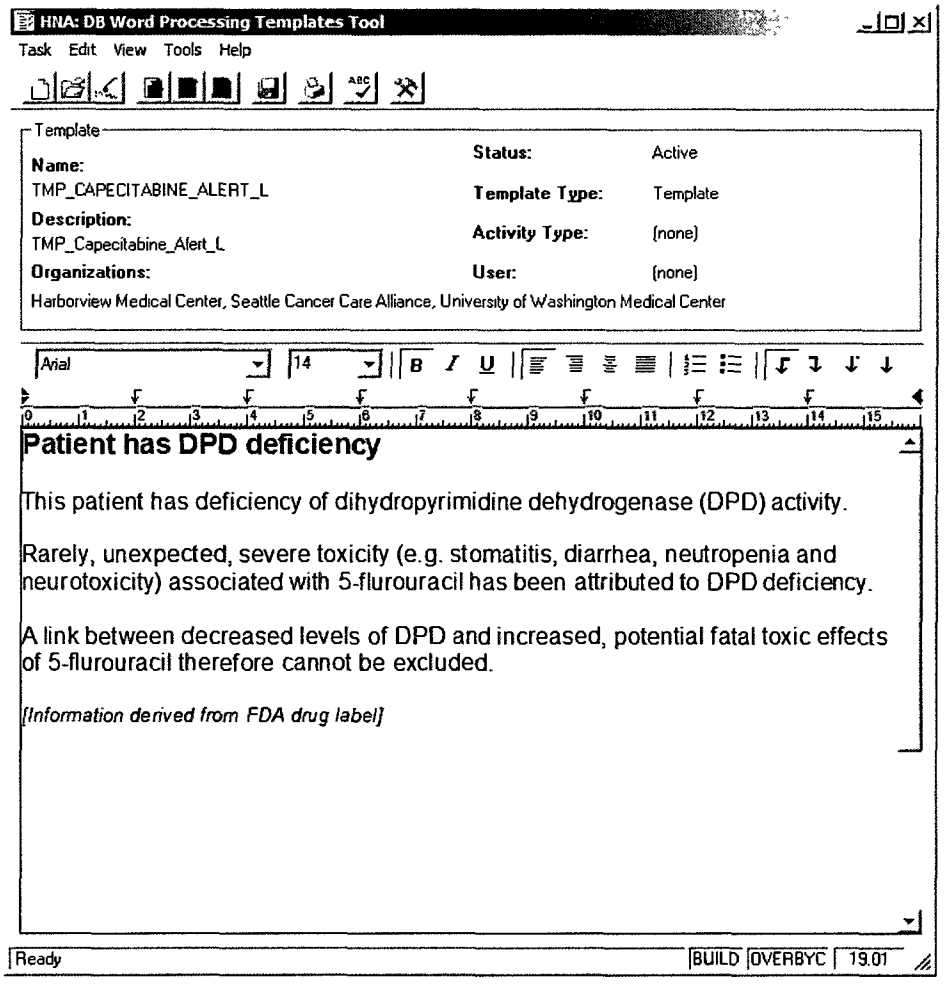

Figure 30. *Example alert message text template defined using the Cerner Word Processing Templates Tool. This is linked to from the Action section of the Discern Expert template in* ***Figure 31****.*

Figure 31 (on the next page) illustrates what would be shown to the ordering physician if the rule defined in *Figure 29* were triggered. Offered choices defined within the Action section of the Discern Expert rules (See Action section of *Figure 29*) included Cancel current order ("Cancel order" alert action shown in *Figure 31*), Override rule/keep order ("Override alert" alert action shown in *Figure 31*), and Edit current order ("Modify order" alert action shown in *Figure 31*). In addition, the alert messages are each configured to include a link to an

OpenInfobutton generated website. The websites are accessed via the "EVIDENCE" button shown on the lower left-hand corner of the example alert message shown in *Figure 31*.

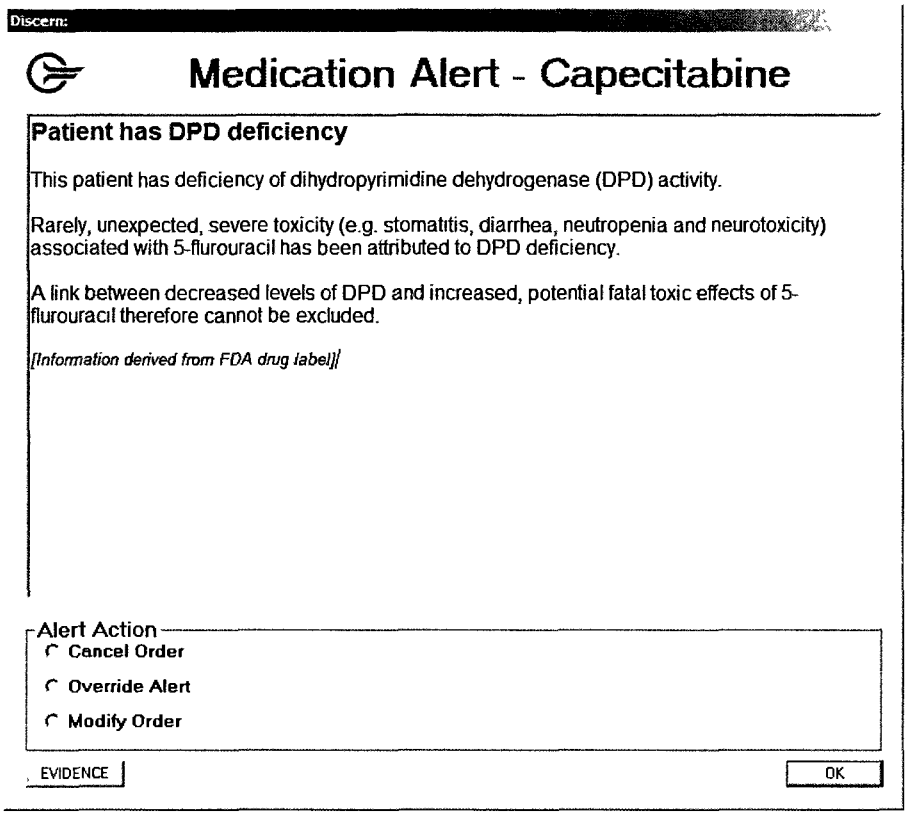

Figure 31. *Example alert message triggered by the rule defined in* ***Figure 29****.*

The logic section of the Discern Expert® defined rules outlines how clinical information is evaluated to determine whether rule logic is satisfied. If satisfied, the action described in the Action section of the Discern Expert® rule. In this work, simulated patient clinical information was used to trigger the Action section and the display of alert messages (See Section 6.4.2.1).

6.4. RESULTS

6.4.1. Aim 3.2: User interface presentation requirements given maturity of pharmacogenomics knowledge

Scenarios constructed in Aim 3.1 (Section 6.3.1) were utilized to perform Aim 3.2 claims analyses. Claims analysis methods were applied to determine UI presentation requirements for implementing PGx CDS within the EHR. The particular methods developed in this work

are described in Aim 3.2 methods (Section 6.3.2). System state models were defined (Section 6.4.1.1) as a preliminary step to constructing and analyzing claims (Section 6.4.1.2). As an outcome of this evaluation, the appropriateness of the conceptual model for PGx CDS (Section 6.3.3.1) was confirmed. In addition, hypotheses were generated about how clinicians will interact with various forms of CDS given the current maturity of PGx knowledge.

6.4.1.1. System state model predictions

System state models is defined by considering what CDS UI properties might be available (i.e. alert message and e-resource website properties) given the maturity of PGx knowledge covered in each PGx knowledge usage scenarios (i.e. recommendations, warnings, information only scenarios). The exploration of system state models is summarized in *Table 26* (on the next page). Features 1 and 3 (described in *Table 19*) both describe semi-active CDS in the form of a link to a website containing electronic PGx knowledge resources. Therefore, the system state models for these features are described in the top portion of *Table 26*. The frequencies of occurrence for particular e-resource website properties (column 1) under 3 PGx knowledge usage scenarios (columns 2-4) were predicted. E-resource website properties considered include (a) the existence of resources within particular evidence categories described in *Table 20*, and (b) the ability to use PGx knowledge resources in the clinical context. Feature 2 (described in *Table 19*) describes active CDS in the form of an alert message. The system state models for these features are described in the bottom portion of *Table 26*. The frequencies of occurrence for certain alert message properties (column 1) under 3 PGx knowledge usage scenarios (columns 2-4) were predicted. The alert message properties considered include (a) properties of the alert text message, and (b) the ability to use the PGx knowledge presented in an alert message in the clinical context.

Table 26. *Evaluation of system state models.*

PGx link to e-resources (Semi-active CDS)	Scenario 1: CPOE & Recommendation	Scenario 2: CPOE & Warning	Scenario 3: CPOE & Information only
Guidelines available	Often	Sometimes	Rarely
All categories of resources available (**Primary literature, FDA information on genomic biomarkers, Metabolism and Pharmacogenetics summary, Evidence-based Synopses, Systematic Reviews**, and **Guidelines**)	Often	Sometimes	Rarely
Able to use context specific resources to determine an action to take prior to completing the entire order	Often	Sometimes	Rarely
In the absence of **Evidence-based Synopses, Systematic Reviews**, and **Guidelines**, the clinician is able to investigate studies reported in the primary literature.	Always	Always	Always
Search leading to questions being answered	Often	Sometimes	Rarely
Search leading to less uncertainty about what action to take	Often	Sometimes	Rarely
PGx alert message (Active CDS)			
A clear statement is presented	Often	Often	Sometimes
Action clinician should take is known/clear	Often	Sometimes	Rarely

Results from exploring system state models for Features 1 & 3 (that provide semi-active CDS) indicated that models are suspected to differ between PGx knowledge usage scenario in the availability and usefulness of knowledge resources that would be provided. For example, resources containing evidence categorized as "Guidelines" would be available *often* for Scenario 1 (CPOE & recommendations), *sometimes* for Scenario 2 (CPOE & warning), and *rarely* for Scenario 3 (CPOE & information only). The hypothesis generated from this exploration was that, it would be most likely for useful resources to be available under Scenario 1, followed by Scenario 2, followed by Scenario 3.

The above hypothesis was further investigated by considering simple scenarios for which low actionable and high actionable messages were derived from approximate decision support rules (See *Table 24* and *Table 25*). Low actionable messages were derived from rules with a post-condition of either "toxicity/complications/change_in_pharmacological_activity" or "study_clinical_outcomes" (See *Table 23*). Simple scenarios for which a low actionable

message was defined but no high actionable message was defined, were therefore considered examples of Scenario 2 (CPOE & warning) or Scenario 3 (CPOE & information only). Two drugs represented within simple scenarios matched that criteria: nilotonib (See *Table 24*) and carvedilol (See *Table 25*). High actionable messages were defined for four oncology medications (capecitabine, irinotecan, mercaptopurine and thioguanine, described in *Table 24*) and for three cardiology medications (clopidogrel, propafenone, and warfarin, described in *Table 25*). Given that high actionable messages were derived from rules with a post-condition of "recommended_treatment_protocol" (See *Table 23*), simple scenarios for which high actionable messages were defined were considered examples of Scenario 1 (CPOE & recommendation). The content subsections represented within websites generated using OpenInfobutton for nine medications are described in *Table 27* (on the next page). The "Drug Genomic Biomarker Clinical Evidence" content subsection contains resources containing guidelines and evidence based synopses, and therefore was considered the subsection that contained the most useful resources. There were no resources categorized under the "Drug Genomic Biomarker Clinical Evidence" content subsection for nilotinib or carvedilol. Alternatively, the majority of the other medications (with high actionable messages) had resources available for the "Drug Genomic Biomarker Clinical Evidence" subsection. This finding indicated that it is possible that useful resources are more often available under Scenario 1 (CPOE & recommendation) when compared to Scenario 2 (CPOE & warning) or Scenario 3 (CPOE & information only). While this finding may help support the hypothesis indicated in the previous paragraph, further investigation is required given the small number of cases considered.

Table 27. Content subsections represented within websites generated using OpenInfobutton for nine medications.

Oncology medications	Drug Genomic Biomarker Clinical Evidence	FDA Drug Label resources	Metabolism and Pharmacogenetics	Search for Articles
capecitabine	x	x	X	X
irinotecan	x	x	X	X
nilotinib	N/A	x	N/A	X
mercaptopurine	x	x	X	X
thioguanine	x	x	X	X
Cardiology medications				
carvedilol	N/A	x	X	X
clopidogrel	x	x	X	X
propafenone	N/A	x	X	X
warfarin	x	x	X	X

Another finding relevant to Features 1 & 3 (features that provide semi-actve CDS), was that for all PGx knowledge usage scenarios, in the absence of e-resources considered to be most supportive for clinical decision-making (i.e. Guidelines, Evidence-based Synopses, and Systematic Reviews), it was suspected that e-resource websites could provide support for investigating relevant studies reported in the literature. The perceived usefulness of providing this form of minimal support was investigated further in the study described in Dissertation Chapter 7.

Results from exploring system state models for Feature 2 (that provides active CDS) indicated that models are suspected to differ between PGx knowledge usage scenarios in the ability to define clear of statements and specify clear actions within alert messages. In particular, it was suspected that clear statements could be defined *often* for Scenario 1 (CPOE & recommendation) and for Scenario 3 (CPOE & warning), but *sometimes* for Scenario 3 (CPOE & information only). This prediction was similar to the prediction made for Feature 1 and Feature 3. "All features indicated that implementation is richest for knowledge classified as a *recommendation*, and least rich for knowledge classified as *information only*. Since knowledge classified as *warnings* vary in level of actionability, the amount of support the CDS features would provide for clinicians need to be evaluated on an individual basis. For example, a warning of low actionability is 'IF patient is being considered for

mercaptopurine therapy AND patient is TPMT homozygous-deficient (two non-functional alleles) AND patient is given usual doses of mecaptopurine THEN patient will accumulate excessive cellular concentrations of active thioguanine nucleotides and patient will be predisposed to PURINETHOL toxicity.' A higher actionable warning would be 'IF patient is being considered for mercaptopurine therapy AND patient is homozygous-TPMT deficient (two non-functional alleles) THEN substantial dose reductions are generally required to avoid the development of life threatening bone marrow suppression.'" (Overby et al., 2011). Findings from exploring system state models facilitated evaluating claims for each feature.

6.4.1.2. Generated claims and claims analysis results

The two outcomes of performing claims analysis in this work were (1) determining CDS features to implement in the prototype implementation of the conceptual model for PGx CDS; and (2) generating hypotheses for how clinicians will interact with PGx CDS embedded in an EHR.

A summary of the claims generated in this work and the results of the claims analysis performed in this work are described in *Table 28* (on the next page). Each claim shown in column 1 has either a (+) positive or (-) negative value indicating a positive or negative effect of a system feature configuration. In addition, *Table 28* illustrates the stage(s) of action indicated by each claim in column 2, and whether each claim is applicable to Feature 1 (semi-active CDS feature), Feature 2 (active CDS feature) and/or Feature 3 (semi-active CDS feature that follows active CDS) in columns 3-5.

Table 28. *Summary of claims analysis.*

Claim	Stage(s) of action	Feature 1	Feature 2	Feature 3
(+) May have been unaware of the association between the biomarker and the medication prior to CDS encounter (education).	interpretation	Y	Y	Y
(+) Clicking on the PGx link displays resources relevant to the medication of interest and the relevant attained patient genetic/genomic tests	execution	Y	N	Y
(+) Incorporating topic links in the PGx website to lead clinicians to content subsections that are closely related to the clinician's question.	execution	Y	N	Y
(+) If clinician is already aware of relevant genetic test results, the PGx website provides resources to assist with interpreting the results in the context of the medication of interest.	specification execution interpretation	Y	N	N
(+) Source for alert message/resource is provided so that the clinician can decide whether they trust the information displayed.	perception interpretation	Y	Y	Y
(+) Supports investigating and determining (alternative) clinical action.	interpretation	Y	N	Y
(+) More directed searches can occur since questions are framed in the context of a recommendation/warning/informational message.	execution	N	N	Y
(+) Supports further investigation of action to take if none is specified in the message.	execution	N	N	Y
(+) Clinician has the option to cancel order, override alert or modify order.	execution evaluation	N	Y	N
(-) Disrupts clinical workflow.	execution perception	N	Y	N
(-) Less likely to know the important questions to ask to guide search when compared to accessing resources following an alert message.	specification execution	Y	N	N
(-) Time to find answers to questions may take longer than if they had proceeded with empirical therapy and triggered an alert message that recommends/warns/informs.	execution	Y	N	N
(-) Clinician may have already considered information/warning/recommendation and time must be taken to respond to the alert.	specification execution interpretation	N	Y	N
(-) Clinician may want to know more about the evidence supporting the recommendation/warning/information, but may not know where to go to investigate.	specification execution interpretation	N	Y	N
(-) Clinician may not know where to investigate what action to take given the available resources/message displayed.	interpretation	Y	Y	Y

The positive and negative claims associated with features illustrated that there were several overlapping applicable contextual factors (See *Table 28*). "Positives that are common across all features include (a) the potential educational gain from CDS messages/resources, and (b) provision of citations to allow the clinician to decide on the extent to which they trust CDS messages and information from various resources. The one con common across all features is that the clinician may not know where to investigate what action to take given the available resources and/or message displayed." (Overby et al., 2011). Interestingly, both claims that are common across all features consider how the system state would be interpreted by the user (i.e. interpretation stage of action).

There were also additional commonalities between Feature 1 and Feature 3 that both provide semi-active CDS. Positive claims common between these features included possible provision of (a) context-sensitive access to resources, (b) content subsections within websites for easier navigation, and (c) support for further investigation. The first two claims consider how actions are executed within the system (i.e. execution stage of action), and the last claim considers how the system state would be interpreted by the user.

The claims that were unique to particular features were of greater interest in this work because the circumstances where one feature may be more or less beneficial than the other could be determined. Unique to Feature 1 (semi-active CDS), a positive claim was that providing semi-active CDS could assist with interpreting test results. However, as indicated by negative claims, searches performed would be less directed and it may be time consuming to find an answer to the clinical question being pursued.

Specific to Feature 2 (active CDS), a positive claim suggested that once presented an alert message, the clinicians would be given options to cancel or modify an order that could have been harmful to the patient. In the case that information presented within the alert message was already considered (for example) the option to override/ignore the alert message would also be provided. However, in practice, when an alert message is triggered the application is often frozen until a cancel, override alert or modify order selection is made. Therefore, presenting an alert message disrupts clinical workflow and there would be no support for further investigation into the appropriate action to take (also indicated as negative claims). This limitation to further investigation is overcome with Feature 3 that provides support for

active CDS followed by semi-active CDS.

Unique to Feature 3 (active CDS followed by semi-active CDS), providing support for further investigation of an action to take if none is specified within an alert message is listed as a positive claim. Moreover, in contrast to negative claims described for Feature 1 regarding the lack of guidance to perform searches, with Feature 3 searches could be performed following the display of an alert message. Searches would therefore be more directed with Feature 3 when compared to Feature 1.

There are clear tradeoffs for implementing each feature. For example, implementation of Feature 1 where an OpenInfobutton link to resources to assist with interpreting genetic laboratory test results is made available prior to prescribing a medication may be more useful when a clinician is already aware of relevant genetic laboratory results. However, this feature would not be appropriate in the case that the clinician is unaware of relevant test results or does not know the important questions to ask to guide their search. In that case, Feature 3 (providing a link to PGx e-resources following a triggered alert message) could be more useful. Therefore, the two features together can compensate for the limitations of either feature alone.

In addition, investigations of the differences between Feature 2 and 3 indicated, "Feature 3 (link to PGx e-resources within an alert message) adds value to the support provided by Feature 2 (alert message alone). A major limitation of Feature 2 is that a clinician may not know where or how to efficiently investigate evidence supporting the recommendation, warning, or information displayed in an alert message further. Feature 3 provides a link to PGx resources to support further investigation and can therefore alleviate this restriction. This type of investigation is particularly useful when an alert message does not specify a specific action the clinician should take, as is true for most informational messages and for some warning messages." (Overby et al., 2011). Given this exploration, Feature 1 and Feature 3 were both included in the prototype PGx CDS model described in Section 6.3.4.

Overall, the hypothesis resulting from this exploration was that the appropriateness of a particular UI presentation would impact the level of effective communication achieved in a clinical context. Where *effective communication* was defined in this work as "a process by which PGx knowledge to support drug therapy individualization is communicated to the care

provider in a format and with supportive information that promotes their appropriate use in making informed healthcare decisions." This hypothesis was investigated further in Dissertation Chapter 7.

6.4.2. Aim 3.4: Prototype pharmacogenomics clinical decision support model implementation in a simulated context

A model for PGx CDS was proposed in Aim 3.3 (Section 6.3.3) that incorporates all potential UI requirements (as described in CDS feature usage scenarios). Following a prototype implementation of the model was developed (Aim 3.4). There were two major technical limitations to implementing a prototype version of the conceptual model for PGx CDS described in Section 6.3.3.1: (1) the incorporation of new or existing standards for data exchange in ORCA were required to connect clinical data to PGx knowledge (See Section 6.4.2.1), and (2) the OpenInfobutton infrastructure that provided a method for implementing semi-active CDS was not configured for use with Cerner products. For the purposes of this dissertation research, the first limitation was addressed by using simulated patients and clinical data. The second was addressed by modifying how PGx knowledge was represented within ORCA.

6.4.2.1. Simulated patients and clinical data

Simulated patients with data to trigger the Cerner rules engine were instantiated in the ORCA build environment (a testing environment, separate from the production system environment). Each simulated patient had at most two instances, one that would trigger a low actionable message upon entering a particular medication, and another that would trigger a high actionable message. Simulated patients defined to receive medications for which no medication alert message was defined (i.e. tamoxifen and metoprolol), were designed to trigger a dummy alert message. The details on all simulated patients are shown in *Table 29* (on the next page).

Table 29. *Details about simulated patient data used to trigger Discern Expert® defined rules.*

Patient Name	Medical Record Number **(MRN)**	Age	Gender	Height	Weight	Dummy Lab Value	Name of the alert message triggered **(PGX_[Drug Name]_ALERT_[L, H, or Dummy])**
RXTEST, PGXRULE1b	U2301011	50	M	71 in	175 lb	Scr=1.03	PGX_CAPECITABINE_ALERT_L
RXTEST, PGXRULE1d	U4301011	50	M	71 in	175 lb	Scr=1.05	PGX_CAPECITABINE_ALERT_H
RXTEST, PGXRULE2b	U2229011	48	M	70 in	175 lb	Scr=1.07	PGX_IRINOTECAN_ALERT_L
RXTEST, PGXRULE2d	U4229011	48	M	70 in	175 lb	Scr=1.09	PGX_IRINOTECAN_ALERT_H
RXTEST, PGXRULE3b	U2228011	45	F	63 in	125 lb	Scr=1.11	PGX_NILOTINIB_ALERT_L
RXTEST, PGXRULE4a	U1227011	68	F	66 in	150 lb	Scr=1.14	PGX_TAMOXIFEN_ALERT_DUMMY
RXTEST, PGXRULE5b	U2226011	22	M	72 in	180 lb	Scr=1.19	PGX_MERCAPTOPURINE_ALERT_L
RXTEST, PGXRULE5d	U4226011	22	M	72 in	180 lb	Scr=1.21	PGX_MERCAPTOPURINE_ALERT_H
RXTEST, PGXRULE6b	U2225011	22	M	72 in	180 lb	Scr=1.23	PGX_THIOGUANINE_ALERT_L
RXTEST, PGXRULE6d	U4225011	22	M	72 in	180 lb	Scr=1.25	PGX_THIOGUANINE_ALERT_H
RXTEST, PGXRULE7b	U2224011	75	M	71 in	175 lbs	Scr=1.27	PGX_WARFARIN_ALERT_L
RXTEST, PGXRULE7d	U4224011	75	M	71 in	175 lbs	Scr=1.29	PGX_WARFARIN_ALERT_H
RXTEST, PGXRULE8b	U2223011	59	M	70 in	175 lbs	Scr=1.31	PGX_CLOPIDOGREL_ALERT_L
RXTEST, PGXRULE8d	U4223011	59	M	70 in	175 lbs	Scr=1.33	PGX_CLOPIDOGREL_ALERT_H
RXTEST, PGXRULE9b	U2222011	45	M	71 in	175 lbs	Scr=1.35	PGX_CARVEDILOL_ALERT_L
RXTEST, PGXRULE10	U2221011	68	F	66 in	150 lbs	Scr=1.39	PGX_PROPAFENONE_ALERT_L
RXTEST, PGXRULE10	U4221011	68	F	66 in	150 lbs	Scr=1.41	PGX_PROPAFENONE_ALERT_H
RXTEST, PGXRULE11	U3200011	37	M	72 in	180 lbs	Scr=1.44	PGX_METOPROLO_ALERT_DUMMY

Many of the genetic laboratory values of interest to this study exist within the ORCA data repository. However, the laboratory values specific to the simple scenarios discussed in this chapter were unable to be linked to decision support rules via Discern Expert® at the time this study was completed. Therefore, dummy Serum Creatinine (Scr) laboratory values were defined for each simulated patient and used to trigger alert messages. Other limitations to

implementing the prototype system were encountered when representing PGx knowledge in ORCA.

6.4.2.2. Representation of pharmacogenomics knowledge in ORCA

PGx knowledge was represented in ORCA using Discern Expert® (for active CDS) and OpenInfobutton (for semi-active CDS). Given that OpenInfobutton cannot currently be configured with Cerner products, infobuttons were unable to be displayed for the laboratory review context and a workaround was implemented for the medication order entry context. To facilitate implementation of semi-active CDS in the laboratory review context, genetic laboratory values were mocked up with infobutton links in a web-based form external to ORCA. Both active CDS and semi-active CDS was able to be implemented for the medication order entry context. Discern Expert® was used to implement active CDS as described in the previous section. Although infobuttons cannot be directly configured within Cerner, websites generated using OpenInfobutton could be accessed from triggered alert messages via an "EVIDENCE" button (semi-active CDS). Therefore, active CDS followed by semi-active CDS was provided in the medication order entry context. Semi-active CDS implemented in the laboratory review context and active CDS followed by semi-active CDS implemented in the medication order entry context was evaluated in a study performed with oncology fellows and cardiology fellows participants described in the following Dissertation Chapter 7.

6.5. Summary & Discussion

This chapter describes the steps taken to (a) construct scenarios describing new interaction possibilities for clinicians using pharmacogenomics clinical decision support embedded in an electronic health record (Aim 3.1), (b) perform claims analysis to determine user interface presentation needs for pharmacogenomics clinical decision support (Aim 3.2), (c) design a conceptual model for pharmacogenomics clinical decision support (Aim 3.3), and (d) establish a prototype implementation of the conceptual model (Aim 3.4). To summarize the work completed for Aim 3.1, two sets of usage scenarios were constructed: one set of scenarios conveyed new interaction possibilities based on current maturity of pharmacogenomics knowledge (PGx knowledge usage scenarios); the other set of scenarios suggested new interaction possibilities in the context of various implementations of clinical

decision support embedded in the electronic health record (CDS feature usage scenarios). Claims analysis was then applied to determine user interface presentation requirements to support PGx knowledge and feature usage scenarios (Aim 3.2).

To summarize findings from Aim 3.2, a suspected trend across all clinical decision support features considered in this work was that implementation would be richest for pharmacogenomics knowledge classified as "recommendation" and least rich for "information only." In addition, several overlapping contextual factors were indicated across clinical decision support features (e.g. all might lead to educational gain, and all should provide citations so that pharmacogenomics knowledge can be evaluated for "trustworthiness"). There were also several contextual factors that were unique to particular clinical decision support features (e.g. implementation of semi-active clinical decision support could facilitate accessing knowledge resources to assist with interpreting genetic laboratory results prior to ordering a medication). After exploring the positive and negative effects of providing various clinical decision support features, it was determined that Feature 1 (semi-active clinical decision support) and Feature 3 (active clinical decision support followed by semi-active clinical decision support) would be included in the prototype pharmacogenomics clinical decision support model implementation (Aim 3.4). The major hypothesis generated from this work was that the appropriateness of various user interface presentations could impact the level of effective communication achieved in a clinical context (the study pursued relevant to this hypothesis is described in Dissertation Chapter 7).

To summarize work completed for Aim 3.3, a conceptual model to support all potential user interface requirements (as described in the CDS feature usage scenarios) was established. A detailed description of the various components for this model is presented in Section 6.3.3.1. A prototype implementation of the model was established in Aim 4.4. Implementation steps are described in the methods section of this chapter (Section 6.3.4), and the technical limitations to implantation are described in the results section (Section 6.4.2).

Technical limitations to implementing a prototype conceptual model for pharmacogenomics clinical decision support were due to (a) the need for standards for exchanging of pharmacogenomics knowledge within University of Washington clinical systems and (b) the need for methods for incorporating infobuttons within Cerner products. The first limitation might be overcome by incorporating a standardized terminology for

genetic laboratory values. For example, the Clinical Bioinformatics Ontology (CBO, www.clinbioinformatics.org) developed by Cerner could provide this form of support. The CBO package is freely available, but requires some configuration within ORCA. The second limitation (methods for incorporating infobuttons) requires enhancements to be made by Cerner. As standards evolve and vendors begin to adopt them (e.g. HL7 InfoButton standard), incorporation of OpenInfobutton into commercial EHR applications is becoming more feasible.

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7. CHAPTER 7: EVALUATING THE UTILITY OF THE PHARMACOGENOMICS CLINICAL DECISION SUPPORT MODEL IMPLEMENTATION (AIM 4)

7.1. INTRODUCTION

The previous chapter (Dissertation Chapter 6), a prototype implementation of a model for providing pharmacogenomics clinical decision support within a local UW clinical system was established and presented. This chapter investigates a hypothesis generated from that work. The relevant hypothesis is that **the appropriateness of a particular user interface presentation would impact the level of effective communication achieved in a clinical context**. The utility of the prototype pharmacogenomics clinical decision support model implementation in a clinical context is therefore investigated by measuring the *perceived appropriateness* of pharmacogenomics knowledge and clinical decision support (CDS) features for drug therapy individualization in a pilot study. The relevant research questions to address this hypothesis were as follows:

- What form of pharmacogenomics knowledge do clinicians perceive as most appropriate? (answered by measuring *perceived usefulness*)
- What is the impact of different levels of actionable knowledge on the effective communication (i.e. *use* and *perceived usefulness*) of pharmacogenomics knowledge?

The choice to evaluate clinicians' perceptions of pharmacogenomics knowledge of different levels of actionability stems from two key facts: (a) many of the available resources that provide access to pharmacogenomics knowledge (potentially for drug therapy individualization) provide knowledge that vary in its maturity in a clinical context (See Dissertation Chapter 3); and (b) there are different ways to implement clinical decision support (CDS) features (e.g. passively, semi-actively, actively) (See Dissertation Chapter 4 and Dissertation Chapter 6). There may be ways to implement CDS features based on the maturity of knowledge such that the level of effective communication achieved can be maximized in the clinical context. This is the first study, to our knowledge, to investigate this subject. In this case, the clinicians' prescribing decisions and the perceived usefulness of

pharmacogenomics knowledge of different levels of actionability were considered surrogate measures for effective communication. Confidence in prescribing decision was considered a secondary measure for effective communication. In order to facilitate answering the above research questions, an experimental design that incorporated the random presentation of low or high actionable alert messages was employed.

In addition to investigating clinical perceptions of pharmacogenomics knowledge and CDS features, an estimate of the clinical impact of embedding pharmacogenomics knowledge in the electronic health record is provided. Specifically, the utility of the model was investigated by measuring the *clinical impact* of pharmacogenomics knowledge provision (delivered through the prototype PGx CDS model) on clinical decisions. Clinical impact represented both the *uptake* of pharmacogenomics knowledge (i.e. was pharmacogenomics knowledge used?) and the *effect* of pharmacogenomics knowledge provision on clinical decisions (i.e. did prescribing decisions change?). The relevant research questions were as follows:

- Clinical impact: uptake of pharmacogenomics knowledge
    - What is the uptake of pharmacogenomics knowledge?
    - What is the uptake of pharmacogenomics knowledge with different levels of actionable knowledge in a clinical setting?
- Clinical impact: effect of pharmacogenomics knowledge provision on clinical prescribing decisions
    - What is the effect of presenting pharmacogenomics knowledge on prescribing decision?
    - What is the effect of presenting pharmacogenomics knowledge + different levels of actionable knowledge on prescribing decision?
- Effect of pharmacogenomics knowledge provision on confidence in prescribing decisions
    - What is the effect of presenting pharmacogenomics knowledge on confidence in prescribing decision?
    - What is the effect of presenting pharmacogenomics knowledge + different levels of actionable knowledge on confidence in prescribing decision?

Research questions about clinical impact were particularly relevant to the overarching gap this dissertation aimed to address: **the need for education and guidance for health care professionals to support accurately using and interpreting patient specific genetic data for drug therapy individualization**. The extent to which providing currently available pharmacogenomics knowledge via the prototype PGx CDS model can address this gap was investigated in this pilot study. In the study, methods for measuring whether knowledge resources are used once they are made accessible, and methods for measuring whether there is an impact on clinical decisions in a simulated environment were introduced. Given the scarcity of resources that provide evidence-based guidance on using genetic data in a clinical context (See Dissertation Chapter 3, Section 3.4.3), the results of this study were considered baseline measurements upon which to provide guidance on ways to improve resources such that they can be presented in a way that satisfies the education and guidance needs of health care professionals.

The above research questions were investigated through conducting the pilot study with oncology and cardiology fellows in a simulated environment where genetic laboratory values and relevant electronic resources were made available via the prototype PGx CDS model. Clinical case scenarios were presented with simulated patient data and fellows were asked to make prescribing decisions. Data on the uptake (i.e. use) and perceptions (i.e. awareness, experience, usefulness, and relative advantage) of pharmacogenomics knowledge were collected under two contexts: (a) reviewing patient genetic laboratory values prior to ordering a medication, and (b) ordering a medication using computerized provider order entry (CPOE).

The questions addressed in this chapter are related to the overarching aim of this dissertation to determine **what needs to be done to incorporate pharmacogenomics knowledge into an electronic health record in a useful way that facilitates drug therapy individualization.** Toward facilitating drug therapy individualization, the specific research questions addressed in this chapter provides (a) insight into how pharmacogenomics knowledge are perceived by physicians (i.e. awareness, experience, relative advantage, usefulness), and (b) provides an estimate of the potential uptake (i.e. use) and effect of pharmacogenomics knowledge on prescribing decisions. Moreover, the pilot study is conducted such that an estimate of what clinical decision support (CDS) feature

implementations are more or less appropriate (based on the level of effective communication achieved) given the presentation needs for pharmacogenomics knowledge can be provided.

This pilot study was conducted in close collaboration with Dr. Beth Devine (Associate Professor in the Pharmaceutical Outcomes Research & Policy Program in the UW School of Pharmacy, and Adjunct Associate Professor in the Division of Biomedical & Health Informatics). Data collection methods for two aligned studies were developed collaboratively and are presented in this chapter. One study is specific to this Aim 4 pilot study and Dr. Beth Devine led the other study that investigated the usability of pharmacogenomics clinical decision support aids in a computerized provider order entry (CPOE) system. Dr. Devine and I were co-investigators for each other's studies. The data analysis methods and results from the Aim 4 pilot study alone are included in this chapter.

7.2. Pilot Study Terminology

The specifications of terminology used in this pilot study are as follows:

- Pharmacogenomics knowledge: includes genetic test results, genetic test OpenInfobutton generated webpage, alert messages, and alert message OpenInfobutton generated webpage.
    - Genetic test results: simulated patient-specific pharmacogenomics test results (includes some interpretation e.g. poor metabolizer)
    - Alert messages: computerized provider order entry (CPOE) alert messages
    - OpenInfobutton generated webpages (also referred to as "optional" pharmacogenomics knowledge because they are optional to access):
        - Genetic test OpenInfobutton generated webpage (also referred to as "laboratory review context e-resources"): laboratory results context e-resources accessible within simulated patient-specific pharmacogenomics test results.
        - Alert message OpenInfobutton generated webpage (also referred to as "medication order entry context e-resources"): medication order entry context e-resources (accessible within alert messages)
- Prescribing decision: Do not change order (or "override alert" in a CPOE system), modify order, or cancel order.

7.3. Related work & Significance

7.3.1. Effective communication of genetic laboratory results

The effective communication of genetic laboratory results was studied in the context of communications between laboratory and clinical professionals. Effective communication in that context was defined by Dr. Ira M. Lubin as "a process by which test results are communicated by the laboratory in a format and with supportive information, when applicable, that promotes their appropriate use by the clinician and/or patient in making informed healthcare decisions." (Quoted from Lubin, I.M. in Ref. (Secretary's Advisory Committee on Genetics, Health and Society, 2008)). In an effort to understand the factors contributing to poor communication between clinicians and laboratory professionals, the current practices for ordering genetic laboratory tests and how results are reported were assessed (Lubin et al., 2008). That investigation identified areas to improve the quality of practices involving laboratory tests ordering and results reporting. For example, to improve communication between the genetic laboratories and clinicians, one proposed solution was to make existing guidelines regarding content and process of communicating relevant information and concepts more specific. The authors investigated the proposed solution further by developing a reporting framework to address information needs of clinicians (Lubin et al., 2009). An evaluation of the usefulness and effectiveness of the framework was performed by introducing clinical scenarios and conducting focus groups with primary care physicians. A national survey to primary care clinicians was also conducted to assess the model reports developed with the framework (Scheuner, Lubin, & Hilborne, 2010). Reports developed based on the reporting framework were found to be more useful and effective then the standard reports.

A general approach similar to the approach taken to study the effective communication of genetic laboratory results was applied to study the effective communication of pharmacogenomics knowledge to support drug therapy individualization in this work. The general approach is summarized in *Figure 32*. Work to improve effective communication of genetic laboratory results and work to improve the effective communication of pharmacogenomics knowledge involved the following general steps: (1) an assessment of the current state of communication; (2) a proposed method of addressing needs identified from

the assessment; and (3) an evaluation of whether applying the proposed method improves the effectiveness of communication.

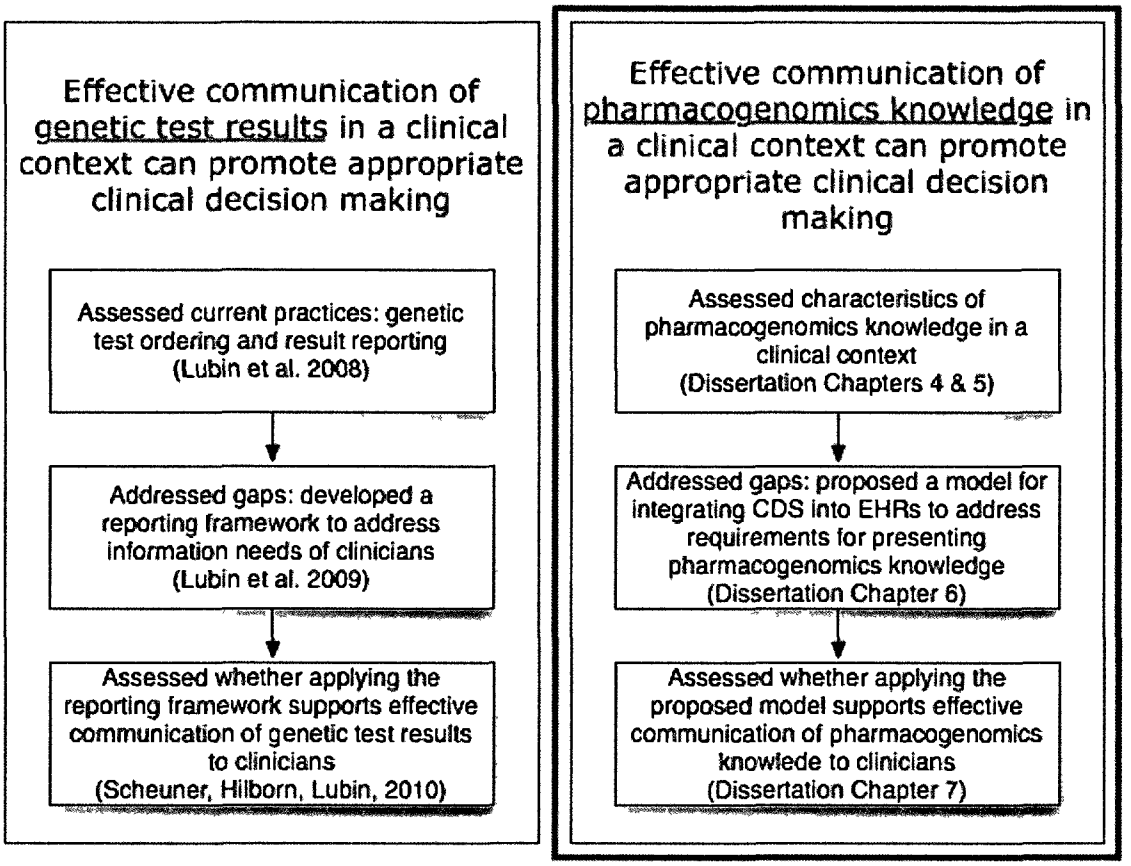

Figure 32. *Approaches taken to study effective communication of (a) genetic laboratory results (on the left) and (b) pharmacogenomics knowledge (on the right), to promote appropriate clinical decision-making. The blue call-out box indicates work covered by this dissertation.*

7.3.2. Mechanisms to achieve effective communication with use of computerized provider order entry

As described previously in Dissertation Chapter 2, computerized provider order entry (CPOE) is one component of an electronic health record that can be used to provide access to information resources and has the functionality to alert providers of potential concerns when ordering medications electronically. Implementing alert messages within CPOE can help insure completeness and correctness of mediation orders. Mechanisms for communicating pharmacogenomics knowledge to the care provider that were investigated in this work included semi- and active- clinical decision support (CDS) implementations within a prototype version of an electronic health record system with CPOE.

With CPOE planned for final release at University of Washington in Spring 2012, this study was useful for providing insight into what circumstances, and in what form, alert messages would be most useful to providers making prescribing decisions. As a result, one future outcome of this work could be providing UW Medicine IT Services with recommendations on how alert messages should be implemented within CPOE. This research was particularly focused on prescribing scenarios involving the use of patient genetic laboratory values. Utilizing findings from pharmacogenomics research is key to achieving more individualized therapy. However, making genetic testing data accessible for physicians to view and providing access to resources that support understanding, interpreting and acting on this new patient data is critical to achieving the vision of drug therapy individualization.

7.3.3. Measurements to assess effective communication

Effective communication was defined in this work as a *process by which pharmacogenomics knowledge to support drug therapy individualization is communicated to the care provider in a format and with supportive information that promotes their appropriate use in making informed healthcare decisions*. Primary measures to assess effective communication were measures of what prescribing decisions were made with access to pharmacogenomics knowledge and measures of the perceived usefulness of the various forms of pharmacogenomics knowledge. A secondary measure was confidence in prescribing decisions. This study was also designed such that testing for possible interactions was possible. Of particular interest was testing whether there was an interaction between use of pharmacogenomics knowledge and participants' prior perceptions about genetics and decision support aids in a clinical context (i.e. awareness, experience, relative advantage).

Constructs for measuring effective communication and potential interacting variables were defined based on two technology acceptance theories: (1) the diffusion of innovations (DOI) theory; and (2) the task technology fit (TTF) theory. The DOI theory was first presented in 1962 by Rogers (Rogers, 1962) and adapted to the field of information systems by Moore and Benbasat in 1991 (Moore & Benbasat, 1991). DOI theory proposes that the rate of technology *adoption* is impacted by users' *perceptions* of using the innovation. The TTF theory suggests that a technology must fit the tasks the user performs and the

technology must be utilized in order for technology to have a positive impact on individual performance. Specifically, the theory proposes: (a) user *attitudes* as predictors of *utilization* and (b) *task-technology fit* as a predictor of *performance* (Goodhue & Thompson, 1995).

A pre- experiment questionnaire was distributed to study participants prior to interacting with the prototype PGx CDS model. Drawing from DOI theory, the questionnaire included questions about users' perceptions in terms of: *awareness*, *experience*, and *relative advantage* of genetic tests and decision support aids in the prescribing context. When analyzing, pre-questionnaire responses can be used to test whether the clinical impact (uptake and effect) of pharmacogenomics knowledge differs among participants with differing perceptions. The DOI theory suggests that user perceptions have an impact on technology adoption.

Drawing from TTF theory, the experimental design incorporates measures of utilization and performance. According to TTF theory, technology characteristics (e.g. low vs. high actionable knowledge; semi-active vs. active CDS) and task characteristics (e.g. prescribing clinical case scenario) impacts the degree to which a technology assists an individual in performing a task. In this case, the degree to which providing pharmacogenomics knowledge in the prototype PGx CDS model assists an individual in performing a prescribing task is measured by: (a) ratings of confidence in their prescribing decision (performance measure), (b) ratings of the usefulness of various forms of pharmacogenomics knowledge (performance measure) and (c) prescribing decisions (utilization measure) with access to pharmacogenomics knowledge.

7.3.4. Supporting the vision of drug therapy individualization as a microcosm of personalized medicine

In this pilot study, pharmacogenomics knowledge resources are made accessible to potentially provide support for using patient genetic laboratory values while making prescribing decisions. The potential *clinical impact* of providing access to genetic laboratory values and pharmacogenomics knowledge resources in a prescribing context is investigated. Clinical impact represents both uptake of pharmacogenomics knowledge and the effect of pharmacogenomics knowledge provision on clinical decisions. In addition, the perceived usefulness for various pharmacogenomics knowledge resources in the prescribing context

was investigated. Therefore, future outcomes of this work could be providing UW Medicine IT Services with recommendations for additional information resources that should be made accessible in ORCA to support making prescribing decisions; and providing organizations that develop and maintain resources explored in this research with recommendations for ways to make their resources more useful to prescribing physicians.

Moreover, the level of effective communication achieved by providing different implementations of clinical decision support that incorporate pharmacogenomics knowledge from various sources was investigated. Therefore, the hypothesis that the appropriateness of a particular user interface presentation provided by an implementation of clinical decision support would impact the level of effective communication achieved in a clinical context (generated by work presented in Dissertation Chapter 6) was tested.

7.4. METHODS

7.4.1. Aim 4.4 Experimental design

An experimental survey instrument and pre-/post- experiment questionnaires were utilized in this study. The experimental survey instrument incorporates the use of clinical case scenarios coupled with three classes of decision tasks. During the experiment, participants were presented clinical case scenarios before and after providing access to pharmacogenomics knowledge (including scenario specific genetic test results). In both cases, participants were asked to specify a dose, frequency and duration at which the proposed medication should be given to the patient in the scenario. Participant classes of prescribing decisions were labeled as follows:

- Do not change order: participant chooses a medication dose/frequency/duration for the patient in the scenario with access to pharmacogenomics knowledge that is the same dose/frequency/duration they chose before having access to pharmacogenomics knowledge.
- Modify order: participant chooses a medication dose/frequency/duration for the patient in the scenario with access to pharmacogenomics knowledge that is different from the dose/frequency/duration they chose before having access to pharmacogenomics knowledge.
- Cancel order: participant chooses not to prescribe the medication for the patient in the scenario after having access to pharmacogenomics knowledge.

Eleven hypothetical clinical case scenario descriptions covering a range of oncology and cardiology clinical cases were developed. Pharmacogenomics knowledge to support interpreting genetic test results while making prescribing decisions was made available as part of the prototype implementation of the PGx CDS model. Specifically, pharmacogenomics knowledge was made available in two contexts: (a) reviewing patient genetic laboratory values prior to ordering a medication, and (b) ordering a medication using computerized provider order entry (CPOE). Within the laboratory review context prior to ordering a medication, PGx knowledge was made available in two forms: (1) an interpretation of simulated patient genetic laboratory data; and (2) an OpenInfobutton context-specific webpage containing gene specific resources. Within the medication order entry context, PGx knowledge was made available in two forms: (1) an ORCA Discern Expert® alert message; and (2) an OpenInfobutton context-specific webpage containing drug genomic biomarker clinical evidence, FDA drug label resources, resources containing information about metabolism & pharmacogenetics, and the resources to facilitate searching for articles.

Details about knowledge resources made available via OpenInfobutton context-specific webpages is described in Dissertation Chapter 6 (Section 6.2.4.1.1). Details about alert messages made available within the ORCA PowerChart application is described in Dissertation Chapter 6 (Section 6.3.4.1.2). A distinction was also made between low and high actionable knowledge contained in alert messages by classifying approximate decision support rule patterns (See Dissertation Chapter 6, Table 7 for the list of rule patterns associated with low or high actionability). Approximate decision support rules derived from the drug labeling of oncology and cardiology medications, depending on their rule pattern classification, were then used to define low and high actionable alert messages for each drug (See Dissertation Chapter 6, Table 8 and Table 9).

In this experiment, the context of the prescribing decision is the controlled variable, and the decision-maker and pharmacogenomics knowledge use is under investigation. The experiment was briefly described to the participants and the availability of pharmacogenomics knowledge and decision support features to aid their prescribing decisions were explained. The participants were then presented with a sequence of five clinical case scenarios, each scenario was presented twice (once without pharmacogenomics

knowledge and once with pharmacogenomics knowledge), both times the participant was asked to record their prescribing decision. Pseudo-randomization was incorporated into the study design in two ways: (1) the selection of low or high actionable alert messages for a scenario; and (2) the order scenarios were presented. The study was designed such that the first and second scenarios were the same for all participants within the same area of practice (oncology or cardiology).

The first scenario was used to introduce the participant to the study set-up (the prototype PGx CDS model with CPOE functionalities and available PGx knowledge resources), and data collected on the second scenario was used to estimate the between subject variability (a measure needed to calculate the power of the study given the population size). The third through fifth scenarios were presented in a pseudo-randomized fashion. Data collected for these scenarios across the study population were used for statistical analyses associated with research questions outlined in the introduction section of this chapter. A flow chart providing an overview of the study design is summarized in *Figure 33*.

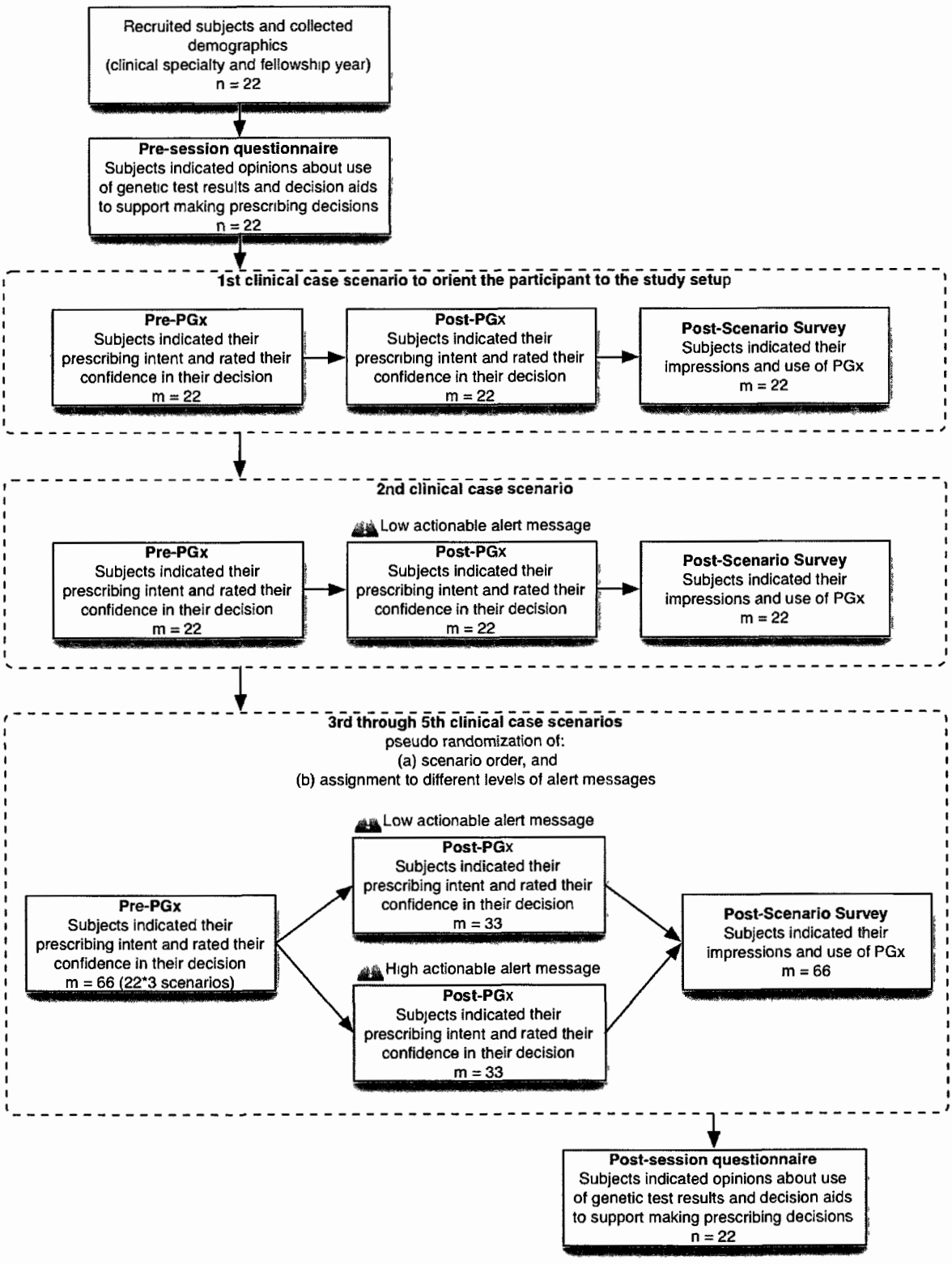

Figure 33. *Summary of pilot study design.*

7.4.2. Aim 4.2: Participants

7.4.2.1. Recruitment strategies

Study participants were recruited from the University of Washington (UW) cardiology and oncology fellowship programs. There were approximately 30 fellows in each program. The primary recruitment strategy involved the delivery of an invitation to participate in the study by the program coordinators of each fellowship program. All together, each program coordinator distributed four recruitment emails to all fellows. In addition, flyers were created and distributed to potential study participants. All recruitment materials included or provided easy access to: (a) a statement that it was a University of Washington research study, (b) the title of the research study, (c) contact information for the researchers, (d) an explanation of the purpose, (e) an explanation of the procedures subjects would be asked to complete, including the time commitment, and (f) a statement regarding potential risks and benefits. Oncology and cardiology fellows interested in participating in the study were asked to read an online consent form.

7.4.2.2. Consent procedure

This study was approved by the UW Human Subjects Institutional Review Board (IRB) with a waiver of documentation of consent. The online consent form contained the same information that was provided as part of the recruitment materials with more detail. In addition, the list of researches, the researchers' statement, alternatives to taking part in the study, information about receiving payment for participation, and the subjects' statement was presented. Fellows that selected "Yes" to the following subjects' statement were able to participate in the study; those who selected "No" were excluded from participation:

- Subjects' Statement: I have read the procedure described above. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I can print a copy of this consent form.

7.4.2.3. Study population demographics

Two data collection methods were applied in this study. The original data collection methods involved completing a pre- experiment questionnaire, completing a one-hour individual laboratory session where the participant interacted directly with a prototype EHR, and completing two post- experiment questionnaires. Data collection methods were later revised to increase the participation of oncology fellows. The revised data collection methods involved a shorter online version of the study that incorporated mock-ups of the prototype EHR interface. Seven cardiology fellows and three oncology fellows completed the study with the original data collection methods. Twelve oncology fellows completed or partially completed the online version of the study (eight completes and four partial completes). The demographics of the study population are summarized in *Table 30*.

Table 30. *Study population demographics*

Participants	Fellows, No. (%) (N=22)
Clinical Specialty	
Oncology fellow	15 (68.2%)
Cardiology fellow	7 (31.8%)
Fellowship year (not collected for 4 fellows)	
First	3 (16.7%)
Second	6 (33.3%)
Third	6 (33.3%)
Fourth	3 (16.7%)

7.4.3. Instrumentation

The main measurement instruments utilized in this work were: (1) a pre- experiment questionnaire, (2) an experimental survey instrument, and (3) a post- experiment questionnaire.

7.4.3.1. Aim 4.3 Questionnaires and experimental survey instrument

Before and after use of the prototype PGx CDS model and at the completion of the experimental survey, a pre- and post- experiment questionnaire (respectively) was administered. Questionnaires included questions concerning clinical awareness of, experience with, relative advantage of, and perceived usefulness of pharmacogenomics knowledge in making prescribing decisions. Responses to pre- and post- experiment

questions about awareness and experience were measured as follows: 0=unaware, 1=aware, 0=never use, 1=use sometimes, and 2=use always. Responses to questions about relative advantage were measured on a 5-point Likert-type scale with anchors specific to the question (i.e. 5=strongly agree, 4=agree, 3=unsure, 2=disagree, and 1=strongly disagree). Responses to questions about perceptions of usefulness of pharmacogenomics knowledge and decision support aids were also measured on a 5-point Likert-type scale: 5=excellent/extremely useful, 4=good/very useful, 3=fair/useful, 2=poor/not very useful, 1=no benefit/not at all useful. Data collected from the pre- and post- experiment questionnaires were used to evaluate the impact of participating in the study (i.e. did opinions change). The pre- experiment questionnaire in particular was used to characterize users' perceptions so that we could test whether there was a relationship between user perceptions and the uptake of pharmacogenomics knowledge in the prescribing context. See Appendix 14 and Appendix 15 for pre- and post- experiment questionnaires, respectively.

For ten participants, an experimental survey instrument was administered in a laboratory-based environment where participants interacted directly with the prototype PGx CDS model. Twelve study participants interacted with a web-based survey instrument that incorporated screenshots of the prototype interface. In both cases (direct interaction with prototype or screenshots of the prototype), clinical case scenarios with simulated test patient data were presented first without, then with pharmacogenomics knowledge (genetic test results, OpenInfobutton webpages, and alert message). For each of five clinical case scenarios, the study participants were presented a test patient medical record information and asked to answer survey questions about (a) their prescribing decision; and (b) their confidence in the prescribing decision (indicated on a 5-point Likert scale i.e. 5=very confident, 4=confident, 3=have doubts, 2=have doubts, 1=not at all confident). Questions were answered before and after providing access to pharmacogenomics knowledge. Upon completing those questions, participants were asked to rate the usefulness of various forms of pharmacogenomics knowledge (indicated on a 5-point Likert scale i.e. (5=excellent/extremely useful, 4=good/very useful, 3=fair/useful, 2=poor/not very useful, 1=no benefit/not at all useful/did not use).

7.4.3.2. Aim 4.1 Clinical case scenarios

All study participants were introduced to five clinical scenarios and asked to make prescribing decisions with and without access to pharmacogenomics knowledge embedded in the EHR. Six clinical scenarios were developed for oncology fellows with the assistance of Dr. Beth Devine and Dr. Jeannine S. McCune, PharmD (Professor of Pharmacy in the UW School of Pharmacy & Associate Member at Fred Hutchinson Cancer Research Center). Five clinical scenarios were developed for cardiology fellows with the assistance of Dr. Beth Devine and Dr. Lingtak-Neander Chan, PharmD (Associate Professor of Pharmacy in the UW School of Pharmacy). Clinical scenarios were constructed such that it would be appropriate to suggest using one medication for which pharmacogenomics knowledge was incorporated into the prototype EHR system (See Dissertation Chapter 6, Section 6.3.4.1). Clinical scenarios for oncology fellows were therefore each constructed to invoke prescribing one of the drugs: capecitabine, irinotecan, mercaptopurine, nilotinib, tamoxifen, or thioguanine (See ***Figure 34*** for an example). Cardiology drugs for which clinical scenarios were constructed included: carvedilol, clopidogrel, metoprolol, propafenone, and warfarin (See ***Figure 35*** for an example). The full set of clinical scenarios constructed for oncology fellows are shown in Appendix 21. The clinical scenarios constructed for cardiology fellows are shown in Appendix 22. The construction of clinical case scenarios involved incorporating the SOAP (subjective, objective, assessment, and plan) note format that is familiar to clinicians (Cameron & Turtle-Song, 2002). The components of a SOAP note are summarized in *Table 31*.

Nilotinib Clinical Case Scenario

45 year old Asian female with imatinib-resistant chronic phase chronic myeloid leukemia. Patient has no history of cardiovascular disease or arrhythmias. All laboratory values, including complete blood count, electrolytes, and liver function tests, are within normal limits. Patient is not taking any other medications. You chose to prescribe nilotinib.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)
UGT1A1	*(TA)^{7}TAA*	*UGT1A1*28/*28*	*Intermediate Metabolizer*

Figure 34. *Example clinical case scenario presented to oncology fellow participants. See Appendix 21 for the full set of oncology clinical case scenarios.*

Carvedilol Clinical Case Scenario

A 45 year old Caucasian male with stable chronic heart failure (NYHA IIb) presents with worsening shortness of breath and fluid retention. He has now been diuresed and is doing well. His current regimen includes an oral nitrate, an ACE inhibitor, and a loop diuretic agent. You now plan to add carvedilol to his existing regimen.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)
CYP2D6	*1846G>A*	*CYP2D6*4/*4*	*Poor Metabolizer*

Figure 35. *Example clinical case scenario presented to cardiology fellow participants. See Appendix 22 for the full set of cardiology clinical case scenarios.*

Table 31. *Summary of SOAP note sections*

Section	Definition
Subjective	Subjective information from the patient (e.g. patient signs and symptoms)
Objective	Factual information (e.g. physical examination results, laboratory data, radiographs)
Assessment	A summarization of the care providers' 'clinical thinking' (e.g. differential diagnosis)
Plan	Identification of the next step the care provider plans to take regarding the patient (e.g. data collection for diagnosis; therapeutics; management)

7.4.4. Data collection

Two data collection methods were applied in this pilot study. One data collection approach asked that participants complete a one hour laboratory session where they interacted directly with the prototype PGx CDS model. The other data collection approach asked that participants complete a 45 minute web-based version of the study where they were presented screenshots of the prototype system. Data collected using both methods were evaluated in this pilot study. Data collected from the laboratory sessions alone were evaluated as part of a separate study led by Dr. Beth Devine.

7.4.4.1. Laboratory session with prototype implementation

Initial recruitment emails included a hyperlink to an electronic consent form created as a UW Catalyst web form specific to this study. Clicking on the link prompted individuals to provide their UW Net ID and password to view the consent forms. After reading the consent form and if individuals agreed to the subject statement (indicating their interest in participating in the study), they were immediately directed to a pre-experiment questionnaire. Upon completing the pre- experiment questionnaire, the study participants were asked to select from a list of available times to participate in a laboratory session. Eight of the laboratory sessions were conducted at the UW in the Biomedical & Health Informatics iLab. Two of the laboratory sessions were conducted at the Fred Hutch Cancer Research Center (FHCRC). An established study oral script explaining the study procedures and details about the study was read to all study participants. The oral script included a brief reminder of the study purpose, step-by-step instructions about what to expect, and tasks to complete.

A usability testing software (Morae™, Techsmith) was utilized to record audio, on-screen activity, and keyboard/mouse input during each participants' session. Sessions were not video recorded to avoid collecting identifiable data. During the laboratory sessions, one investigator acted as the "observer" and one investigator acted as the "facilitator." The facilitator introduced the participant to the study set-up and explained how they should "think aloud" and use Morae™ auto-pilot functions to indicate the starting and ending of tasks. During the session, whenever needed, the facilitator would prompt the participant to continue thinking-aloud, or ask that they indicate the completion of a task before moving on. The observer utilized the Morae™ observation feature that facilitated viewing the Morae™

recording live from anywhere via a network (LAN/VPN). To flag important moments during the laboratory session, the observer used pre-defined marker definitions based on usability heuristics (Graham et al., 2004; Zhang, Johnson, Patel, Paige, & Kubose, 2003) and knowledge utilization concepts (Estabruuks & Milncr,)(some concepts stemming from ideas related to the diffusions of innovations theory (Rogers, 1962)). These data were collected as part of studies separate (though related) to the work presented in this dissertation. As such, the details on the analysis of data collected using the Morae™ software are not included in this dissertation.

7.4.4.1.1. Overview of study set-up

Two monitors were utilized in this study. On one monitor, the participant would read the clinical case scenarios, view simulated patient genetic laboratory values, indicate prescribing intent prior to accessing pharmacogenomics knowledge, and indicate ratings of the usefulness of various forms of pharmacogenomics knowledge within a UW Catalyst web form. On the other monitor, the participant interacted with the prototype system and completed the prescribing tasks with access to PGx knowledge and using CPOE functionalities. Morae™ auto-pilot tasks were also displayed on that monitor. ***Figure 36*** illustrates the monitors that are used to complete various tasks (scenarios two through five). Both monitors are used for the first scenario to orient the subject to the study set-up. The particular monitor that is used for each scenario 1 task is not indicated in ***Figure 36***. Overall, study participants completed fourteen tasks related to scenario 1 (Task 1 and Tasks 1a - 1m). Study participants completed five tasks for scenario 2 (Task 2, Task 2a, Task 2e-g), scenario 3 (Task 3, Task 3a, Task 3e-g), scenario 4 (Task 4, Task 4a, Task 4e-g) and scenario 5 (Task 5, Task 5a, Task 5e-g). Following the completion of five scenarios, Task 6 asks that the study participant complete two post- experiment questionnaires. Details about each task are provided in Appendix 16.

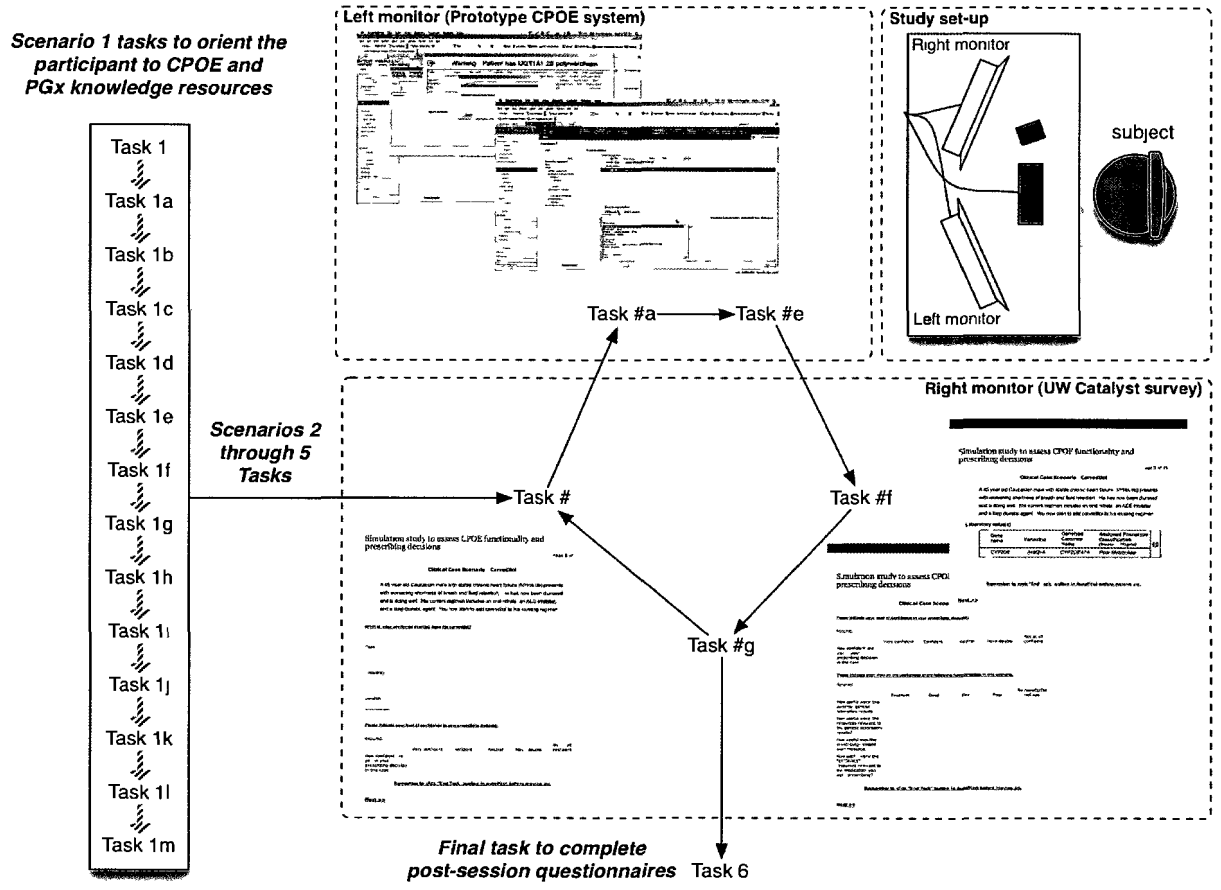

Figure 36. *Summary of the study set-up and tasks completed by study participants. The study set-up is shown in the upper right hand corner. The task numbers completed for scenario 1 are shown on the far left. The center of the image summarizes tasks numbers that are repeated for scenarios 2 through 5. The pound sign '#' is a place-holder for the number scenario being completed. Study participants interact with the prototype system displayed on the left monitor for Task #a and Task #e. Study participants interact with the UW Catalyst survey on the right monitor for Task #, Task #f and Task #g. Details about each task are described in Appendix 16.*

7.4.4.1.1. Post- experiment questionnaires

Subjects that participated in the one-hour laboratory session completed two post-experiment questionnaires. One questionnaire was similar to the pre-experiment questionnaire and data were used to evaluate the impact of participating in the study on clinical perceptions of pharmacogenomics knowledge and clinical decision support. The second post- experiment questionnaire was the Post-study System Usability Questionnaire (PSSUQ) (Lewis, 1992) chosen to gain insight into the perceived usability of the prototype PGx CDS model. Data collected from the PSSUQ survey was analyzed as part of the study led by Dr. Devine, therefore results of that analysis are not included in this dissertation.

7.4.4.2. *Web-based study with screen shots of the prototype implementation*

After ten participants completed one-hour laboratory sessions, the data collection methods were updated such that oncology fellows could complete the study in their own time, on a computer of their choice and at a location of their choice. At the time this change was made, only three oncology fellows had completed the one-hour laboratory sessions. In addition, the literature indicates that ten participants is sufficient to illuminate the majority of system usability problems (Virzi, 1992). Therefore, our updated data collection strategies no longer involved collecting usability measures previously collected using the Morae™ software and PSSUQ post- experiment questionnaire. The SurveyGizmo online survey software was used to construct an online version of the experimental survey that included screenshots of the prototype PGx CDS implementation.

7.4.5. *Statistical analysis*

Statistical analyses were performed on data collected for the third through fifth scenarios. The last three scenarios presented to cardiology fellows were warfarin, clopidogrel, and propafenone. For oncology fellows, scenarios involved the medications irinotecan, capecitabine, mercaptopurine and thioguanine. Participants were presented either mercaptopurine or thioguanine, but not both. The two drugs may be used to treat the same types of cancers and are similarly dosed. Therefore, the same clinical case was used for both medications and the prescribing recommendations were the same. We evaluated data collected for mercaptopurine or thioguanine as data from the same scenario. The frequency of scenarios presented to cardiology fellows and oncology fellows are shown in *Table 32* and *Table 33*, respectively. All statistically analyses were performed using Stata 11.2 (StataCorp, LP, College Station, TX).

Table 32. *Distribution of the third through fifth clinical case scenarios that were pseudo randomly presented to cardiology fellows.*

Distribution of scenarios presented to cardiology fellows	No. (%) of Scenarios (N=21)
Medications	
Clopidogrel	7 (33.3%)
Propafenone	7 (33.3%)
Warfarin	7 (33.3%)
Actionable messages	
Low	11 (52.4%)
High	10 (47.6%)

Table 33. *Distribution of the third through fifth clinical case scenarios that were pseudo randomly presented to oncology fellows.*

Distribution of scenarios presented to oncology fellows	No. (%) of Alerts (N=36)
Medications	
Capecitabine	13 (36%)
Irinotecan	11 (30.6%)
Mercaptopurine/Thioguanine	12 (33.3%)
Actionable messages	
Low	20 (55.6%)
High	16 (44.4%)

7.4.5.1. Perceived appropriateness of pharmacogenomics knowledge and usefulness of clinical decision support features

Perceptions of usefulness were evaluated as a proxy for perceptions of appropriateness of pharmacogenomics knowledge. Questions about perceptions of usefulness of pharmacogenomics knowledge (measured on a 5-point Likert-type scale) were collapsed into the binary values: 1=useful (collapsed values 5=excellent/extremely useful, 4=good/very useful) and 0=not useful (collapsed value 3=fair/useful, 2=poor/not very useful, 1=no benefit/not at all useful). Frequencies of scenarios where oncology and cardiology fellows found pharmacogenomics knowledge useful were reported. The effect of providing different levels of actionable knowledge on perceptions about the usefulness of pharmacogenomics knowledge was also investigated. The primary outcome was whether pharmacogenomics knowledge was useful. The predictor was the presence of a low or high actionable alert message. Generalized estimating equations (GEE) were used with an exchangeable correlation structure to test for associations and odds ratios were reported.

The impact of participating in the pilot study on the perceived appropriateness of pharmacogenomics knowledge was also investigated. The McNemar's test was used to compare pre-study and post-study responses to questions about the usefulness of various forms of pharmacogenomics knowledge. A p-value was reported, as well as the frequency and percentage of pharmacogenomics knowledge forms that were found useful prior to and after participating in the study.

7.4.5.2. Clinical impact: uptake of pharmacogenomics knowledge

Uptake (or use) was measured using the same questions that ask about perceptions of usefulness of pharmacogenomics knowledge and decision support aids (measured on a 5-

point Likert-type scale). Responses were collapsed into binary values for 1=use (collapsed values 5=excellent/extremely useful, 4=good/very useful, 3=fair/useful, 2=poor/not very useful) and 0=no use (collapsed value 1=no benefit/not at all useful/did not use). Frequencies of pharmacogenomics knowledge use were reported. The effect of providing different levels of actionable knowledge on use of pharmacogenomics knowledge was also investigated. The primary outcome was whether pharmacogenomics knowledge was used when it was made available. The predictor was the presence of a low or high actionable alert message. Generalized estimating equations (GEE) were used with an exchangeable correlation structure to test for associations and odds ratios were reported.

7.4.5.3. Clinical impact: effect of pharmacogenomics knowledge provision on clinical prescribing decisions

The two-tailed Wilcoxon signed rank test was used to examine the statistical significance of changes in prescribing doses before and after providing access to pharmacogenomics knowledge. Z and p-values were reported, as well as the mean dose values prior to and after having access to pharmacogenomics knowledge. The effect of providing different levels of actionable knowledge on prescribing decisions was also investigated. In order to facilitate analyses, prescribing tasks were collapsed into the binary values: 1=change ("CANCEL order" or "MODIFY order") or 0=no change ("OVERRIDE order"). The primary outcome was whether or not a change in prescribing occurred after providing access to pharmacogenomics knowledge. The predictor was the presence of a low or high actionable alert message. Generalized estimating equations (GEE) were used with an exchangeable correlation structure to test for associations and odds ratios were reported.

7.4.5.4. Effect of pharmacogenomics knowledge provision on confidence in clinical prescribing decisions

Confidence was measured on a Likert-type scale prior to and after having access to pharmacogenomics knowledge. Frequencies of confidence in prescribing decisions were reported. The McNemar's test was used to compare pre-intervention and post-intervention responses to questions about confidence. A p-value was reported, as well as the frequency and percentage of scenarios for which participants were confident with their prescribing decision prior to and after having access to pharmacogenomics knowledge. To facilitate

evaluating the effect of providing different levels of actionable knowledge on confidence in prescribing decisions, responses were collapsed into the binary values 1=confident (collapsed values 5=very confident, 4=confident) and 0=not confident (collapsed values 3=neutral, 2=have doubts, 1=not confident at all). The primary outcome was whether participants were confident with their prescribing decision after having access to pharmacogenomics knowledge. The predictor was the presence of a low or high actionable alert message. Generalized estimating equations (GEE) were used with an exchangeable correlation structure to test for associations and an odds ratio was reported.

7.4.5.5. Impact of user awareness experience and relative advantage of genetic tests in a clinical context on uptake of pharmacogenomics knowledge

The primary outcome of interest was whether or not pharmacogenomics knowledge was used. Three predictors related to user perceptions were evaluated: *awareness* of genetic testing use, *experience* with using genetic tests and perceptions on the *relative advantage* of using genetic tests. Awareness was already captured as a binary value (1=aware of use, 0=unaware of use); experience was collapsed into a binary value 1=use (collapsed values 1=use sometimes, 2=use often) and 0=no use; relative advantage was collapsed into a binary value 1=agree (collapsed values 5=strongly agree, 4=agree) and 0=don't agree (collapsed values 3=uncertain, 2=disagree, 1=strongly disagree). For each metric of user perception, generalized estimating equations (GEE) were used with an exchangeable correlation structure to test for associations and odds ratios were reported. Odds ratios that were unable to be calculated based on indicated prior perceptions are not reported.

7.5. RESULTS

7.5.1. Perceived appropriateness of pharmacogenomics knowledge and clinical decision support features

Perceptions of usefulness were evaluated as a proxy for perceptions of appropriateness of pharmacogenomics knowledge. Participants found genetic laboratory values to be useful 40% of the time, laboratory review context resources were useful 56% of the time, alert messages were useful 44% of the time, and medication order entry context e-resources were useful 65% of the time. In investigating the effect of providing different levels of actionable knowledge on perceptions about the usefulness of pharmacogenomics knowledge we found

no association (See *Table 34*). Even so, results warrant consideration. For example, participants were less likely to find genetic laboratory values useful when presented with a high actionable message compared to when presented a low-actionable alert message (odds ratio, 0.75; 95% confidence interval, 0.28-0.97). The data also suggest that participants were more likely to find resources available in the laboratory review context useful when presented with a high-actionable alert message compared to when they were presented with a low-actionable alert message (odds ratio, 1.07; 95% confidence interval, 0.63-1.81). In the medication order entry context, participants were less likely to find the alert message useful when presented with a high-actionable alert message compared to when they were presented with a low-actionable alert message (odds ratio, 0.53; 95% confidence interval, 0.18-1.53). Participants were more likely to find the medication order entry context electronic resources useful when presented with a high-actionable alert compared to when they were presented with a low-actionable alert message (odds ratio, 1.50; 95% confidence interval, 0.65-3.39).

Table 34. *Impact of alert message actionability on the perceived usefulness of pharmacogenomics knowledge*

Perceived usefulness of pharmacogenomics knowledge with low and high actionable messages	**Odds Ratio (95% CI)**
Genetic laboratory values usefulness	0.74 (0.38,0.97)
Laboratory review context e-resources usefulness	1.07 (0.63,1.81)
Alert message usefulness	0.53 (0.18,1.53)
Medication order entry context e-resources usefulness	1.50 (0.65,3.39)

The impact of participating in the pilot study on participant perceptions (perceived usefulness and relative advantage) of pharmacogenomics knowledge was also investigated. Of the 18 participants that completed both pre-and post- session questionnaires, prior to participating in the study, 66.7% indicated that they found genetic test results useful, 55.6% found laboratory review context e-resources useful, 44.4% found alert messages useful, 66.7% found medication order entry context e-resources useful, 61.1% agreed that genetic test results should be used to adjust drug dose, and 83.3% agreed that decision support aids improve the quality of prescribing decisions. After participating in the study, 50% indicated that they found genetic test results useful, 33.3% found laboratory review context e-resources useful, 27.8% found alert messages useful, 44.4% found medication order entry context e-resources useful, 61.1% agreed that genetic test results should be used to adjust drug dose,

and 94.4% agreed that decision support aids improve the quality of prescribing decisions. There were no statistically significant changes in perceptions of pharmacogenomics knowledge sources before and after participating in the study. The perceived usefulness of pharmacogenomics sources is summarized in *Table 35*. The relative advantage of genetic tests and decision support aids is summarized in *Table 36*.

Table 35. *Analysis of pre/post study perceptions about pharmacogenomics knowledge sources (% perceive to be useful).*

	P-value
Genetic laboratory values usefulness	0.4531
Laboratory review context e-resources usefulness	0.2891
Alert message usefulness	0.4531
Medication order entry context e-resources usefulness	0.3438

Table 36. *Analysis of pre/post study relative advantage of genetic tests and decision support aids (% agree).*

	P-value
Agreement that genetic tests should be used to adjust drug dose	1.0
Agreement that decision support aids improve quality of prescribing decisions	0.5

7.5.2. Clinical impact: uptake of pharmacogenomics knowledge

Focusing on the use of resources that were optional for fellows to access, participants indicated that they used the laboratory review context e-resources 88% of the time and used the medication order entry context e-resources 74% of the time. We found no association between the different levels of actionable knowledge on the use of optional pharmacogenomics resources, but results of statistical evaluations are presented for discussion purposes (See *Table 37*). Participants were less likely to use the laboratory review context e-resources when presented with a high actionable message compared to when they were presented with a low-actionable alert message (odds ratio, 0.91; 95% confidence interval, 0.21-3.98). Similarly, participants were less likely to use the medication order entry review context e-resources with a high actionable message than if presented with a low-actionable alert message (odds ratio, 0.91; 95% confidence interval, 0.26-3.17).

Table 37. *Impact of alert message actionability on the uptake of pharmacogenomics knowledge*

Use of optional pharmacogenomics knowledge with low and high actionable messages	**Odds Ratio (95% CI)**
Laboratory review context e-resources used	0.91 (0.21,3.98)
Medication order entry context e-resources used	0.91 (0.26,3.17)

7.5.3. *Clinical impact: effect of pharmacogenomics knowledge provision on clinical prescribing decisions*

Overall, 65% of participants completed clinical scenarios that led to a change in prescribing once pharmacogenomics knowledge was made available. Of the scenarios evaluated in this work, results suggested that there was a statistically significant difference between the distributions of prescribed doses for capecitabine (z=3.047, p=0.0023) and mercaptopurine/thioguanine (z=2.519, p = 0.0118) prior to and after having access to pharmacogenomics knowledge (See *Table 38*). No statistically significant difference was found for other drugs (capecitabine, warfarin, clopidogrel, and propafenone). We also found no association between the different levels of actionable knowledge on prescribing decision, but results are presented for discussion purposes (See *Table 39*). The data indicated that participants were less likely to change their prescribing decision (modify or cancel their order) with a high actionable message compared to a low actionable message.

Table 38. *Impact of pharmacogenomics knowledge provision on clinical prescribing decisions*

	Pre-PGx	Post-PGx	Z-value	P-value
Drug prescribed				
Warfarin dose	Mean=5 (SD=1.44) N=7	Mean=4.07 (SD=1.17) N=7	1.410	0.158
Clopidogrel dose	Mean=75 (SD=0) N=7	Mean=45 (SD=67.08) N=5	1.000	0.317
Propafenone dose	Mean=228.33 (SD=196.89) N=6	Mean=100 (SD=77.46) N=6	1.706	0.088
Irinotecan dose	Mean=59.09 (SD=4.91) N=11	Mean=40.62 (SD=25.69) N=8	1.971	0.049*
Capecitabine dose	Mean=1046.15 (SD 123.26) N=13	Mean=237.58 (SD=444.17) N=12	3.047	0.002***
Mercaptopurine/ Thioguanine dose	Mean=59.73 (SD=22.78) N=11	Mean=18.78 (SD=25.09) N=9	2.519	0.012**

Table 39. *Impact of alert message actionability on prescribing strategy*

Prescribing strategy with low and high actionable messages	Odds Ratio (95% CI)
Dosing strategy changed	0.50 (0.21-1.16)

7.5.4. Effect of pharmacogenomics knowledge provision on confidence in clinical prescribing decisions

Table 40 shows the Pre/Post intervention analysis for presenting pharmacogenomics knowledge. There was a significant decrease in the proportion of participants reporting they were confident in their prescribing decision after they had access to pharmacogenomics knowledge (McNemar's test P=0.02). Also, participants were less likely to be confident after having access to pharmacogenomics knowledge when they were confident prior to having access compared to when they were not confident prior to having access (odds ratio, 0.18; 95% confidence interval 0.02-0.83). We found no association between the different levels of actionable knowledge on the confidence in prescribing decisions, but results of statistical evaluations are presented for discussion purposes (See *Table 41*). Participants were more likely to be confident with their prescribing decision when presented with a high actionable message compared to when they were presented with a low-actionable alert message (odds ratio, 1.84; 95% confidence interval, 0.55-6.20).

Table 40. *Analysis of confidence. Pre/post scenario access to pharmacogenomics knowledge (% confident).*

	P value Chi-Square McNemar's	Odds ratio (95% CI)
Confidence in prescribing decision	p = 0.02*	0.18 (0.02-0.83)*

Table 41. *Impact of alert message actionability on confidence in prescribing decisions*

Confidence in prescribing decisions with low and high actionable messages	Odds ratio (95% CI)
Confidence in prescribing decision post-PGx	1.84 (0.55-6.20)

7.5.5. Impact of user awareness, experience and relative advantage of genetic tests in a clinical context on uptake of pharmacogenomics knowledge

This evaluation focused on use of resources that were optional for fellows to access (i.e. electronic resources made available in the laboratory context, and electronic resources made

available in the medication order entry context). We found no association between the prior perceptions about genetic testing in a clinical context on the use of optional pharmacogenomics resources, but results of statistical evaluations are presented for discussion purposes (See *Table 42*). Participants were more likely to use the laboratory review context resources when they were aware of genetic testing prior to participating in the study (odds ratio, 1.21; 95% confidence interval 0.17-8.6). Participants were also more likely to use the medication order entry context resources when they were aware of genetic testing prior to participating in the study (odds ratio, 1.14; confidence interval 0.22-5.99). In addition, participants were more likely to use medication order entry context resources when they had prior experience using genetic testing in clinical practice (odds ratio, 3.92; confidence interval 0.42-36.23). When participants agreed that genetic testing should be used to adjust drug dose prior to participating in the study, they were more likely to use laboratory review context e-resources (odds ratio, 5.59; confidence interval 0.55-56.93). In contrast, participants were less likely to use the medication order entry context resources when they agreed that genetic testing should be used to adjust drug dose prior to participating in the study (odds ratio, 0.35; confidence interval, 0.07-1.63). One odds ratio value was missing because the model did not converge.

Table 42. *Imact of prior perceptions on use of pharmacogenomics knowledge resources*

	Laboratory review context e-resources	**Medication order entry context e-resources**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**
Awareness of genetic testing use	1.21 (0.17,8.6)	1.14 (0.22,5.99)
Experience using genetic tests	-	3.92 (0.42,36.23)
Agreement that genetic tests should be used	5.59 (0.55, 56.93)	0.35 (0.07,1.63)

7.6. SUMMARY & DISCUSSION

The utility of the prototype pharmacogenomics clinical decision support model in a simulated clinical context was investigated by measuring (a) the perceived appropriateness of pharmacogenomics knowledge, (b) the clinical impact in terms of uptake of pharmacogenomics knowledge, (c) the clinical impact of knowledge provision on prescribing decisions, and (d) the confidence in prescribing decisions with access to pharmacogenomics knowledge. Additional investigations of whether there were associations between the above

measurements and the actionability of alert messages indicated that there were no associations. Lastly, we investigated whether prior perceptions about pharmacogenomics knowledge impacted uptake of pharmacogenomics knowledge. No associations were found but we provide some discussion of the results.

Participants found pharmacogenomics knowledge that was optional to access (laboratory review context & medication order entry context resources) useful slightly more often (56% and 65%) than with the genetic laboratory values and alert messages (40% and 44%). This finding suggests that participants may prefer non-intrusive modes of accessing pharmacogenomics knowledge. Results also indicated that participants were less likely to find genetic laboratory values useful when presented with a high actionable message compared to when presented a low-actionable alert message. In some cases, a physician may spend unnecessary time interpreting genetic laboratory values only to have the same information available in an alert message. This might become truer with a high actionable alert message compared to a low actionable alert.

There were some limitations to interpreting participant perceptions about the usefulness of optional pharmacogenomics knowledge resources. Specifically, participants were asked to respond to Likert-scale type questions where one value was did not benefit/not at all useful/did not use. There were occurrences where participants did not use (or did not access) pharmacogenomics knowledge. These occurrences were evaluated as though the participant did not find it useful. Therefore, the perceived usefulness of pharmacogenomics knowledge is underestimated. This is particularly true for optional pharmacogenomics knowledge resources made available in the laboratory review context and medication order entry context. Even with an underestimate of the perceived usefulness, results indicated that participants were more likely to find optional pharmacogenomics resources useful (in the laboratory review context and in the medication order entry context) when presented with a high-actionable alert message. Building on the exploration performed in Dissertation Chapter 4, one explanation for optional pharmacogenomics resources being considered more useful with a highly actionable message might be that a physician is able to perform more targeted searches. Consequently, physicians might be able to find answers to their questions more quickly in the electronic resources following the presentation of a high actionable alert when compared to low actionable alert message.

While participants were more likely to find optional pharmacogenomics knowledge useful when presented with a high actionable message compared to when they were presented with a low-actionable alert message, participants were less likely to use (i.e. access) the resources with a high actionable message compared to a low actionable message. This finding suggests that when participants were presented with high actionable messages, they did not need to access optional resources as often compared to when a low actionable message is presented. It would therefore be logical to believe that high actionable messages might be more useful than low actionable messages.

However in contrast, in the medication order entry context, the data suggested that participants were less likely to find the alert message useful when presented with a high-actionable alert message compared to when they were presented with a low-actionable alert message. Also consistent with this finding, the data indicated that participants were less likely to change their dosing strategy (modify or cancel their order) with a high actionable message compared to a low actionable message. These results were unexpected given the belief that more actionable messages would be more useful then low actionable messages. More investigation into factors that influence whether or not an alert is considered useful is required to understand these findings. A 2006 review paper synthesizing findings from studies investigating physician response to drug safety alerts recommended that a distinction be made between appropriate alerts and useful alerts (van der Sijs, Aarts, Vulto, & Berg, 2006). Appropriate alerts are alerts that are correct and current for the patient at hand, but are not always perceived as useful. Information content factors unique to useful alert messages include unambiguity, providing justification, conciseness, accessibility, seriousness, and presenting of alternatives. Low and high actionable messages were defined in a systematic manner (described in Dissertation Chapter 6), although we did not consider all information content factors that might influence whether or not an alert is perceived as useful (e.g. was an alternative action presented?). Consequently, if confirmed that high actionable messages were considered less useful than low actionable messages then, it makes sense that it would also be less likely for participants to change their dosing strategy (as the results suggest).

Another possibility is that high-actionable messages may have been more likely to confirm their chosen strategy when compared to low-actionable messages. The participants

were presented/provided access to pharmacogenomics knowledge at two major points, in the laboratory review context and in the medication order entry context. Given that genetic laboratory values were presented with the clinical scenario prior to ordering the medication, it is possible that participants decided their prescribing decision prior to ordering the medication. In those cases, when an alert message was presented, the participant would select "OVERRIDE alert" because pharmacogenomics knowledge presented within the laboratory review context already influenced their prescribing decision.

Unlike prescribing task measurements, measurements for confidence were not influenced by the point at which pharmacogenomics knowledge was reviewed. Confidence in prescribing decision was indicated after completing the prescribing task prior to and after having access to pharmacogenomics knowledge. Results indicated a significant decrease in the proportion of participants reporting they were confident in their prescribing decision after they had access to pharmacogenomics knowledge. This finding is not surprising given it isn't currently common practice to use pharmacogenomics knowledge (including genetic laboratory values) to make prescribing decisions. Also, though not a significant finding, participants were more likely to be confident with their prescribing decision when presented with a high actionable message compared to when they were presented with a low-actionable alert message. This finding could support the notion that high-actionable messages were more likely to confirm the participants' chosen strategy when compared to low-actionable messages. It would help explain why changes in dose strategy were less likely but participants were more confident in their decisions with high-actionable messages compared to low actionable messages.

Further investigations into participant dosing strategies indicated that 65% of completed clinical scenarios used that led to a change in prescribing once pharmacogenomics knowledge was made available. Interestingly, the drug doses for scenarios with cardiology drugs before and after having access to pharmacogenomics knowledge did not differ significantly, where as all of the drug doses differed for scenarios involving the use of oncology medications. A plausible explanation is that doses of chemotherapy agents are less standardized than are doses of cardiology drugs. Thus, there is much wider variability in how oncologists prescribe chemotherapy agents, when compared to how cardiologists prescribe cardiology drugs. It is likely that cardiologists modified their initial doses when

first presented with the clinical scenario, so that no further adjustment was needed when presented with pharmacogenomics resources. On the other hand, oncologists manage subjects with life-threatening illnesses in the nearer term, and may tend to be more aggressive in their prescribing doses; only modifying when presented with clinical information indicating that they need to dose adjust.

Lastly, the impact of user perceptions of genetic testing prior to participating in this study was evaluated. It appears that participants were generally more likely to use optional pharmacogenomics knowledge resources when they had positive perceptions and some experience using genetic tests prior to participating in the study.

Overall, the major limitation to this pilot study was the small sample size. Despite the employment of well-executed and repetitive recruitment strategies, fewer subjects volunteered to complete the study than desired. Thus, it is likely that the lack of statistical significance in the results are primarily due to the pilot study being underpowered. Underpowered studies are prone to type II errors, that is, the inability to detect differences if differences exist. Regardless, the pilot study has proven to be a useful way to structure research that explores the effect and appropriate use of a user interface on the level of clinical decision-making in the prescribing context. The study has provided valuable information that will inform a future, larger study that explores these concepts with greater power.

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8. CHAPTER 8: CONCLUSIONS

8.1. DRAWING THE FINDINGS TOGETHER

Drug therapy individualization is investigated in this work to better understand how informatics solutions can best support achieving the vision of personalized medicine. Findings from pharmacogenomics studies have the potential to be applied in clinical practice to individualize drug therapy such that efficacy is improved and the occurrence of adverse drug effects is reduced. However, before this potential can be realized, education and guidance for health care professionals to support accurately using and interpreting patient specific genetic data to individualize drug therapy must be provided. This work investigates methods for providing access to pharmacogenomics knowledge as a form of guidance through clinical decision support (CDS) embedded in the electronic health record (EHR). The overarching research question this dissertation aimed to address was: **What needs to be done to incorporate pharmacogenomics knowledge into an EHR in a useful way that facilitates drug therapy individualization**? In order to enhance our understanding of how pharmacogenomics knowledge should be made accessible via CDS in an EHR, requirements were investigated by considering characteristics of the knowledge, the technical capabilities of current clinical systems and user characteristics. This chapter draws together the findings from these investigations and discusses their implications for future research. The approaches taken to address research questions proposed in this dissertation are summarized in *Table 43*.

A systematic approach to defining decision support rules was taken such that pharmacogenomics knowledge of different levels of maturity could be evaluated with different CDS implementations. The influence of technical characteristics, characteristics of pharmacogenomics knowledge, and user characteristics on the adoption and success of clinical decision support for drug therapy individualization were performed in a simulated clinical context. A summary of the key research findings and themes across all chapters is shown in *Table 44*. Findings from completing the specific aims of this research, their relation to themes, and contributions to the field are discussed in the following subsections. Synthesis of these findings enables highlighting factors that might influence (a) the implementation of clinical decision support embedded in the EHR with available

pharmacogenomics knowledge, and (b) the ability of current pharmacogenomics knowledge resources to be incorporated into existing CDS frameworks. This chapter also provides suggestions for new directions to improve upon our current ability to present pharmacogenomics knowledge in a way that satisfies the educational and guidance needs of health care professionals.

Table 43. *Summary of approaches taken to address dissertation research questions.*

Aim 1: Characterizing pharmacogenomics knowledge resources (Chapter 4) ***Research Question:* What are the characteristics and the value of current pharmacogenomics knowledge in the context of CDS within an EHR?**	
Approach	**Details**
Assess characteristics of pharmacogenomics knowledge in a clinical context.	• Characterized the availability of pharmacogenomics knowledge appropriate for use in a clinical context • Characterized pharmacogenomics knowledge translated into a form suitable to incorporate into an EHR
Aim 2: Determining capabilities of current clinical decision support systems (Chapter 5) ***Research Question:* How do current decision support systems align with requirements of characterized pharmacogenomics knowledge in computable form?**	
Approach	**Details**
Assess technical requirements for pharmacogenomics knowledge in a clinical context.	• Assessed the availability of discrete data to support linking patient-specific data to pharmacogenomics knowledge • Assessed the feasibility of current systems to support technical requirements for presenting pharmacogenomics knowledge in a clinical context
Aim 3: Developing a prototype implementation of a model for pharmacogenomics clinical decision support (Chapter 6) ***Research Question:* How can patient genetic test results and just-in-time pharmacogenomics knowledge be presented to users with electronic health record clinical data so that it aligns with requirements of pharmacogenomics knowledge?**	
Approach	**Details**
Propose a model for integrating CDS into EHRs to address requirements for presenting pharmacogenomics knowledge.	• Characterized user interface requirements for presenting pharmacogenomics knowledge in a clinical context. • Proposed a model to support both technical requirements and the user interface requirements of pharmacogenomics knowledge • Established a prototype implementation of the proposed model
Aim 4: Evaluating the utility of the pharmacogenomics clinical decision support model implementation (Chapter 7) ***Research Question:* What needs to be done to achieve effective communication of pharmacogenomics knowledge embedded in the EHR?**	
Approach	**Details**
Assess whether applying the proposed model supports effective communication of pharmacogenomics knowledge to clinicians.	• Measured the perceived appropriateness of the prototype PGx CDS model • Measured the effect of pharmacogenomics knowledge provision on prescribing decisions • Measured the effect of pharmacogenomics knowledge on confidence in prescribing decisions • Measured uptake of pharmacogenomics knowledge • Measured the impact of prior perceptions on the uptake of pharmacogenomics knowledge

Table 44. Summary of key research findings from this dissertation (Continued on the following page)

Themes	Major findings	Chapter
	Technical implementation	
Data availability	Data availability for PGx CDS within local systems was 78% and could be increased to 90% with the addition of disease status definitions and laboratory value data fields.	Chapter 5
Data exchange	There was a need for standards for exchanging PGx knowledge locally.	Chapter 6
	There were instances where genetic laboratory results were captured in laboratory systems separate from the major local clinical data repositories.	Chapter 6
KB management and integration	Additional knowledge was required for 50% of the PGx decision support rules to be implemented in the local clinical system indicating a need for methods to facilitate simple derivation (e.g. IF patient is <18 THEN patient is a child).	Chapter 5
	PGx knowledge of most value was captured as free-text and therefore required translation into a computable form.	Chapter 4
	There was a need for methods to manage evolving genomic knowledge.	Chapter 3
	All genetic laboratory values would require simple derivation indicating a need for methods to manage genetic laboratory data for clinical interpretation (e.g. IF patient has genotype CYP2C9*2/*3 THEN patient is a poor metabolizer).	Chapter 5
CDS capabilities	Functional capabilities for CDS varied between clinical systems.	Chapter 5
CDS integration	Many requirements for implementing PGx decision support rules were CPOE functionalities.	Chapter 5
	There was a need for methods to incorporate semi-active CDS functionalities locally.	Chapter 6
	Identified contextual factors that could be common among various CDS implementations (e.g. facilitating educational gain).	Chapter 6
	Identified contextual factors that could be unique among various CDS implementations (e.g. semi-active CDS could be used to provide support for interpreting laboratory values prior to prescribing a medication, active CDS was not applicable in this context).	Chapter 6
CDS adoption	Different implementations of PGx CDS appears to influence perceptions of usefulness of PGx CDS.	Chapter 7
	Different implementations of PGx CDS appears to influence uptake of PGx knowledge.	Chapter 7

Themes	Major findings	Chapter
Pharmacogenomics (PGx) knowledge		
Availability	Useful resources with PGx knowledge were more likely to be available when decision support rules providing recommendations (vs. information only) could be derived from FDA drug labels.	Chapter 6
	Changes are being made to drug label content and genomic knowledge at a fast pace.	Chapters 3&4
	There is an increasing prevalence of PGx biomarker information in drug labels.	Chapter 3
	The maturity of PGx knowledge in a clinical context is changing.	Chapter 3
	There are several sources for PGx knowledge (e.g. stakeholder organization websites, drug databases).	Chapter 3
Representation	PGx knowledge of most value in electronically available resources was captured as free-text.	Chapter 4
	The majority of rules derived from drug labels were represented by a small number of rule patterns.	Chapter 4
Application	The majority of knowledge in drug labels support the post-analytic phase of genetic testing.	Chapter 4
	The applicability of PGx knowledge to clinical practice varies between resources.	Chapter 3
	The applicability of PGx knowledge to clinical practice varies within individual resources.	Chapter 4
	Much of pharmacogenomics knowledge contained in drug labels requires supplemental knowledge to facilitate computer interpretation (e.g. IF patient has genotype CYP2C9*2/*3 THEN patient is a poor metabolizer).	Chapter 5
User		
Perceptions	User perceptions of usefulness of PGx appears to be influenced by the particular implementation of PGx CDS.	Chapter 7
	User perceptions of usefulness of PGx did not appear to change after participating in the pilot study.	Chapter 7
Uptake	User uptake of PGx knowledge appears to be influenced by the particular implementation of PGx CDS.	Chapter 7
	User perceptions (awareness, experience and relative advantage) of genetic testing appear to influence the uptake of PGx knowledge.	Chapter 7
Effect on prescribing decisions	PGx CDS appears to influence prescribing decisions. For oncology fellows, there were significant changes in doses prescribed after being presented with PGx CDS.	Chapter 7
Confidence in prescribing decisions	PGx CDS appears to influence confidence in prescribing decisions	Chapter 7

8.2. Review of key findings by Aim

8.2.1. Chapter 4: Characterizing pharmacogenomics knowledge resources (Aim 1)

The FDA labeling of drugs listed on the "Table of valid genomics biomarkers in the context of approved drug label" and the Pharmacogenomics Knowledge Base (PharmGKB) were two pharmacogenomics resources of particular focus in this aim. Characterization of pharmacogenomics knowledge resources involved determining (a) the degree of overlap of evidence coverage in the two resources; and (b) the types of electronically available knowledge produced by the FDA and contained within the PharmGKB. Findings suggested that little overlap of evidence might be in part due different approaches taken to identify relevant drug-biomarker relationships indicated in the literature. The evidence captured in PharmGKB in particular may be less clinically relevant than the evidence provided in FDA drug labeling. There are however "evidence categories" that might be useful to determine the relevance of publication contents to drug therapy individualization and its potential to enhance knowledge contained in FDA drug labels. Further investigation of resources indicated that the pharmacogenomics knowledge of most value for drug therapy individualization was captured primarily as free-text captured as textual summaries in PharmGKB and tagged sections within DailyMed that makes drug labels available electronically.

Findings from translating free-text knowledge containing in FDA drug labels into a form suitable to incorporate into an EHR indicated that the majority of the rules involved drug metabolizing enzymes and were defined for oncology and cardiology medications. In addition, the majority of the clinically relevant knowledge in the drug label supports the post-analytic phase of genetic testing, more than three times more than the amount of knowledge available to support the pre-analytic phase of genetic testing. Findings also indicated that the majority of rules could be represented by a small number of rule patterns (pre-and post-condition combinations).

Overall, findings from this aim highlighted implications for representing and integrating pharmacogenomics knowledge into existing clinical frameworks (see Section 8.3), and implications for representing and applying pharmacogenomics knowledge in a clinical setting (see Section 8.4). Methods for parsing free-text within clinical systems or new modes of representing knowledge by the groups that maintain knowledge resources are required to

facilitate incorporation into existing clinical frameworks. In addition, findings highlight the need for a larger knowledge base to support the pre-analytic phase of genetic testing. Findings also provide justification for prioritizing initial target users for which to develop decision support for drug therapy individualization, and for prioritizing EHR decision support framework requirements based on common rule patterns.

The major biomedical & health informatics contributions of this chapter are providing (a) a formal characterization of the representation and availability of pharmacogenomics knowledge, and (b) a reusable approach for translating pharmacogenomics knowledge into computable form. The major clinical or genetics contributions are providing (a) an evaluation of the current state of pharmacogenomics knowledge (i.e. how mature/actionable), and (b) a formal characterization of pharmacogenomics knowledge in a clinical context. Categories of support provided by the approximate decision support rules determined in this chapter were used to determine functional requirements for providing pharmacogenomics knowledge in the context of clinical decision support embedded in an electronic health record in the following chapter.

8.2.2. Chapter 5: Determining capabilities of current clinical decision support systems (Aim 2)

Findings from assessing data availability in local clinical systems indicated that additional supportive knowledge (e.g. IF patient is <18 THEN patient is a child) was required in order for 50% or the pharmacogenomics knowledge contained in drug labels to be incorporated into exiting clinical frameworks. This was particularly true for findings from genetic tests, all of which required some form of additional interpretation (e.g. IF patient has genotype CYP2C9*2/*3 THEN patient is a 'poor metabolizer'). The feasibility of local clinical systems to support technical requirements for implementing pharmacogenomics knowledge decision support rules was also determined. This assessment facilitated identifying a local system that best supports technical requirements. In addition, many of the functional requirements for pharmacogenomics knowledge were computerized provider order entry (CPOE) functionalities.

Overall, findings from this aim highlighted implications for representing and integrating pharmacogenomics knowledge into existing clinical frameworks (see Section 8.3) and for

applying pharmacogenomics knowledge in a clinical setting (see Section 8.4). In addition, a scheme for evaluating the capabilities of local clinical systems was provided. Findings highlighted data access enhancements that should be prioritized to facilitate the delivery of clinical decision support for drug therapy individualization. Findings also highlighted the need for a knowledge base that provides supportive knowledge that can be integrated into existing clinical frameworks such that approximate pharmacogenomics decision support rules can be translated directly into an implementable form.

The major biomedical & health informatics contributions of this chapter are (a) providing a formal characterization of data access needs to support incorporating pharmacogenomics knowledge into existing frameworks, (b) adapting an existing taxonomy for rule-based support to evaluate local clinical systems, (c) providing a formal characterization of clinical decision support functional requirements for incorporating pharmacogenomics knowledge into existing clinical frameworks, and (d) providing a formal evaluation of whether existing clinical frameworks can support pharmacogenomics clinical decision support given data access needs and clinical decision support functional requirements for incorporating pharmacogenomics knowledge. Functional requirements for pharmacogenomics clinical decision support identified in this chapter informed the design of a conceptual model for pharmacogenomics clinical decision support described in the following chapter.

8.2.3. Chapter 6: Developing a prototype implementation of a model for pharmacogenomics clinical decision support (Aim 3)

Findings from exploring possible user interface requirements for presenting pharmacogenomics knowledge in a clinical context suggested that implementation could be richest for more mature pharmacogenomics knowledge. In addition, there were suggested contextual factors that could be common among various implementations of clinical decision support (e.g. facilitating educational gain). There were also suggested contextual factors that were unique to different implementations (e.g. semi-active CDS could be used to provide support for interpreting laboratory values prior to prescribing a medication, active CDS was not applicable in this context). Given this exploration, we hypothesized that **the appropriateness of a particular user interface presentation would impact the level of effective communication achieved in a clinical context**. As such, a model to support

various implementations of clinical decision support that supports both technical requirements and user interface requirements for presenting pharmacogenomics knowledge was proposed. Establishing a prototype implementation of the model for pharmacogenomics clinical decision support highlighted the need for standards for exchanging pharmacogenomics knowledge and the need for methods of incorporating semi-active clinical decision support functionalities in local clinical systems.

Overall, findings from exploring the user interface requirements highlighted differentiating characteristics of pharmacogenomics knowledge that might impact the appropriateness of clinical decision support implementation (see Section 8.3). For example, a hypothesis was generated based on the finding that useful resources with pharmacogenomics knowledge were more likely to be available when decision support rules providing recommendations (vs. information only) could be derived from FDA drug labels. In addition, this aim highlighted unique requirements for integration and data exchange in order to implement the proposed model for pharmacogenomics clinical decision support.

The major biomedical & health informatics contributions of this chapter are (a) a proposed model for implementing clinical decision support incorporating pharmacogenomics knowledge that allows for different implementations (i.e. semi-active and active clinical decision support), (b) a proposed model for pharmacogenomics clinical decision support that uses a commercial system (Cerner PowerChart) and an open standard (OpenInfobutton), (c) a proposed model for pharmacogenomics clinical decision support that incorporates public domain knowledge resources (CDC Summaries of EGAPP recommendation statements, PLoS Currents Evidence on Genomic Tests, CPIC guidelines, eMedicine Genomic Medicine articles, PharmGKB, PubMed, and DailyMed), and (d) developing a prototype pharmacogenomics clinical decision support model. The clinical and genetics contributions are (a) constructing six reusable scenarios describing interactions of clinical system users with pharmacogenomics knowledge and clinical decision support functionalities and (b) performing claims analyses that led to the generation of hypotheses for how clinical users will interact with the proposed model (i.e. the appropriateness of a particular user interface presentation will impact the level of effective communication achieved in a clinical context). The following chapter describes a pilot study conducted to evaluate the utility of the

prototype model for providing pharmacogenomics clinical decision support within a local UW clinical system described in this chapter.

8.2.4. Chapter 7: Evaluating the utility of the pharmacogenomics clinical decision support model implementation (Aim 4)

A pilot study was conducted to assess whether applying the proposed model for pharmacogenomics clinical decision support facilitated effective communication of pharmacogenomics knowledge to clinicians. Findings suggested that different implementations/configurations of the model appear to influence the perceived usefulness of pharmacogenomics knowledge. In addition, investigations of the clinical impact indicated that delivery of pharmacogenomics knowledge via the model appears to influence prescribing decisions and confidence in prescribing decisions. Different implementations of clinical decision support also appear to influence uptake of pharmacogenomics knowledge. Evaluations of the impact of prior user perceptions (awareness, experience and relative advantage) indicated that prior perceptions appear to influence uptake of pharmacogenomics knowledge. User perceptions about usefulness of pharmacogenomics knowledge did not appear to change after participating in the pilot study.

Overall, findings from this aim highlighted how characteristics of the user and the way in which pharmacogenomics knowledge is presented might effect use and perceptions of the pharmacogenomics knowledge by the user (see Section 8.3 and Section 8.4). While we were unable to provide conclusive evidence of associations, findings lend themselves to further investigation in a larger study. In addition, given the results from this pilot study, we are able to refine methods for data collection such that additional research questions might be investigated.

The major biomedical & health informatics contributions of this chapter are (a) estimating the influence of prior perceptions about genetic testing on use of pharmacogenomics knowledge, and (b) estimating the level of effective communication (use and perceived usefulness) achieved by different implementations of pharmacogenomics clinical decision support. The major clinical and genetics contributions are (a) estimating clinical perceptions about the usefulness of pharmacogenomics clinical decision support, (b) estimating the impact of implementing pharmacogenomics clinical decision support on

prescribing decisions, and (c) estimating the impact of pharmacogenomics provision on confidence in prescribing decisions.

8.3. Implementing Clinical Decision Support for Drug Therapy Individualization – Research Contributions, Limitations and Future Directions

Synthesizing findings from this research, it is possible to enhance our current understanding of principles for designing and implementing clinical decision support for drug therapy individualization. This in turn can inform us about informatics support for genome-based personalized medicine more broadly. A reverse process of implementing a model for the delivery of personalized healthcare based on the characteristics of existing genomics knowledge was pursued. It is considered a reverse process because previous efforts have primarily developed new genomics knowledge bases that are made accessible within local clinical systems. This approach facilitated evaluating how local clinical system CDS capabilities align with data requirements, functional requirements and user interface requirements for providing just-in-time pharmacogenomics knowledge derived from existing resources. In regard to knowledge management and knowledge integration, pharmacogenomics knowledge of most value in a clinical context was captured as free-text indicating a need for methods for both retrieving and translating knowledge into a computable form. In addition, supplemental knowledge was required to implement decision support rules derived from FDA drug labels. These findings indicated a need for methods to support simple and complex derivation of free-text knowledge to facilitate full translation into computer readable form. Natural language processing or advanced information retrieval techniques may be required, particularly for complex derivation of data elements (i.e. triggers) of decision support rules. Given that advanced techniques such as these carry a degree of uncertainty, there may also be a need to associate levels of confidence associated with these forms of derivation/data extraction.

Considering data exchange and data availability in current clinical systems, the need for standards for the exchange of pharmacogenomics knowledge to facilitate linking genetic laboratory results with knowledge to support their interpretation in a clinical context was highlighted. Also, as a preliminary step, genetic laboratory results must first be made

available within local clinical systems before they are able be connected with pharmacogenomics knowledge/evidence. There were instances where the genetic laboratory results were captured within local laboratory databases but were not accessible within the major local clinical data repositories. Incorporating these data and disease definitions were considered feasible to build into current clinical data repositories so that CDS could be connected with more laboratory results and conditions of interest.

Missing functional and user interface capabilities needed to properly facilitate CDS integration that could support pharmacogenomics requirements were identified. Many functional requirements were computerized provider order entry (CPOE) capabilities. These capabilities were absent from two clinical systems and were supported (but not implemented) in the other clinical system at the time the evaluation was conducted. Exploration of pros and cons of scenarios incorporating pharmacogenomics knowledge of varying maturity in a clinical context indicated that providing access to knowledge of low actionabilitiy might be better provided non-intrusively via semi-active CDS. These finding indicated that incorporating CPOE capabilities and providing support for semi-active CDS may be priorities to facilitate proper delivery of pharmacogenomics knowledge for drug therapy individualization.

In this work, a prototype implementation of a model for pharmacogenomics clinical decision support was developed and evaluated. Implementation occurred in a simulated context such that limitations of current UW clinical system CDS capabilities could be accounted for. A pilot study was conducted where measurements of physicians' use and the perceived usefulness of pharmacogenomics knowledge delivered via the model implementation were collected. Though not significant, results suggested that participants were more likely to find semi-active CDS useful for scenarios in which they were presented a high actionable message compared to when a low actionable message was presented. Results also suggested that participants were less likely to use semi-active CDS (i.e. access optional pharmacogenomics knowledge) with a high actionable message compared to a low actionable message. Claims generated when exploring user interface requirements indicated that CDS implementation would be richest when recommendations could be defined (i.e. more mature knowledge) compared to when information only (i.e. less mature knowledge) was provided. That is, the higher the actionability of the alert message (active CDS), the

more likely useful resources could be made available (semi-active CDS, e.g. practice guidelines). Building on this notion, findings from the pilot study would suggest that physicians may not need semi-active CDS as often when a higher actionable message is displayed. However, when they do decide to explore optional resources in those scenarios the resources are considered more useful.

Findings from the pilot study, although not significant, suggested that active CDS was less likely to be found useful for scenarios where a high actionable alert message was presented compared to when a low actionable message was presented. We did not evaluate whether or not active CDS was used because alert messages were not optional to access given that they must respond to the message before moving on with prescribing. Similarly, though not considered active CDS in an actual clinical context, genetic laboratory values with some interpretation (e.g. "poor metabolizer") were presented as part of the clinical case scenarios participants responded to. As such, use of these forms of pharmacogenomics knowledge was not optional and was considered another form of active CDS in the experiment. Given the exploration of user interface requirements, it was expected that active CDS was more likely to be found useful when more mature pharmacogenomics knowledge was available. Further investigation is required to more fully understand why findings in our pilot study suggesting the opposite notion. It is possible that there are factors influencing perceptions about the usefulness of CDS in play that are distinct from factors related to the appropriateness of CDS. For example, participants may prefer non-intrusive modes of CDS delivery, which influences their perceptions of active CDS. In addition, low and high actionable messages were defined in a systematic manner, but several content factors related to perceptions of usefulness (e.g. unambiguity, presentation of alternatives, etc.) were not evaluated prior to conducting the pilot study. Such evaluations to better understand how information content factors of the alert messages influence perceptions of usefulness would be an interesting future direction to pursue.

Across all of the aims completed in this work, it is clear that characteristics of pharmacogenomics knowledge can help govern decisions about clinical decision support implementation. In addition to providing principles for the design and implementation of clinical decision support from a clinical organization perspective, we can also provide suggestions from the perspective of organizations managing knowledge resources.

8.4. PROVIDING PHARMACOGENOMICS KNOWLEDGE IN A CLINICAL CONTEXT – RESEARCH CONTRIBUTIONS, LIMITATIONS AND FUTURE DIRECTIONS

Synthesizing finds from this research it is possible to enhance our current understanding of pharmacogenomics knowledge characteristics in a clinical context. There are unique characteristics of pharmacogenomics knowledge that impact its ability to be applied in a clinical context and its ability to be represented and made available within current clinical frameworks. There are also unique aspects of user interactions with pharmacogenomics knowledge that might impact the adoption and success rate of clinical decision support incorporating pharmacogenomics knowledge.

There are several characteristics of currently available pharmacogenomics knowledge that impact its ability to be represented and made available within current clinical frameworks that were highlighted in this work. Pharmacogenomics knowledge of most value in electronic resources is currently captured as free-text. Representing knowledge in a way that better facilitates download and data access are needed for knowledge contained in resources to be integrated into clinical systems. Given that the majority of rules derived from drug labels were represented by a small number of rule patterns, representing knowledge to support automatic extraction of relevant data fields are areas of prioritization for organizations that maintain pharmacogenomics knowledge repositories. There are also changes being made to drug label content and genomics knowledge at a fast pace, the prevalence of biomarker information in drug labels is increasing, and the maturity of knowledge in a clinical context is evolving. Given the evolving nature of genomic knowledge, there is a need for modes of identifying updates (that also carry provenance information) in pharmacogenomics knowledge repositories. There is also a need in the to capture levels of evidence/certainty of the knowledge. Making these data available would facilitate making the most relevant and accurate knowledge available in a clinical context.

Characteristics that impact ways in which pharmacogenomics knowledge can be applied in a clinical context were also highlighted in this work. For example, we found that knowledge might support the pre- or post- analytic phase of genetic testing. The focus of this research was on providing CDS to support the post- analytic phase of genetic testing. A similar investigation to what was performed in this work to identify user interface requirements might also be applied to investigate appropriate ways to support the pre-

analytic phase of genetic testing with use of CDS functionalities. In addition, this work indicated that much of the pharmacogenomics knowledge contained in drug labels required supplemental knowledge to facilitate computer interpretations (e.g. IF patient has genotype CYP2C9*2/*3 THEN patient is a poor metabolizer). This finding indicated a need for a new (authoritative) knowledge resource to facilitate clinical interpretation such that pharmacogenomics knowledge can be connected with CDS.

In conducting the pilot study, it was determined that characteristics of the user may influence the uptake of pharmacogenomics knowledge in a clinical context. There were significant findings indicating that oncology fellows prescribed different medication doses after being presented pharmacogenomics knowledge, but cardiology fellows did not. It was also determined, although not a statistically significant finding, that prior perceptions of genetic testing in clinical practice influenced uptake of pharmacogenomics knowledge. It could be that physicians that practice medical oncology might be more aware and have more experience using genetic testing in their practices. These perceptions in turn may influence whether they incorporate recommendations. Alternatively, it might be possible that there are other ways for cardiology fellows to respond to recommendations (e.g. increased patient monitoring) that are not picked up by considering dose adjustments. The influence of user characteristics on uptake and perceptions of pharmacogenomics knowledge is an area worth investigating further in future research.

8.5. Concluding comments

This research enhanced our understanding of principles for designing and implementing clinical decision support for drug therapy individualization; and our current understanding of pharmacogenomics knowledge characteristics in a clinical context. The results highlight several areas that have practical and more general implications for future biomedical and health informatics research. These include the characteristics of pharmacogenomics knowledge that can help govern decisions about clinical decision support implementation and can help guide decisions made by groups that develop and maintain knowledge resources such that delivery of content in a clinical context is supported.

This research may be of particular importance for scientific inquiry related to applying a reverse process to implement a model for the delivering personalized healthcare more

broadly. The strategy for evaluating clinical system capabilities based on pharmacogenomics knowledge characteristics in a clinical context adds to the foundation of clinical decision support system design and can be applied to systems outside of a local setting. In addition the conceptual model for pharmacogenomics clinical decision support was designed such that both semi-active and active CDS could be supported, which highlights the need to evaluate circumstances where different implementations and configurations would be preferred. Similar strategies to investigating these possibilities employed in this work (and incorporating characteristics of the clinical user) can be applied on a broader scale.

Another area for scientific inquiry is related to characterizing current pharmacogenomics knowledge. As part of this work, pharmacogenomics knowledge was translated into a form capable of being incorporated in current clinical system frameworks. This process highlighted several venues for investigating more automated methods for representing knowledge and new representations of knowledge such that integration into clinical decision support systems is supported. Lastly, clinical system knowledge management and integration solutions based on pharmacogenomics knowledge characteristics identified in this work are another area of scientific inquiry.

APPENDIX 1. APPROXIMATE PHARMACOGENOMICS DECISION SUPPORT RULES

Rule ID	Decision Support Rule	FDA Drug label
45.1	IF the patient is taking abacavir AND the patient is negative for HLA-B*5701, THEN the patient has a significantly lower chance of developing a hypersensitivity reaction to abacavir when compared to HLA-B*5701-positive patients	Abacavir
45.2	IF the patient is taking abacavir AND the patient carries the HLA-B*5701 allele THEN the patient is at high risk for experiencing a hypersensitivity reaction to abacavir	Abacavir
45.3	IF the patient is taking abacavir AND the patient carries the HLA-B*5701 allele THEN the patient is at high risk for experiencing a hypersensitivity reaction to abacavir	Abacavir
45.4	IF abacavir is being considered as therapy for the patient, THEN ask the patient whether or not they have been tested for the HLA-B*5701 allele	Abacavir
45.5	IF the patient is taking abacavir, THEN screening for the HLA-B*5701 allele is recommended	Abacavir
45.6	IF the patient is [being considered for] taking abacavir AND the patient is of unknown HLA-B*5701 status AND the patient has taken ZIAGEN in the past, THEN screening for the allele is recommended prior to re-initiation of ZIAGEN	Abacavir
45.7	IF re-initiation of abacavir in the patient is being considered AND patient has unknown HLA-B*5701 status AND the patient has previously tolerated abacavir, THEN screening for the HLA-B*5701 allele is recommended	Abacavir
12.1	IF patient is [being considered for] taking aripiprazole AND patient is taking an agent that induces CYP3A4 THEN patient could have increased in aripiprazole clearance and lower blood levels	Aripiprazole
12.2	IF patient is [being considered for] taking aripiprazole AND (patient is taking a medication that is an inhibitor of CYP3A4 OR patient is taking a medication that is an inhibitor of CYP2D6) THEN the medication can inhibit aripiprazole elimination and cause increased blood levels	Aripiprazole
12.3	IF patient is [being considered for] taking aripiprazole AND patient is taking quinidine, a potent inhibitor of CYP2D6, THEN for a 10 mg single dose of aripiprazole with quinidine (116 mg/day for 13 days), the AUC of aripiprazole is increased by 112% AND the AUC of its active metabolite, dehydro-aripiprazole, is decreased by 35%	Aripiprazole
12.4	IF patient is [being considered for] taking aripiprazole AND patient is [being considered for] taking quinidine [a CYP2D6 inhibitor] concomitantly, THEN the dose of aripiprazole should be reduced to one-half of its normal dose	Aripiprazole
12.5	IF patient is [being considered for] taking aripiprazole AND patient is [currently] taking an inhibitor of CYP2D6, THEN it would be expected that taking an inhibitor of CYP2D6 would have similar effects [as when taking quinidine] and should lead to similar dose reductions as with taking quinidine [aripiprazole dose should be reduced to one-half of its normal dose when quinidine is given concomitantly with aripiprazole]	Aripiprazole
12.6	IF patient is [currently] taking aripiprazole AND patient is [currently] taking an inhibitor of CYP2D6 AND patient is [being considered for] withdrawing from combination therapy with an inhibitor of CYP2D6, THEN aripiprazole dose should be increased	Aripiprazole
12.7	IF patient is [being considered for] taking aripiprazole AND patient is taking drugs metabolized by cytochrome P450 enzymes THEN aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes	Aripiprazole
12.8	IF patient is [being considered for] taking aripiprazole AND patient is [being considered for] taking drugs metabolized by cytochrome P450 enzymes THEN In vivo studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism in vitro	Aripiprazole
12.9	IF patient is [being considered for] taking aripiprazole AND patient is [being considered	Aripiprazole

	for] taking dextromethorphan [a CYP2D6 and CYP3A4 substrate] THEN aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway dependent on CYP3A4 activity	
12.10.	IF patient is [being considered for] taking aripiprazole AND patient is [being considered for] taking dextromethorphan [a CYP2D6 and CYP3A4 substrate] THEN No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole	Aripiprazole
12.11	IF patient is [being considered for] taking aripiprazole AND patient is [being considered for] taking venlafaxine XR, a CYP2D6 substrate THEN coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate	Aripiprazole
12.12	IF patient is [being considered for] taking aripiprazole AND patient is [currently] taking venlafaxine XR, a CYP2D6 substrate THEN no dosage adjustment of venlafaxine is required	Aripiprazole
12.13	IF patient is [being considered for] taking aripiprazole THEN aripiprazole accumulation is predictable from single-dose pharmacokinetics At steady-state, the pharmacokinetics of aripiprazole are dose-proportional Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4	Aripiprazole
12.14	IF patient is [being considered for] taking aripiprazole THEN Aripiprazole is metabolized primarily by three biotransformation pathways dehydrogenation, hydroxylation, and N-dealkylation Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4 Aripiprazole is the predominant drug moiety in the systemic circulation At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma	Aripiprazole
12.15	IF patient is Caucasian AND patient is [being considered for] taking aripiprazole, THEN approximately 8% of Caucasians that lack the capacity to metabolize CYP2D6 substrates are classified as poor metabolizers and have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to extensive metabolizers resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to extensive metabolizers AND 92% of Caucasians are extensive metabolizers	Aripiprazole
12.16	IF patient is [being considered for] taking ABILIFY AND patient is taking a known inhibitor of CYP2D6 AND patient is an EM THEN aripiprazole plasma exposure in EMs approximately doubles and dose adjustment is needed	Aripiprazole
12.17	IF patient is an EM [of CYP2D6] AND patient is taking aripiprazole THEN the mean elimination half-lifes are about 75 hours for aripiprazole	Aripiprazole
12.18	IF patient is an PM [of CYP2D6] AND patient is taking aripiprazole THEN the mean elimination half-lifes are about 146 hours for aripiprazole	Aripiprazole
13.1	IF patient is [being considered for] taking arsenic trioxide THEN arsenic trioxide causes damage or degradation of the fusion protein PML/RAR-alpha	Arsenic Trioxide
13.2	IF patient has APL AND (patient is refractory to retinoid and anthracycline chemotherapy OR patient has relapsed from retinoid and anthracycline chemotherapy) AND (the patients' APL is characterized by the presence of the t(15,17) translocation) OR (the patients' APL is characterized by PML/RAR-alpha gene expression) THEN TRISEXOX is indicated for induction of remission and consolidation in the patient	Arsenic Trioxide
46.1	IF the patient is taking STRATTERA AND the patient has a CYP2D6 variant AND the variant causes poor metabolism THEN the patient will have a 10 fold higher AUC AND a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers	Atomoxetine
46.2	IF the patient is taking STRATTERA AND the patient has a CYP2D6 variant AND the variant causes poor metabolism THEN the patient has a higher chance of some adverse effects of STRATTERA	Atomoxetine

46.3	IF the patient is taking STRATTERA AND the patient is Caucasian THEN the patient has a 7% chance of being a poor metabolizer	Atomoxetine
46.4	IF patient is [being considered for] taking atomoxetine AND patient is [being considered for] taking a strong CYP2D6 inhibitor AND (patient is a child or adolescent over 70 kg body weight OR patient is an adult) THEN STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated	Atomoxetine
46.5	IF the patient is taking STRATTERA AND (the patient is taking a medication that is a strong CYP2D6 inhibitor OR (the patient has a CYP2D6 variant AND the variant causes poor metabolism), THEN dosage adjustment of STRATTERA may be necessary	Atomoxetine
46.6	IF the patient is taking Atomoxetine AND (the patient has hepatic impairment OR the patient is taking a medication that is a strong CYP2D6 inhibitor OR the patient is a CYP2D6 poor metabolizer) THEN the dose of Atomoxetine should be adjusted	Atomoxetine
46.7	IF the patient is taking a medication that is a strong CYP2D6 inhibitor AND the patient is taking STRATTERA, THEN no dose adjustment for medications that are metabolized by CYP2D6 is necessary	Atomoxetine
46.8	IF the patient is taking STRATTERA AND the patient is a child AND the patient is 70 kg body weight or below AND (the patient is taking a medication that is a strong CYP2D6 inhibitor OR the patient is a CYP2D6 poor metabolizer) THEN the dose of STRATTERA should be initiated at 0 5 mg/kg/day AND (IF symptoms fail to improve after 4 weeks AND initial dose is well tolerated, THEN the dose of STRATTERA should be increased to 1 2 mg/kg/day)	Atomoxetine
47.1	IF the patient is taking LIPITOR AND the patient is homozygous FH, THEN LIPITOR may reduce LDL-C in the patient AND it is likely that the patient will not respond to other lipid-lowering medications	Atorvastatin
47.2	IF the patient is homozygous FH AND the patient is taking other lipid-lowering medications OR other lipid-lowering medications are unavailable THEN treat the patient with LIPTOR	Atorvastatin
47.3	IF the patient is homozygous FH AND (the patient is taking other lipid-lowering treatments OR the patient no other lipid-lowering treatments are available), THEN treat patient with LIPITOR	Atorvastatin
47.4	IF the patient is heterozygous FH AND the patient is taking other lipid-lowering OR apo B-lowering treatment AND (the patient is a male OR the patient is a female AND the patient is postmenarchal) AND the patient is between the ages of 10 and 17 AND the patient has recieved an adequate trial of diet therapy where LDL-C remains >= 190 mg/dL OR (LDL-C remains >= 160 mg/dL AND there is a positive family history of premature CV OR two or more other CVD risk factors are present), THEN treat the patient with LIPITOR	Atorvastatin
47.5	IF the patient is taking LIPITOR AND the patient is between the age of 10 and 17 AND the patient is heterozygous FH, THEN the recommended starting dose of LIPITOR is 10 mg/day AND the maximum recommended dose is 20 mg/day	Atorvastatin
47.6	IF the patient is taking LIPITOR AND the patient is homozygous FH THEN the dosage of LIPITOR should be 10-80 mg daily	Atorvastatin
48.1	IF the patient is taking busulfan AND the patient has chronic myelogenous leukemia AND the patient lacks the Ph1 chromosome, THEN busulfan will be less effective in the patient	Busulfan
3.1	IF patient is [being considered for] taking XELODA AND (patient has known hypersensitivity to capecitabine or to any of its components OR patient has a known hypersensitivity to 5-fluorouracil OR patient has known dihydropyrimidine dehydrogenases (DPD) deficiency OR patient has severe renal impairment) THEN XELODA is contraindicated in patient	Capecitabine
3.2	IF patient is [being considered for] taking capecitabine AND patient has deficiency of dihydropyrimidine dehydrogenase (DPD) activity THEN rarely, unexpected, severe toxicity (e g , stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to DPD deficiency AND a link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be	Capecitabine

	excluded	
49.1	IF the patient is negative for HLA-B*1502, THEN the patient is at low risk of SJS/TEN	Carbamazepine
49.2	IF the patient is taking Carbamazepine AND the patient has HLA-B*1502 allele THEN serious and sometimes fatal dermatologic reactions including TEN and SJS may occur during treatment with Carbamazepine	Carbamazepine
49.3	IF the patient is taking carbamazepine AND the patient is of ancestry in populations in which HLA-B*1502 may be present, THEN testing for HLA-B*1502 should be performed prior to starting carbamazepine therapy	Carbamazepine
49.4	IF the patient is taking Carbamazepine AND the patient is genetically at-risk for having HLA-B*1502, THEN high-resolution 'HLA-B*1502 typing' is recommended	Carbamazepine
49.5	IF the patient is taking carbamazepine AND the patient is of ancestry in populations in which HLA-B*1502 may be present, THEN testing for HLA-B*1502 should be performed prior to starting carbamazepine therapy	Carbamazepine
49.6	IF the patient is taking Carbamazepine AND patient is Asian AND (patient is from Hong Kong OR patient is from Thailand OR patient is from Malaysia OR patient is from the Philippines) THEN Greater than 15% of the population is reported positive (for HLA-B*1502) in Hong Kong, Thailand, Malaysia, and parts of the Philippines	Carbamazepine
49.7	IF the patient is taking Carbamazepine AND patient is Asian AND patient is from Taiwan THEN About 10% of the population is reported positive (for HLA-B*1502) in Taiwan	Carbamazepine
49.8	IF the patient is taking Carbamazepine AND the patient is Asian AND patient is from North China THEN About 4% of the population is reported positive (for HLA-B*1502) in North China	Carbamazepine
49.9	IF the patient is taking Carbamazepine AND the patient is South Asian (including Indians) THEN South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups	Carbamazepine
49.10.	IF the patient is taking Carbamazepine AND (patient is from Japan OR patient is from Korea) THEN HLA-B*1502 is present in <1% of the population in Japan and Korea	Carbamazepine
49.11	IF the patient is taking Carbamazepine AND patient is not of Asian origin THEN HLA-B*1502 is largely absent in individuals not of Asian origin (e g Caucasians, African-Americans, Hispanics, and Native Americans)	Carbamazepine
49.12	IF the patient is taking Carbamazepine AND the patient is positive for HLA-B*1502, THEN do not treat patient with Carbamazepine unless the benefits clearly outweigh the risks	Carbamazepine
49.13	IF the patient is taking Carbamazepine AND the patient tests positive for HLA-B*1502 allele THEN do not treat with Carbamazepine unless the benefit clearly outweighs the risk	Carbamazepine
49.14	IF either one or two HLA-B*1502 alleles are detected, THEN the test is positive	Carbamazepine
49.15	IF no HLA-B*1502 alleles are detected, THEN the test is negative	Carbamazepine
4.1	IF patient is [being considered for] taking carvedilol AND patient is [being considered for] taking a potent inhibitor of CYP2D6 THEN Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol	Carvedilol
4.2	IF patient is [being considered for] taking carvedilol AND patient is a poor 2D6 metabolizer THEN Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer	Carvedilol
4.3	IF patient is [being considered for] taking carvedilol THEN The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1 CYP2D6 is thought to be the major enzyme in the 4- and 5-hydroxylation of carvedilol, with a potential contribution from 3A4 CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol	Carvedilol

4.4	IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin (a marker for cytochrome P450 2D6) THEN 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers	Carvedilol
4.5	IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin THEN plasma levels of S(-)carvedilol are increased only about 20% to 25%, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol	Carvedilol
4.6	IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of S-mephenytoin (deficient in cytochrome P450 2C19) THEN the pharmacokinetics of carvedilol do not appear to be different	Carvedilol
50.1	IF the patient is [being considered for] taking Celecoxib AND patient is taking other drugs that are inhibitors or metabolized by enzymes CYP2C9 or CYP2D6 THEN taking Celecoxib may interact with other drugs the patient is taking that are inhibitors or metabolized by enzymes CYP2C9 or CYP2D6	Celecoxib
50.2	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolism THEN Celecoxib should be administered to the patient with caution	Celecoxib
50.3	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant genotype is *3/*3 THEN Celecoxib systemic levels are 3- to 7- fold higher in the patient when compared to patients with CYP2C9 variant genotypes *1/*1 or *1/*3	Celecoxib
50.4	IF the patient is taking Celecoxib AND the patient is a child AND the patient has a CYP2C9 variant AND the variant causes poor metabolism AND the patient has JRA THEN consider therapy other than Celecoxib	Celecoxib
50.5	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolism AND the patient has JRA THEN consider using alternative management of Celecoxib	Celecoxib
50.6	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolism THEN the dose of Celecoxib should be reduced by 50%	Celecoxib
50.7	IF the patient is taking Celecoxib AND the patient has a CYP2C9 variant AND the variant causes poor metabolism THEN it's recommended that the lowest dose of Celecoxib be reduced by 50%	Celecoxib
50.8	IF the patient is taking Fluconazole AND the patient is taking Celecoxib THEN the lowest dose of Celecoxib should be given to the patient	Celecoxib
52.1	IF the patient is taking irinotecan AND the patient has EGFR-expressing metastatic colorectal carcinoma AND the patient is refractory to irinotecan-based chemotherapy, THEN there may or may not be an improvement in increased survival with the addition of Erbitux treatment	Cetuximab (1)
52.2	IF the patient has EGFR-expressing metastatic colorectal carcinoma AND the patient is refractory to irinotecan-based chemotherapy, THEN treat the patient with Erbitux	Cetuximab (1)
52.3	IF the patient is taking Erbitux AND the patient has EGFR expressing colorectal cancer AND (the patient has had failure of irinotecan-based regimens AND the patient has had failure of oxaliplatin-based regimens) OR (the patient is intolerant to irinotecan-based regimens), THEN threat the patient with Erbitux	Cetuximab (1)
14.1	IF patient is [being considered for] taking Cetuximab AND patient has tumors with KRAS mutations in codon 12 or 13 THEN Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had KRAS mutations in codon 12 or 13	Cetuximab (2)
14.2	IF patient is [being considered for] taking Cetuximab AND patient has tumors with KRAS mutations in codon 12 or 13 THEN Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations	Cetuximab (2)
14.3	IF patient is [being considered for] taking Cetuximab THEN Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha In vitro assays and in vivo animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased	Cetuximab (2)

	matrix metalloproteinase and vascular endothelial growth factor production Signal transduction through the EGFR results in activation of wild-type KRAS protein However, in cells with activating KRAS somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation	
14.4	IF patient is [being considered for] taking Cetuximab AND patient has CRC containing KRAS mutations THEN Retrospective analyses across seven randomized clinical trials suggest that anti-EGFR monoclonal antibodies are not effective for the treatment of patients with mCRC containing KRAS mutations In these trials, patients received standard of care (ie, BSC or chemotherapy) and were randomized to receive either an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy In all studies, investigational tests were used to detect KRAS mutations in codon 12 or 13 The percentage of study populations for which KRAS status was assessed ranged from 23% to 92%	Cetuximab (2)
15.1	IF patient is [being considered for] taking Cevimeline THEN Isozymes CYP2D6 and CYP3A3/4 are responsible for the metabolism of cevimeline After 24 hours, 86 7% of the dose was recovered (16 0% unchanged, 44 5% as cis and trans-sulfoxide, 22 3% of the dose as glucuronic acid conjugate and 4% of the dose as N-oxide of cevimeline) Approximately 8% of the trans-sulfoxide metabolite is then converted into the corresponding glucuronic acid conjugate and eliminated Cevimeline did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4	Cevimeline
15.2	IF patient is [being considered for] taking Cevimeline AND patient is [being considered for] taking drugs which inhibit CYP2D6 and CYP3A3/4 THEN Drugs which inhibit CYP2D6 and CYP3A3/4 also inhibit the metabolism of cevimeline	Cevimeline
15.3	IF patient is [being considered for] taking cevimeline AND patient is suspected to be deficient in CYP2D6 activity THEN Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events	Cevimeline
15.4	IF patient is [being considered for] taking cevimeline THEN In an in vitro study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline	Cevimeline
67.1	IF patient is [being considered for] taking Chloroquine AND patient has G-6-PD (glucose-6 phosphate dehydrogenase) deficiency THEN The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency	Chloroquine
5.1	IF patient is [being considered for] taking Plavix THEN the effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19	Clopidogrel
5.2	IF patient is [being considered for] taking Plavix AND patient is a CYP2C19 poor metabolizer THEN Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patient	Clopidogrel
5.3	IF patient is a poor metabolizer (of CYP2C19) AND (patient has acute coronary syndrome OR patient is undergoing percutaneous coronary intervention) AND patient is [currently] taking Plavix THEN Plavix at recommended doses exhibit higher cardiovascular event rates in patient then with patients that have normal CYP2C19 functions	Clopidogrel
5.4	IF patient is [being considered for] taking Plavix THEN tests are available to identify a patient's CYP2C19 genotype AND CYP2C19 genotype tests can be used as an aid in determining therapeutic strategy	Clopidogrel
5.5	IF patient is [being considered for] taking Plavix AND patient is identified as a CYP2C19 poor metabolizer THEN consider alternative treatment or treatment strategies in patient	Clopidogrel
5.6	IF patient is [currently] taking Omeprazole, a moderate CYP2C19 inhibitor AND patient is [being considered for] taking Plavix THEN Omeprazole reduces the pharmacological activity of Plavix AND (concomitant use of Plavix with Omeprazole should be avoided OR use of Omeprazole should occur 12 hours apart with Plavix) AND use of another acid reducing agent with less CYP2C19 inhibitory activity should be considered	Clopidogrel
5.7	IF patient is [currently] taking Omeprazole AND patient is [being considered for] taking Plavix THEN a higher dose regimen of clopidogrel concomitantly administered with	Clopidogrel

	omeprazole increases antiplatelet response AND an appropriate dose regimen has not been established	
5.8	IF patient [is being considered] for Plavix AND patient is [currently] taking Omeprazole, a moderate CYP2C19 inhibitor THEN Omeprazole has been shown to reduce the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart	Clopidogrel
5.9	IF patient [is being considered] for Plavix AND patient is [currently] taking Omeprazole, a moderate CYP2C19 inhibitor THEN using another acid reducing agent with less CYP2C19 inhibitory activity should be considered	Clopidogrel
5.10.	IF patient [is being considered] for Plavix AND patient is [currently] taking Pantoprazole, a weak CYP2C19 inhibitor THEN Pantoprazole has less of an effect on the pharmacological activity of Plavix than omeprazole	Clopidogrel
5.11	IF patient [is being considered] for clopidogrel AND patient [is being considered] for drugs that inhibit the activity of CYP2C19 THEN concomitant use of clopidogrel with drugs that inhibit the activity of CYP2C19 result in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition	Clopidogrel
5.12	IF patient [is being considered] for clopidogrel AND patient is white AND patient is a poor metabolizer of CYP2C19 THEN 85% of reduced function alleles found in a patient with this status are CYP2C19*2 and *3, other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5,*6, *7, and *8	Clopidogrel
5.13	IF patient [is being considered] for clopidogrel AND patient is Asian AND patient is a poor metabolizer of CYP2C19 THEN 99% of reduced function alleles found in a patient with this status are CYP2C19*2 and *3, other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5,*6, *7, and *8	Clopidogrel
5.14	IF patient [is being considered] for clopidogrel AND patient is a poor metabolizer of CYP2C19 THEN patient possess two loss-of-function alleles	Clopidogrel
5.15	IF patient [is being considered] for clopidogrel THEN tests are available to determine a patient's CYP2C19 genotype	Clopidogrel
5.16	IF patient [is being considered] for clopidogrel AND patient is a poor metabolizer of CYP2C19 THEN A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen	Clopidogrel
5.17	IF patient [is being considered] for clopidogrel AND patient is a poor metabolizer of CYP2C19 THEN an appropriate dose regimen for this patient population has not been established in clinical outcome trials	Clopidogrel
5.18	IF patient is [being considered for] taking Plavix AND (patient is an intermediate metabolizer of CYP2C19 OR patient is a poor metabolizer of CYP2C19) THEN the majority of published cohort studies show that patients of this status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers, and in only one cohort study, the increased event rate was observed only in poor metabolizers	Clopidogrel
16.1	IF patient is [being considered for] taking clozapine THEN risk of metabolic interactions caused by an effect on an individual isoform is minimized because clozapine is a substrate for many CYP450 isozymes	Clozapine
16.2	IF patient is [being considered for] taking clozapine AND patient is receiving other drugs that are either inhibitors or inducers of CYP450 isozymes (in particular 1A2, 2D6, and 3A4) THEN caution should be used in patients receiving concomitant treatment with other drugs that are either inhibitors or inducers of these enzymes	Clozapine
16.3	IF patient is [being considered for] taking clozapine AND patient is a poor metabolizer of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6 THEN the patient may develop higher than expected plasma concentrations of clozapine	Clozapine

	when given usual doses	
16.4	IF patient is [being considered for] taking clozapine AND patient is taking certain drugs that are metabolized by P450 2D6 including antidepressants THEN drugs metabolized by P450 2D6 may inhibit the activity of P450 2D6 and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction	Clozapine
16.5	IF patient is [being considered for] taking clozapine AND patient is [currently] taking other drugs metabolized by cytochrome P450 2D6 THEN patient may require lower doses than usually prescribed for either clozapine or the other drugs	Clozapine
16.6	IF patient is [being considered for] taking clozapine AND (patient is [being considered for] taking other drugs metabolized by cytochrome P450 2D6 including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics e g propafenone, flecainide and encainide, THEN coadministration of clozapine with other drugs metabolized by cytochrome P450 2D6 should be approached with caution	Clozapine
16.7	IF patient is [being considered for] taking clozapine AND patient is [being considered for] taking other drugs that inhibit cytochrome P450 2D6 e g quinidine THEN coadministration of clozapine with other drugs that inhibit cytochrome P450 2D6 should be approached with caution	Clozapine
53.1	IF the patient is taking medications that are inhibitors of CYP2D6 AND (the patient is taking codeine OR the patient is taking morphine) THEN the patient may have a decrease in plasma concentrations of codeines' active metabolites, morphine and morphine-6-glucuronide	Codeine sulfate
53.2	IF the patient is taking codeine AND the patient has the CYP2D6*2x2 genotype THEN the patient may be an ultra-rapid metabolizer AND the lowest effective dose for the shortest period of time should be used for codeine-containing drugs	Codeine sulfate
53.3	IF the patient is taking a medication that is an inducer or inhibitor of CYP2D6 or CYP3A4 AND the patient is taking codeine THEN the patient may have an altered response to codeine AND the patient should be monitored for analgesic activity AND the patient should be monitored for adverse drug reactions	Codeine sulfate
53.4	IF the patient is taking Codeine AND the patient has the CYP2D6*2x2 genotype THEN the patient should be informed about risks and the signs of morphine overdose	Codeine sulfate
17.1	IF patient is [being considered for] taking ACZONE THEN glucose 6-phosphate dehydrogenase (G6PD) levels should be obtained prior to initiating therapy	Dapsone
17.2	IF patient is [being considered for] taking ACZONE AND patient has a history of anemia AND patient has predisposition to increased hemolytic effect with dapsone (e g G6PD deficiency) THEN closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented	Dapsone
17.3	IF patient is [being considered for] taking ACZONE THEN glucose 6-phosphate dehydrogenase (G6PD) levels should be obtained prior to initiating therapy	Dapsone
17.4	IF patient is [being considered for] taking ACZONE AND (patient is glucose 6-phosphate dehydrogenase deficient OR patient has a history of anemia) THEN patient is at risk, and routine follow-up for complete blood count and reticulocyte count should be implemented	Dapsone
17.5	IF patient is [being considered for] taking oral Dapsone AND (patient has glucose-6-phosphate dehydrogenase OR patient doesn't have glucose-6-phospate dehydrogenase) THEN dose-related hemolysis is the most common adverse event	Dapsone
17.6	IF patient is [being considered for] taking Dapsone AND (patient has G6PD deficiency OR patient has methemoglobin reductase deficiency OR patient has hemoglobin M) THEN hemolysis may be exaggerated in patient	Dapsone
17.7	IF patient is [being considered for] taking Dapsone AND patient is G6PD deficient THEN While clinical studies conducted did not demonstrate evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin level were noted to be associated in a G6PD deficient patient treated with ACZONE Gel, 5%, for acne vulgaris who had a complete blood count performed Only 25 patients with low plasma glucose 6 phosphate dehydrogenase activity treated with ACZONE Gel, 5%, were included in the clinical study program Safety of ACZONE Gel, 5%, has not been	Dapsone

	fully evaluated in patients with G6PD deficiency	
17.8	IF patient is [being considered for] taking Dapsone THEN patient should tell their physician if they have any history of anemia or an enzyme deficiency (such as G6PD deficiency)	Dapsone
17.9	IF patient is [being considered for] taking ACZONE THEN glucose 6-phosphate dehydrogenase levels should be obtained prior to initiating therapy with ACZONE	Dapsone
17.10.	IF patient is [being considered for] taking ACZONE AND (patient is G6PD deficient OR patient has a history of anemia) THEN baseline complete blood counts, including a reticulocyte count, should be obtained	Dapsone
17.11	IF patient is [being considered for] taking Dapsone AND patient is "at risk" THEN routine follow-up for complete blood count and reticulocyte could should be implemented	Dapsone
54.1	IF the patient is an adult AND the patient has ALL AND the patient has the Ph1 chromosome, THEN treat the patient with SPRYCEL	Dasatinib
54.2	IF the patient is an adult AND the patient has ALL AND the patient has the Ph1 chromosome AND the patient is resistant or intolerant to prior therapy, THEN treat the patient with SPRYCEL	Dasatinib
18.1	IF patient is receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e g thioridazine and pimozide) AND patient is [being considered for] taking Dextromethorphan and Quinidine THEN NUEDEXTA is contraindicated, as effects on QT interval may be increased	Dextromethorphan and Quinidine
18.2	IF patient is [being considered for] taking NUEDEXTA AND CYP2D6 is not genetically absent or its activity otherwise pharmacologically inhibited in the patient THEN the quinidine in NUEDEXTA inhibits CYP2D6	Dextromethorphan and Quinidine
18.3	IF patient is [being considered for] taking NUEDEXTA AND patient is [being considered for] taking drugs that are metabolized by CYP2D6 THEN because of this effect of CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6	Dextromethorphan and Quinidine
18.4	IF patient is [being considered for] taking NUEDEXTA THEN the quinidene component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethophan can be achieved compared to when dextromethophan is given alone	Dextromethorphan and Quinidine
18.5	IF patient is [being considered for] taking NUEDEXTA AND patient is Caucasian THEN 7-10% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs)	Dextromethorphan and Quinidine
18.6	IF patient is [being considered for] taking NUEDEXTA AND patient is African American THEN 7-10% of African Americans lack the capacity to metabolize CP2D6 substrates and are classified as poor metabolizers (PMs)	Dextromethorphan and Quinidine
18.7	IF patient is [being considered for] taking NUEDEXTA AND patient is a PM THEN The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible	Dextromethorphan and Quinidine
18.8	IF patient is [being considered for] taking NUEDEXTA AND patient may be at risk of significant toxicity due to quinidine THEN genotyping to determine if the are PMs should be considered prior to making the decision to treat with NUEDEXTA	Dextromethorphan and Quinidine
18.9	IF patient is [being considered for] taking NUEDEXTA AND patient is [being considered for] taking drugs that prolong QT interval and are metabolized by CYP2D6 THEN do not use NUEDEXTA with drugs that both prolong QT interval and are metabolized by CYP2D6	Dextromethorphan and Quinidine
18.10.	IF patient is [being considered for] administration of NUEDEXTA AND patient [being considered for] administration of drugs that undergo extensive CYP2D6 metabolism THEN altered drug effects may result due to accumulation of parent drug and/or failure of metabolite formation	Dextromethorphan and Quinidine
18.11	IF patient is [currently] taking NUEDEXTA AND (patient is [being considered for] taking medications that are primarily metabolized by CYP2D6 AND medications have a relatively narrow therapeutic index) THEN medications should be initiated at a low dose	Dextromethorphan and Quinidine

18.12	IF patient is [being considered for] taking NUEDEXTA AND patient is [currently] taking a drug primarily metabolized by CYP2D6 THEN the need for dose modification of the original medication should be considered	Dextromethorphan and Quinidine
18.13	IF patient is [currently] taking NUEDEXTA AND patient is [being considered for] taking prodrugs whose actions are mediated by the CYP2D6-produced metabolites THEN it may not be possible to achieve the desired clinical benefits in the presence of NUEDEXTA due to quinidine-mediated inhibition of CYP2D6 Consider use of alternative treatment with NUEDEXTA	Dextromethorphan and Quinidine
18.14	IF patient is [being considered for] taking Dextromethorphan and Quinidine AND patient is [being considered for] taking Desipramine [a CYP2D6 substrate] THEN Desipramine is a tricyclic antidepressant desipramine is metabolized primarily by CYP2D6	Dextromethorphan and Quinidine
18.15	IF patient is [being considered for] taking Dextromethorphan and Quinidine AND patient is [being considered for] taking Desipramine [a CYP2D6 substrate] THEN A drug interaction study was conducted between a higher combination dose of dextromethorphan (dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg) and desipramine 25 mg The combination dose of dextromethorphan/quinidine increased steady state desipramine levels approximately 8-fold	Dextromethorphan and Quinidine
18.16	IF patient is [currently] taking NUEDEXTA AND patient is [being considered for] taking desipramine [a CYP2D6 substrate] concomitantly THEN If NUEDEXTA and desipramine are prescribed concomitantly, the initial dose of desipramine should be markedly reduced The dose of desipramine can then be adjusted based on clinical response, however, a dose above 40 mg/day is not recommended	Dextromethorphan and Quinidine
18.17	IF patient is [currently] taking NUEDEXTA AND patient is [being considered for] taking paroxetine [a CYP2D6 inhibitor and substrate] concomitantly THEN Consideration should be given to initiating treatment with a lower dose of paroxetine if given with NUEDEXTA The dose of paroxetine can then be adjusted based on clinical response, however dosage above 35 mg/day is not recommended	Dextromethorphan and Quinidine
18.18	IF patient is [being considered for] taking Dextromethorphan AND patient is [being considered for] taking Quinidine THEN Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in NUEDEXTA to increase the systemic bioavailability of dextromethorphan	Dextromethorphan and Quinidine
18.19	IF patient has pseudobulbar AND patient is [being considered for] taking Dextromethorphan AND patient is [being considered for] taking Quinidine THEN Dextromethorphan (DM) is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan The mechanism by which dextromethorphan exerts therapeutic effects in patients with pseudobulbar affect is unknown	Dextromethorphan and Quinidine
18.20.	IF patient is [being considered for] taking Dextromethorphan and Quinidine AND patient is a CYP2D6 extensive metabolizer THEN The effect of dextromethorphan hydrobromide 30 mg/quinidine sulfate 10 mg (for 7 doses) on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype Mean changes in QTcF were 6 8 ms for dextromethorphan hydrobromide 30 mg/quinidine sulfate 10 mg and 9 1 ms for the reference positive control (moxifloxacin) The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10 2 (12 6) ms This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype	Dextromethorphan and Quinidine
18.21	IF patient is [being considered for] taking Dextromethorphan AND patient is [being considered for] taking Quinidine THEN NUEDEXTA contains dextromethorphan and quinidine, both of which are metabolized primarily by liver enzymes Quinidine's primary pharmacological action in NUEDEXTA is to competitively inhibit the metabolism of dextromethorphan catalyzed by CYP2D6 in order to increase and prolong plasma concentrations of dextromethorphan	Dextromethorphan and Quinidine
18.22	IF patient is [being considered for] taking Dextromethorphan AND patient is [being considered for] taking Quinidine [a CYP2D6 inhibitor] THEN Studies were conducted	Dextromethorphan and Quinidine

	with the individual components of NUEDEXTA in healthy subjects to determine single-dose and multiple-dose kinetics of orally administered dextromethorphan hydrobromide in combination with quinidine sulfate The increase in dextromethorphan levels appeared approximately dose proportional when the dextromethorphan hydrobromide dose increased from 20 mg to 30 mg in the presence of 10 mg of quinidine sulfate	
18.23	IF patient is [being considered for] taking Dextromethorphan and Quinidine AND patient is an extensive metabolizer THEN NUEDEXTA is a combination product containing dextromethorphan hydrobromide and quinidine sulfate Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4 After dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg administration in extensive metabolizers, the elimination half life of dextromethorphan was approximately 13 hours and the elimination half life of quinidine was approximately 7 hours	Dextromethorphan and Quinidine
18.25	IF patient is [being considered for] taking Dextromethorphan and Quinidine THEN The potential for dextromethorphan and quinidine to inhibit or induce cytochrome P450 in vitro were evaluated in human microsomes Dextromethorphan did not inhibit (<20% inhibition) any of the tested isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 microM Quinidine did not inhibit (<30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 microM Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration (IC50) of less than 0 05 microM Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4 8 microM	Dextromethorphan and Quinidine
18.26	IF patient is [currently] taking NUEDEXTA AND (patient is [being considered for] taking a drugs undergoing CYP2D6 metabolism AND concomitant medication depends primarily on CYP2D6 metabolism AND (concomitant medication has a narrow therapeutic index OR if the concomitant medication relies on CYP2D6 for conversion to an active species)) THEN concomitant administration should be evaluated for appropriate dose adjustment or alternative medication	Dextromethorphan and Quinidine
18.27	IF patient is [currently] taking NUEDEXTA AND (patient is [being considered for] taking drugs like paroxetine that inhibit CYP2D6 OR patient is [being considered for] taking drugs that are extensively metabolized by CYP2D6) THEN Based on study results, whenever NUEDEXTA is prescribed with drugs like paroxetine that inhibit or are extensively metabolized by CYP2D6, consideration should be given to initiating treatment with a lower dose The dose of paroxetine can then be adjusted based on clinical response, however, dosage above 35 mg/day is not recommended	Dextromethorphan and Quinidine
19.1	IF patient is [being considered for] taking diazepam THEN inter-individual variability in clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism, about 3-5% of Caucasians have little or no activity and are poor metabolizers) and CYP3A5	Diazepam
19.2	IF patient is [being considered for] taking diazepam AND patient is [being considered for] coadministration with agents that affect CYP2C19 and CYP3A4 activity THEN potential interactions may occur	Diazepam
19.3	IF patient is [being considered for] taking diazepam AND (patient is [being considered for] taking an inhibitor of CYP2C19 OR patient is [being considered for] taking an inhibitor of CYP3A4) THEN potential inhibitors of CYP2C19 (e g , cimetidine, quinidine, and tranylcypromine) and CYP3A4 (e g , ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination	Diazepam
19.4	IF patient is [being considered for] taking diazepam AND (patient is [being considered for] taking an inducer of CYP2C19 OR patient is [being considered for] taking an inducer of CYP3A4) THEN potential inducers of CYP2C19 (e g , rifampin) and CYP3A4 (e g , carbamazepine, phenytoin, dexamethasone and phenobarbital) could increase the rate of elimination of diazepam	Diazepam
19.5	IF patient is [currently] taking diazepam AND (patient is [being considered for] taking drugs which are substrates for CYP2C19 OR patient is [being considered for] taking drugs which are substrates for CYP3A4) THEN it is possible that diazepam may interfere with the metabolism of drugs which are substrates for CYP2C19, (e g omeprazole, propranolol, and imipramine) and CYP3A4 (e g cyclosporine, paclitaxel, terfenadine,	Diazepam

	theophylline, and warfarin) leading to a potential drug-drug interaction	
20.1	IF patient is [being considered for] taking Silenor THEN Silenor is primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9	Doxepin
20.2	IF patient is [being considered for] taking Silenor AND patient is [being considered for] an inhibitor of CYP2C19, CYP2D6, CYP1A2, and/or CYP2C9 THEN inhibitors of CYP2C19, CYP2D6, CYP1A2, and/or CYP2C9 may increase the exposure of doxepin	Doxepin
20.3	IF patient is [being considered for] taking Silenor THEN Silenor is not an inhibitor of any CYP isozymes at therapeutically relevant concentrations The ability of Silenor to induce CYP isozymes is not known	Doxepin
20.4	IF patient is [being considered for] taking Doxepin THEN In vitro studies have shown that CYP2C19 and CYP2D6 are the major enzymes involved in doxepin metabolism, and that CYP1A2 and CYP2C9 are involved to a lesser extent	Doxepin
20.5	IF patient is [being considered for] taking doxepin AND patient is [being considered for] taking an inhibitor of CYP2C19 and CYP2D6 THEN since doxepin is metabolized by CYP2C19 and CYP2D6, inhibitors of these CYP isozymes may increase the exposure of doxepin	Doxepin
20.6	IF patient is [being considered for] taking cimetidine [a non-specific inhibitor of CYP1A2, 2C19, 2D6, and 3A4] AND patient is [being considered for] taking Silenor THEN The effect of cimetidine, a non-specific inhibitor of CYP1A2, 2C19, 2D6, and 3A4, on Silenor plasma concentrations was evaluated in healthy subjects When cimetidine 300 mg BID was co-administered with a single dose of Silenor 6 mg, there was approximately a 2-fold increase in Silenor Cmax and AUC compared to Silenor given alone	Doxepin
20.7	IF (patient is an adult OR patient is elderly) AND patient is [being considered for] taking doxepin AND patient is [considered for] being co-administered cimetidine [a non-specific inhibitor of CYP1A2, 2C19, 2D6, and 3A4] THEN a maximum dose of doxepin should be 3 mg	Doxepin
20.8	IF patient is a poor metabolizer of CYP2C19 and CYP2D6 AND patient is [being considered for] taking doxepin THEN patient may have higher doxepin plasma levels than normal subjects	Doxepin
21.1	IF patient is [being considered for] taking Drospirenone and Ethinyl Estradiol THEN In in vitro studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme	Drospirenone and Ethinyl Estradiol
21.2	IF patient is [being considered for] taking Drospirenone and Ethinyl Estradiol THEN The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 in vivo	Drospirenone and Ethinyl Estradiol
22.1	IF patient is [being considered for] taking Esomeprazole AND patient is [being considered for] taking a combined inhibitor of CYP 2C19 and 3A4 THEN the combined inhibitor of CYP2C19 and 3A4 may raise esomeprazole levels	Esomeprazole
22.2	IF patient is [being considered for] taking Esomeprazole THEN possible interaction mechanisms are via CYP 2C19	Esomeprazole
22.3	IF patient is [being considered for] taking Esomeprazole THEN Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP3A4	Esomeprazole
22.4	IF patient is [being considered for] taking Esomeprazole] THEN Esomeprazole may potentially interfere with CYP 2C19, the major esomeprazole metabolizing enzyme	Esomeprazole
22.5	IF patient is [being considered for] taking Esomeprazole AND patient is [being	Esomeprazole

	considered for] taking diazepam [a CYP2C19 substrate] THEN coadministration of esomeprazole 30mg and diazepam, a CYP 2C19 substrate, resulted in a 45% decrease in clearance of diazepam	
22.6	IF patient is [being considered for] taking Esomeprazole AND patient is [being considered for] taking a combined inhibitor of CYP 2C19 and CYP 3A4 such as voriconazole THEN Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP 3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure	Esomeprazole
22.7	IF patient is [being considered for] taking Esomeprazole AND patient is [being considered for] taking a combined inhibitor of CYP 2C19 and CYP 3A4 such as voriconazole THEN Dose adjustment of esomeprazole is not normally required	Esomeprazole
22.8	IF patient is [being considered for] taking Esomeprazole AND patient is [being considered for] taking a combined inhibitor of CYP 2C19 and CYP 3A4 such as voriconazole AND patient has Zollinger-Ellison's Syndrome THEN Dose adjustment of esomeprazole is not normally required However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered	Esomeprazole
22.9	IF patient is [being considered for] taking Esomeprazole THEN Omeprazole acts as an inhibitor of CYP 2C19	Esomeprazole
22.10.	IF patient is [being considered for] taking Esomeprazole AND patient is [being considered for] taking cilostazol [a CYP2C19 substrate] THEN Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased Cmax and AUC of cilostazol by 18% and 26% respectively Cmax and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4 7 times the activity of cilostazol, were increased by 29% and 69% respectively	Esomeprazole
22.11	IF patient is [being considered for] taking Esomeprazole AND patient is [currently taking/being considered for] taking cilostazol [a CYP2C19 substrate] THEN co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite [CYP2C19]	Esomeprazole
22.12	IF patient is [being considered for] taking Esomeprazole AND patient is [currently taking/being considered for] taking cilostazol [a CYP2C19 substrate] THEN a dose reduction of cilostazol from 100 mg b i d to 50 mg b i d should be considered	Esomeprazole
22.13	IF patient is [being considered for] taking Esomeprazole THEN Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system AND the metabolites of esomeprazole lack antisecretory activity AND the major part of esomeprazole's metabolism is dependent upon the CYP 2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole	Esomeprazole
22.14	IF patient is [being considered for] taking Esomeprazole AND patient is Caucasian THEN CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole Some 3% of Caucasians a lack CYP 2C19 and are termed Poor Metabolizers	Esomeprazole
22.15	IF patient is [being considered for] taking Esomeprazole AND patient is Asian THEN CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole Some 15 to 20% of Asians lack CYP 2C19 and are termed Poor Metabolizers	Esomeprazole
22.16	IF patient is [being considered for] taking Esomeprazole AND patient is a Poor Metabolizer [lacks CYP2C19] THEN at steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2	Esomeprazole
68.1	IF patient is [being considered for] taking Fluorouracil AND patient has dihydropyrimidine dehydrogenase (DPD) enzyme deficiency THEN Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency	Fluorouracil
68.2	IF patient is [being considered for] taking Fluorouracil THEN A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD)	Fluorouracil
68.3	IF patient is [being considered for] taking Fluorouracil AND patient has dihydropyrimidine dehydrogenase (DPD) enzyme deficiency THEN DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to	Fluorouracil

	cytotoxic activity and potential toxicities	
68.4	IF patient is taking Fluorouracil AND symptoms of DPD enzyme deficiency develop THEN Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop	Fluorouracil
68.5	IF patient is [being considered for] parenteral administration of Fluorouracil AND patient has systemic toxicity (e g stomatitis, diarrhea, neutropenia, and neurotoxicity) THEN Rarely, unexpected, systemic toxicity (e g stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase DPD activity	Fluorouracil
68.6	IF patient is [being considered for] parenteral administration of Fluorouracil AND patient has deficiency of dihydropyrimidine dehydrogenase DPD activity THEN Rarely, unexpected, systemic toxicity (e g stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase DPD activity	Fluorouracil
68.7	IF patient is [being considered for] topical use of 5% fluorouracil AND patient has complete absence of DPD enzyme activity THEN One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil	Fluorouracil
68.8	IF patient is [being considered for] taking Fluorouracil AND patient lacks a specific enzyme, DPD THEN A few patients have reported side effects such as stomach pain, diarrhea, vomiting, fever, or chills, possibly due to the lack of a specific enzyme, DPD, in their body	Fluorouracil
68.9	IF patient is taking Fluorouracil AND patient has reported side effects such as stomach pain, diarrhea, vomiting, fever, or chills THEN A few patients have reported side effects such as stomach pain, diarrhea, vomiting, fever, or chills, possibly due to the lack of a specific enzyme, DPD, in their body If you experience any of these symptoms, discontinue therapy immediately, and contact your doctor	Fluorouracil
23.1	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking Olanzapine THEN Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount	Fluoxetine and Olanzapine
23.2	IF patient is [being considered for] taking drugs that inhibit CYP2D6 AND patient is [being considered for] thioridazine THEN drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine	Fluoxetine and Olanzapine
23.3	IF patient is [being considered for] taking Olanzapine THEN In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6	Fluoxetine and Olanzapine
23.4	IF patient is [being considered for] taking Olanzapine THEN Olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme (CYP2D6)	Fluoxetine and Olanzapine
23.5	IF patient is [being considered for] taking Fluoxetine THEN Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer	Fluoxetine and Olanzapine
23.6	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking other drugs that are metabolized by CYP2D6 THEN Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e g , TCAs), antipsychotics (e g , phenothiazines and most atypicals), and antiarrhythmics (e g , propafenone, flecainide, and others) should be approached with caution	Fluoxetine and Olanzapine
23.7	IF (patient is taking Fluoxetine OR patient has taken Fluoxetine in the previous 5 weeks) AND (patient is being considered for taking medications that are predominantly metabolized by the CYP2D6 system AND the medications have a relatively narrow therapeutic index) THEN initiation of therapy should be initiated at the low end of the dose range	Fluoxetine and Olanzapine

23.8	IF patient is taking a drug metabolized by CYP2D6 AND patient is being considered for fluoxetine THEN the need for a decreased dose of the original medication should be considered AND drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, propafenone, vinblastine, and TCAs)	Fluoxetine and Olanzapine
23.9	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking Olanzapine THEN Fluoxetine (administered as a 60-mg single dose or 60mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%)	Fluoxetine and Olanzapine
23.10.	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking Olanzapine THEN In a study, a decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12mg with concomitant fluoxetine doses of 25,mg or more The decrease in clearance reflects an increase in bioavailability The terminal half-life is not affected, and therefore the time to reach steady state should not be altered The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies	Fluoxetine and Olanzapine
23.11	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking Olanzapine THEN The small change in olanzapine clearance, observed in two studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination	Fluoxetine and Olanzapine
23.12	IF patient is [being considered for] taking Fluoxetine and Olanzapine THEN CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme	Fluoxetine and Olanzapine
23.13	IF patient is [being considered for] taking Fluoxetine and Olanzapine THEN Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway A number of unidentified metabolites exist	Fluoxetine and Olanzapine
23.14	IF patient is [being considered for] taking Fluoxetine and Olanzapine AND patient is a poor metabolizer of CYP2D6 THEN When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers Thus, the net pharmacodynamics activities were essentially the same Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit	Fluoxetine and Olanzapine
23.15	IF patient is [being considered for] taking Fluoxetine AND patient is [being considered for] taking a drug metabolized by CYP2D6 THEN because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions	Fluoxetine and Olanzapine
55.1	IF the patient is taking Fluoxetine AND the patient is taking other drugs that are metabolized by CYP2D6, THEN coadministration should be approached with caution	Fluoxetine HCL
55.2	IF the patient is taking Thioridazine AND the patient will be taking Fluoxetine THEN Fluoxetine will produce elevated plasma levels of Thioridazine	Fluoxetine HCL
55.3	IF the patient will be taking Fluoxetine AND the patient has normal CYP2D6 metabolic activity, THEN administering Fluoxetine may make the patient CYP2D6 metabolic activity resemble that of a poor metabolizer	Fluoxetine HCL
55.4	IF the patient is taking Fluoxetine HCL AND the patient has a CYP2D6 variant AND the variant causes poor metabolism, THEN In a study 86 involving labeled and unlabeled enantiomers administered as a racemate, these individuals 87 metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of 88 S-fluoxetine Consequently, concentrations of S-nor fluoxetine at steady state were lower The 89 metabolism of R-fluoxetine in these poor metabolizers appears normal When compared with 90 normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active 91 enantiomers was not significantly greater among poor metabolizers Thus, the net 92 pharmacodynamics activities were essentially the same	Fluoxetine HCL

55.5	IF the patient is taking Fluoxetine HCL THEN the patient has about a 7% chance of having reduced CYP2D6 enzyme activity	Fluoxetine HCL
69.1	IF patient is [being considered for] taking Fulvestrant THEN Many breast cancers have estrogen receptors (ER) and the growth of these tumors can be stimulated by estrogen Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells	Fulvestrant
69.2	IF patient is [being considered for] taking Fulvestrant AND patient is a women AND patient is postmenopausal AND patient has primary breast cancer THEN In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation	Fulvestrant
24.1	IF patient is [being considered for] taking Gefitinib THEN The mechanism of the clinical antitumor action of gefitinib is not fully characterized Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK) EGFR is expressed on the cell surface of many normal cells and cancer cells	Gefitinib
24.2	IF patient is [being considered for] taking Gefitinib THEN No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to gefitinib	Gefitinib
24.3	IF patient is [being considered for] taking Gefitinib THEN Five metabolites were identified in human plasma Only O-desmethyl gefitinib has exposure comparable to gefitinib Although this metabolite has similar EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays	Gefitinib
56.1	IF the patient has ASM AND the patient has a tumor without a D816V c-Kit mutation THEN treat the patient with Gleevec	Imatinib (1)
56.2	IF the patient has gastrointestinal stromal tumors (GISTs) AND the GISTs have the Kit (CD117) mutation AND (the patient has GISTs that are unresectable OR the patient has GISTs that are metastatic malignant) THEN treat the patient with Gleevec	Imatinib (1)
56.3	IF the patient is an adult AND the patient had gastrointestinal stromal tumors (GISTs) in the past AND the GISTs had the Kit (CD117) mutation AND the patient is already receiving treatment AND the patient has had a resection of the GISTs THEN treat the patient with Gleevec	Imatinib (1)
56.4	IF the patient has ASM AND the patient is taking Gleevec AND the patient has a tumor with a D816V c-Kit mutation THEN recommended dose of Gleevec is 400 mg/day	Imatinib (1)
25.1	IF patient has Philadelphia chromosome positive chronic myeloid leukemia AND (in blast crisis, accelerated phase OR in chronic phase after failure of interferon-alpha therapy) THEN Imatinib is indicated for use	Imatinib (2)
25.2	IF patient is a pediatric patient AND patient has Ph+ CML in chronic phase AND (patient is newly diagnosed OR disease has recurred after stem cell transplant OR patient is resistant to interferon-alpha therapy) THEN Imatinib is indicated for use, but there are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease related symptoms or increased survival	Imatinib (2)
25.3	IF patient is an adult AND (patient has relapsed Philadelphia chromosome positive acute lymphoblastic leukemia OR patient has refractory Philadelphia chromosome positive acute lymphoblastic leukemia) THEN Imatinib is indicated for use	Imatinib (2)
25.4	IF patient is [being considered for] taking Imatinib AND patient is a child AND patient is diagnosed with Ph+ CML THEN the recommended dose of Gleevec is 340 mg/m^2/day (not to exceed 600 mg)	Imatinib (2)
25.5	IF patient is [being considered for] taking Imatinib AND patient is a child AND patient is diagnosed with Ph+ chronic phase CML AND (recurrent after stem cell transplant OR resistant to interferon-alpha treatment) THEN the recommended dose of Gleevec is 260	Imatinib (2)

	mg/m^2/day	
25.6	IF patient is [being considered for] taking Imatinib AND patient is an adult AND patient has relapsed/refractory Ph+ ALL THEN the recommended dose of Gleevec is 600 mg/day	Imatinib (2)
25.7	IF patient is [being considered for] taking Imatinib AND patient has newly diagnosed Ph+ CML in chronic phase AND (patient has cardiac disease OR patient has risk factors for cardiac failure) THEN In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0 7% of patients taking Gleevec compared to 0 9% of patients taking IFN + Ara-C Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated	Imatinib (2)
25.8	IF patient is [being considered for] taking Imatinib AND (patient has Ph+ ALL OR patient has Ph+ CML) THEN adverse reactions are similar for Ph+ ALL as for Ph+ CML The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edemas	Imatinib (2)
25.9	IF patient is [being considered for] taking Imatinib AND (patient has Ph+ ALL OR patient has Ph+ CML) THEN Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edemas These edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec	Imatinib (2)
25.10.	IF patient is [being considered for] taking Imatinib AND (patient is in the HES/CEL (Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia) patient population OR patient is in other hematologic malignancy populations, such as Ph+ CML) THEN the safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders Hematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia and anemia	Imatinib (2)
25.11	IF patient is [being considered for] Imatinib AND patient is a child AND (patient has newly diagnosed Ph+ chronic phase CML OR patient has Ph+ chronic phase CML with recurrence after stem cell transplantation OR patient has resistance to interferon-alpha therapy THEN there are no data in children under 2 years of age Follow up in children with newly diagnosed Ph+ chronic phase CML is limited	Imatinib (2)
25.12	IF patient is [being considered for] taking Imatinib AND patient has a Philadelphia chromosome abnormality in CML THEN Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML Imatinib inhibits proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia Imatinib inhibits colony formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients	Imatinib (2)
25.13	IF patient is [being considered for] taking Imatinib AND patient is a pediatric patient AND patient has Ph+ chronic phase CML AND (disease is recurrent after stem cell transplant OR disease is resistant to interferon-alpha therapy) THEN One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy Patients ranged in age from 3-20 years old, 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old Patients were treated at doses of 260 mg/m^2/day (n=3), 340 mg/m^2/day (n=4), 440mg/m^2/day (n=5) and 570 mg/m^2/day (n=2) In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had a minimal cytogenetic response	Imatinib (2)
25.14	IF patient is [being considered for] taking Imatinib AND patient has Ph+ chronic phase CML AND patient is resistant to interferon-alpha therapy THEN In a study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a	Imatinib (2)

	complete cytogenetic response at doses of 242 and 257 mg/m^2/day	
25.15	IF patient is [being considered for] taking Imatinib AND patient has relapsed/refractory Ph+ ALL THEN Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 16 The median duration of hematologic response was 3 4 months and the median duration of MCyR was 2 3 months	Imatinib (2)
70.1	IF patient is an adult AND patient has myelodysplastic/ myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements THEN Imatinib is indicated for use	Imatinib (3)
70.2	IF patient is [being considered for] taking Imatinib AND patient has is suffering from life-threatening diseases associated with PDGFR protein tyrosine kinases THEN An open label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases Only 1(7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly	Imatinib (3)
71.1	IF patient is an adult AND (patient has hypereosinophilic syndrome OR patient has chronic eosinophilic leukemia) AND (patient has FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) OR ((patient has HES OR patient has CEL) AND (patient is FIP1L1-PDGFRα fusion kinase negative) OR (patient is FIP1L1-PDGFRα fusion kinase unknown whether it's positive or negative) THEN Imatinib is indicated for use	Imatinib (4)
71.2	IF patient is [being considered for] taking Imatinib AND patient has ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα THEN a starting dose of 100 mg/day is recommended Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy	Imatinib (4)
71.3	IF patient is taking Imatinib AND patient has ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα AND patient demonstrates and insufficient response to therapy AND patient has not experienced any adverse drug reactions THEN Dose increase from 100 mg to 400 mg for these patients may be considered	Imatinib (4)
71.4	IF patient is [being considered for] taking Imatinib AND patient is an adult AND patient has HES/CEL AND patient has demonstrated FIP1L1-PDGFRα fusion kinase THEN a starting dose of 100mg/day is recommended Dose increase from 100mg to 400mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy	Imatinib (4)
71.5	IF patient is taking Imatinib AND patient is an adult AND patient has HES/CEL AND patient has demonstrated FIP1L1-PDGFRα fusion kinase AND patient demonstrates an insufficient response to therapy AND patient has not experienced any adverse drug reactions THEN Dose increase from 100 mg to 400 mg for these patients may be considered	Imatinib (4)
71.6	IF patient is [being considered for] taking Imatinib AND patient is an adult AND patient has HES/CEL AND patient has demonstrated FIP1L1-PDGFRα fusion kinase THEN a starting dose of 100mg/day is recommended Dose increase from 100mg to 400mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy	Imatinib (4)
71.7	IF patient is taking Imatinib AND patient is an adult AND patient has HES/CEL AND patient has demonstrated FIP1L1-PDGFRα fusion kinase AND patient demonstrates and insufficient response to therapy AND patient has not experienced any adverse drug reactions THEN Dose increase from 100 mg to 400 mg for these patients may be considered	Imatinib (4)
6.1	IF patient is [being considered for] taking irinotecan AND patient has a genetic polymorphism that leads to reduced enzyme activity such as the UGT1A1*28 polymorphism THEN The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver In	Irinotecan

	vitro studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite UGT1A1 activity is reduced in this patient	
6.2	IF patient is [being considered for] taking irinotecan AND patient has a UGT1A1*28 polymorphism THEN a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2 on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype)	Irinotecan
6.3	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking atazanavir sulfate THEN coadministration of irinotecan and atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor, has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan, patients should take this into consideration with co-administering these drugs	Irinotecan
6.4	IF patient is [being considered for] taking irinotecan AND patient is homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) THEN patient is at increased risk for neutropenia following initiation of CAMPTOSAR treatment	Irinotecan
6.5	IF patient is [being considered for] taking irinotecan AND patient is homozygous for the UGT1A1*28 allele THEN in a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%	Irinotecan
6.6	IF patient is [being considered for] taking irinotecan AND patient is heterozygous for the UGT1A1*28 allele (UGT1A1 6/7 genotype) THEN In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12 5%	Irinotecan
6.7	IF patient is [being considered for] taking irinotecan AND patient is homozygous for the wild-type UGT1A1 allele (UGT1A1 6/6 genotype) THEN In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), no grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype)	Irinotecan
6.8	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is homozygous for the UGT1A1*28 allele THEN In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4 5%	Irinotecan
6.9	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is heterozygous for the UGT1A1*28 allele THEN In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients heterozygous for this allele the incidence was 5 3%	Irinotecan
6.10.	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is homozygous for the wild-type (UGT1A1) allele THEN In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, grade 4 neutropenia was observed in 1 8% of patients homozygous for the wild-type allele	Irinotecan
6.11	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is homozygous for the UGT1A1*28 allele THEN In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18 2%	Irinotecan
6.12	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is heterozygous for the UGT1A1*28 allele THEN In another study in which 109 patients were treated with	Irinotecan

	CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients heterozygous for this allele was 11 1%	
6.13	IF patient is [being considered for/currently] taking irinotecan AND patient is [being considered for/currently] taking 5-FU/LV AND patient is heterozygous for the UGT1A1*28 allele THEN In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, grade 4 neutropenia was observed in 6 8% of patients homozygous for the wild-type allele	Irinotecan
6.14	IF patient is [being considered for] taking irinotecan AND patient is homozygous for the UGT1A1*28 allele THEN a reduction in the starting dose by at least one level of CAMPTOSAR should be considered However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment	Irinotecan
6.15	IF patient is [being considered for] taking irinotecan THEN a laboratory test is available to determine the UGT1A1 status of patients Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes	Irinotecan
26.1	IF patient is [being considered for] taking Isosorbide and Hydralazine AND patient is a slow acetylate for Hydralazine THEN About 2/3 of a 50-mg dose of 14 C-hydralazine HCl given in gelatin capsules was absorbed in hypertensive subjects In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators for Hydralazine Administration of doses escalating from 75 mg to 1000 mg tid to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism	Isosorbide and Hydralazine
26.2	IF patient is [being considered for] taking Hydralazine THEN Metabolism is the main route for the elimination of hydralazine Negligible amounts of unchanged hydralazine are excreted in urine Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid Acetylation occurs predominantly during the first pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype About 50% of patients are fast acetylators and have lower exposure	Isosorbide and Hydralazine
27.1	IF patient is [being considered for] taking Lapatinib THEN Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER2 [ErbB2]) receptors (estimated Ki app values of 3nM and 13nM, respectively) with a dissociation half-life of >=300 minutes	Lapatinib
27.2	IF patient is [being considered for] taking Lapatinib AND patient has ErbB-driven tumor cell growth THEN Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models	Lapatinib
57.1	IF the patient has transfusion dependent anemia AND the transfusion dependent anemia was caused by Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, THEN treat the patient with REVLIMID	Lenalidomide
57.2	IF the patient is taking Lenalidomide AND the patient is on therapy for del 5q myelodysplastic syndromes, THEN the patient should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter	Lenalidomide
57.3	IF the patient is taking Lenalidomide AND the patient is on therapy for del 5q myelodysplastic syndromes, THEN the patient may require dose interruption or reduction, and the patient may require use of blood product support or growth factors	Lenalidomide
57.4	IF the patient is being treated for del 5q myelodysplastic syndromes AND the patient is taking REVLIMID, THEN the patient should be told that their blood counts should be checked weekly during the first 8 weeks of treatment with REVLIMD and at least monthly thereafter	Lenalidomide
58.1	IF the patient is taking SELZENTRY THEN tropism testing AND treatment history should guide the use of SELZENTRY to treat the patient	Maraviroc
58.2	IF the patient is an adult AND the patient is infected with an HIV virus that is CCR5-tropic AND the virus is resistant to multiple antiretrovirals AND the patient has evidence of viral replication, THEN treat the patient with SELZENTRY	Maraviroc

58.3	IF the patient is infected with an HIV virus that is CXCR4-tropic THEN do not treat the patient with SELZENTRY	Maraviroc
1.1	IF patient is [being considered for] taking mercaptopurine THEN Mercaptopurine is inactivated via two major pathways One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP	Mercaptopurine
1.2	IF patient is [being considered for] taking mercaptopurine THEN TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene Approximately 0 3% (1 300) of patients have two non-functional alleles (homozygous-deficient of the TPMT gene and have little or no detectable enzyme activity Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles	Mercaptopurine
1.3	IF patient is TPMT homozygous-deficient (two non-functional alleles) AND patient is given usual doses of mercaptopurine THEN patient will accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to PURINETHOL toxicity	Mercaptopurine
1.4	IF patient TPMT heterozygous with low or intermediate TPMT activity AND patient is [being considered for] taking mercaptopurine THEN Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity	Mercaptopurine
1.5	IF patient is [being considered for] taking mercaptopurine THEN TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity	Mercaptopurine
1.6	IF patient is [being considered for] taking mercaptopurine AND patient is homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene THEN patient is unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment	Mercaptopurine
1.7	IF patient is [being considered for] taking mercaptopurine THEN Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status	Mercaptopurine
1.8	IF patient is [being considered for] taking mercaptopurine AND patient is homozygous-TPMT deficient (two non-functional alleles) THEN substantial dose reductions are generally required to avoid the development of life threatening bone marrow suppression	Mercaptopurine
1.9	IF patient is [being considered for] taking mercaptopurine AND patient is heterozygous-TPMT deficient with intermediate TPMT activity THEN Although heterozygous patients with intermediate TPMT activity may have increased mercaptopurine toxicity, this is variable, and the majority of patients tolerate normal doses of PURINETHOL	Mercaptopurine
1.10.	IF a patient is [currently] taking mercaptopurine AND patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression THEN TPMT testing should be considered	Mercaptopurine
1.11	IF patient is [being considered for] taking mercaptopurine AND patient is [being considered for] taking allopurinol concomitantly THEN bone marrow toxicity may be more profound in patient	Mercaptopurine
1.12	IF patient is [being considered for] taking mercaptopurine AND patient is [being considered for] taking drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine, concomitantly THEN bone marrow toxicity may be exacerbated	Mercaptopurine
1.13	IF patient is [currently] taking mercaptopurine AND patient has clinical or laboratory evidence of severe bone marrow toxicity, particularly myelosuppression THEN TPMT testing should be considered	Mercaptopurine
1.14	IF patient is homozygous for TPMT*2, TPMT*3A or TPMT*3C THEN patient is TPMT deficient	Mercaptopurine
1.15	IF patient is heterozygous for TPMT*2, TPMT*3A or TPMT*3C THEN patient has variable TPMT (low or intermediate) activity	Mercaptopurine
1.16	IF patient is [being considered for] phenotypic testing to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes THEN Phenotypic testing determines the	Mercaptopurine

	level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative	
1.17	IF patient is [being considered for] phenotypic testing to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes AND patient is currently taking other drugs THEN Caution must be used with phenotyping since some coadministered drugs can influence measurement of TPMT activity in blood	Mercaptopurine
1.18	IF patient is [being considered for] phenotypic testing to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes AND patient has recently had a blood transfusion THEN Caution must be used with phenotyping since recent blood transfusions will misrepresent a patient's actual TPMT activity	Mercaptopurine
1.19	IF patient is [being considered for] taking aminosalicylate derivatives (e g olsalazine, mesalazine, or sulphasalazine) that inhibit the TPMT enzyme AND patient is [being considered for] mercaptopurine therapy concurrently THEN medications should be administered with caution	Mercaptopurine
1.20.	IF patient is [being considered for] taking mercaptopurine AND patient is without TPMT enzyme activity (homozygous-deficient) THEN patient is particularly susceptible to hematologic toxicity	Mercaptopurine
1.21	IF patient is [being considered for] taking mercaptopurine AND patient has low or intermediate TPMT enzyme activity THEN patient is more susceptible to hematologic toxicity than patients with normal TPMT activity, although the latter can also experience severe toxicity	Mercaptopurine
1.22	IF patient is [being considered for] taking mercaptopurine AND patient has normal TPMT activity THEN patient can experience severe toxicity	Mercaptopurine
1.23	IF patient is [being considered for] taking mercaptopurine AND patient has inherited little or no thiopurine S-methyltransferase (TPMT) activity THEN Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction	Mercaptopurine
1.24	IF patient is [being considered for] taking mercaptopurine AND patient is homozygous deficient for TPMT THEN The optimal starting dose for homozygous deficient patients has not been established	Mercaptopurine
1.25	IF patient is [being considered for] taking mercaptopurine AND patient is heterozygous TPMT deficient THEN most patients with heterozygous TPMT deficiency tolerated recommended PURINETHOL doses, but some require dose reduction	Mercaptopurine
1.26	IF patient is [being considered for] taking mercaptopurine THEN genotypic and phenotypic testing of TPMT status are available	Mercaptopurine
11.1	IF patient is [being considered for] taking metoprolol AND patient is [being considered for] taking a CP2D6 inhibitor THEN CYP2D6 Inhibitors are likely to increase metoprolol concentration	Metoprolol
11.2	IF patient is [being considered for] taking metoprolol AND patient is [being considered for] taking drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone THEN drugs that inhibit CYP2D6 are likely to increase metoprolol concentration	Metoprolol
11.3	IF patient is [being considered for] taking metoprolol AND patient is healthy AND patient has CYP2D6 extensive metabolizer phenotype AND patient is [being considered for] taking quinidine THEN In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life These increases in plasma concentration would decrease the cardioselectivity of metoprolol	Metoprolol
11.4	IF patient is [being considered for] taking metoprolol AND patient has cardiovascular disease AND patient is [being considered for] taking propafenone [a CYP2D6 inhibitor] AND patient is a CYP2D6 extensive metabolizer THEN In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half life In four patients with cardiovascular disease, coadministration of propafenone 150 mg t i d with immediate-release metoprolol 50 mg	Metoprolol

	t i d resulted in two- to five-fold increases in the steady-state concentration of metoprolol These increases in plasma concentration would decrease the cardioselectivity of metoprolol	
11.5	IF patient is [being considered for] taking metoprolol THEN Plasma levels achieved are highly variable after oral administration Only a small fraction of the drug (about 12%) is bound to human serum albumin Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6 When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine, the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity	Metoprolol
11.6	IF patient is [being considered for] taking metoprolol AND patient is Caucasian THEN Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers)	Metoprolol
11.7	IF patient is [being considered for] taking metoprolol AND patient is not Caucasian THEN Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 2% of most populations other than Caucasians	Metoprolol
11.8	IF patient is [being considered for] taking metoprolol AND (patient is a poor metabolizer OR patient is an extensive metabolizer) AND patient is concomitantly using CYP2D6 inhibiting drugs THEN patient will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity	Metoprolol
28.1	IF patient is [being considered for] taking Nelfinavir THEN In vitro, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir	Nelfinavir
28.2	IF patient is [being considered for] taking Nelfinavir THEN CYP3A and CYP2C19 appear to be the predominant enzymes that metabolize nelfinavir in humans	Nelfinavir
28.3	IF patient is [being considered for] taking Nelfinavir AND (patient is [being considered for] taking drugs that induce CYP3A OR patient is [being considered for] taking drugs that induce CYP2C19) THEN Nelfinavir is metabolized by CYP3A and CYP2C19 Coadministration of VIRACEPT and drugs that induce CYP3A or CYP2C19 may decrease nelfinavir plasma concentrations and reduce its therapeutic effect	Nelfinavir
28.4	IF patient is [being considered for] taking Nelfinavir AND (patient is [being considered for] taking drugs that inhibits CYP3A OR patient is [being considered for] taking drugs that inhibits CYP2C19) THEN Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations	Nelfinavir
28.5	IF patient is [being considered for] taking Nelfinavir AND (patient is [being considered for] taking drugs that induce CYP3A OR patient is [being considered for] taking drugs that induce CYP2C19) THEN Coadministration of VIRACEPT and drugs that induce CYP3A or CYP2C19, such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect	Nelfinavir
28.6	IF patient is [being considered for] taking Nelfinavir AND (patient is [being considered for] taking drugs that inhibits CYP3A OR patient is [being considered for] taking drugs that inhibits CYP2C19) THEN Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations	Nelfinavir
51.1	IF patient has newly diagnosed Ph+ CML-CP THEN Nilotinib is indicated for use	Nilotinib (1)
51.2	IF patient is an adult AND patient has newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase THEN Nilotinib is indicated for use AND further data will be required to determine long-term outcome	Nilotinib (1)
51.3	IF (patient has chronic phase (CP) Ph+ CML OR accelerated phase (AP) Ph+ CML) AND patient is an adult AND (patient is resistant to prior therapy that included imatinib OR patient is intolerant to prior therapy that included imatinib) THEN Nilotinib is indicated for use	Nilotinib (1)
51.4	IF patient is [being considered for] taking Nilotinib AND (patient has newly diagnosed Ph+ CML-CP OR patient has resistant or intolerant Ph+ CML-CP OR patient has resistant or intolerant Ph+ CML-AP) THEN the most commonly reported non-hemotologic adverse reactions (>=10%) were rash, pruritus, headache, nausea, fatigue,	Nilotinib (1)

	myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia The most commonly reported hematologic adverse drug reactions include myelosuppression thrombocytopenia, neutropenia and anemia	
51.5	IF patient is an adult AND patient has newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase THEN Tasigna (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase	Nilotinib (1)
51.6	IF patient is [being considered for] taking Nilotinib THEN The effectiveness of Tasigna is based on major molecular response and cytogenetic response rates (See Clinical Studies 14 2) The study is ongoing and further data will be required to determine long-term outcome	Nilotinib (1)
51.7	IF (patient has chronic phase Philadelphia chromosome positive chronic myelogenous leukemia OR patient has accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia) AND patient is an adult AND (patient is resistant to prior therapy that included imatinib OR patient is intolerant to prior therapy that included imatinib) THEN Tasigna is indicated for treatment The effectiveness of Tasigna is based on hematologic and cytogenetic response rates (See Clinical Studies 14 2)	Nilotinib (1)
51.8	IF patient develops clinically significant moderate or severe non-hematologic toxicity AND patient is taking Nilotinib AND patient is being treated for newly diagnosed Ph+ CML-CP THEN withhold dosing, and resume at 400 mg once daily when the toxicity has resolved If clinically appropriate, escalation of the dose back to 300 mg twice daily should be considered For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400mg once daily Test serum lipase levels monthly or as clinically indicated For Grade 3 to 4 bilirubin or hepatic transaminase elevations, dosing should be withheld, and may be resumed at 400mg once daily Test bilirubin and hepatic transaminases levels monthly or as clinically indicated	Nilotinib (1)
51.9	IF patient develops clinically significant moderate or severe non-hematologic toxicity AND patient is taking Nilotinib AND patient is being treated for resistant or intolerant Ph+ CML-CP and CML-AP THEN withhold dosing, and resume at 400 mg once daily when the toxicity has resolved If clinically appropriate, escalation of the dose back to 400 mg twice daily should be considered For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400mg once daily Test serum lipase levels monthly or as clinically indicated For Grade 3 to 4 bilirubin or hepatic transaminase elevations, dosing should be withheld, and may be resumed at 400mg once daily Test bilirubin and hepatic transaminases levels monthly or as clinically indicated	Nilotinib (1)
51.10.	IF patient is taking Nilotinib AND patient is [being considered for] taking a strong CYP3A4 inhibitor AND patient is being treated for resistant or intolerant Ph+ CML THEN based on pharmacokinetic studies, consider a dose reduction to 300 mg once daily	Nilotinib (1)
51.11	IF patient is taking Nilotinib AND patient is [being considered for] taking a strong CYP3A4 inhibitor AND patient is being treated for newly diagnosed Ph+ CML-CP THEN based on pharmacokinetic studies, consider a dose reduction to 200 mg once daily	Nilotinib (1)
51.12	IF patient is taking Nilotinib AND patient is [being considered for] taking a strong CYP3A4 inhibitor AND (patient is being treated for newly diagnosed Ph+ CML-CP OR patient is being treated for resistant or intolerant Ph+ CML) THEN There are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors	Nilotinib (1)
51.13	IF patient is taking Nilotinib AND patient is [being considered for] discontinuing a strong CYP3A4 inhibitor AND (patient is being treated for newly diagnosed Ph+ CML-CP OR patient is being treated for resistant or intolerant Ph+ CML) THEN a washout period should be allowed before the Tasigna dose is adjusted upward to the indicated dose	Nilotinib (1)
51.14	IF patient is taking Nilotinib AND patient is taking a strong CYP3A4 inhibitor AND (patient is being treated for newly diagnosed Ph+ CML-CP OR patient is being treated for resistant or intolerant Ph+ CML) THEN Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors	Nilotinib (1)

51.15	IF patient is [being considered for] taking Nilotinib AND patient has Ph+ CML in chronic phase THEN In a randomized trial in newly diagnosed patients with Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279) The median time on treatment in the nilotinib 300 mg twice daily group was 18 6 months The median actual dose intensity was 593 mg/day in the nilotinib 300 mg twice daily group	Nilotinib (1)
51.16	IF patient is [being considered for] taking Nilotinib AND patient as Ph+ CML THEN Nilotinib is an inhibitor of the Bcr-Abl kinase Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of Abl protein In vitro, nilotinib inhibited Bcr-Abl mediated proliferation of murine leukemic cell lines and human cell lines derived from patients with Ph+ CML Under the conditions of the assays, nilotinib was able to overcome imatinib resistance resulting from Bcr-Abl kinase mutations, in 32 out of 33 mutations tested	Nilotinib (1)
51.17	IF patient is [being considered for] taking Nilotinib AND patient as Ph+ CML THEN In vivo, nilotinib reduced the tumor size in a murine Bcr-Abl xenograft model Nilotinib inhibited the autophosphorylation of the following kinases at IC50 values as indicated Bcr-Abl (20-60 nM), PDGFR (69 nM), c Kit (210 nM), CSF-1R (125-250 nM) and DDR1a (3 7 nM)	Nilotinib (1)
51.18	IF patient has Ph+ CML and patient is an adult THEN Tasigna is a prescription medicine used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in adults	Nilotinib (1)
7.1	IF patient is [being considered for] taking Nilotinib AND patient is [being considered for] taking drugs eliminated by CYP3A4, CYP2C8, CYP2C9, CYP2D6 and/or UGT1A1 THEN nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro potentially increasing the concentrations of drugs eliminated by these enzymes	Nilotinib (2)
7.2	IF patient is [being considered for] taking Nilotinib AND patient is [being considered for] taking drugs eliminated by CYP2B6, CYP2C8 and/or CYP2C9 THEN in vitro studies suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and decrease the concentrations of drugs which are eliminated by these enzymes	Nilotinib (2)
7.3	IF patient is [being considered for] taking Nilotinib AND patient has UGT1A1 (TA)7/(TA)7 genotype THEN Tasigna can increase bilirubin levels A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients	Nilotinib (2)
29.1	IF patient has epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) AND patient has experienced disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens THEN Vectibix is indicated as a single agent for treatment	Panitumumab (1)
29.2	IF patient is [being considered for] taking Panitumumab AND patient has EGFR-expressing, metastatic colorectal carcinoma THEN the effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival (see Clinical Studies)	Panitumumab (1)
29.3	IF patient is [being considered for] taking Panitumumab AND patient has EGFR-expressing, metastatic colorectal carcinoma THEN Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix	Panitumumab (1)
29.5	IF patient is [being considered for] taking Panitumumab THEN detection of EGFR protein expression is necessary for selection of patients appropriate for Vectibix therapy because these are the only patients studied and for whom benefit has been shown	Panitumumab (1)
29.6	IF patient is [being considered for] taking Panitumumab AND patient is [being considered for] EGFR testing THEN Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay instructions, and failure to	Panitumumab (1)

	include appropriate controls for assay validation can lead to unreliable results	
29.7	IF patient is [being considered for] taking Panitumumab AND patient is [being considered for] EGFR testing THEN Refer to the package insert for the Dako EGFR pharmDx test kit, or other test kits approved by FDA, for identification of patients eligible for treatment with Vectibix and for full instructions on assay performance	Panitumumab (1)
29.8	IF patient is [being considered for] taking Panitumumab AND patient is pregnant THEN Based on animal models, EGFR is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo Human IgG is known to cross the placental barrier, therefore, panitumumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women	Panitumumab (1)
29.9	IF patient is [being considered for] taking Panitumumab THEN Vectibix (panitumumab) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR)	Panitumumab (1)
29.10.	IF patient is [being considered for] taking Panitumumab THEN Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR	Panitumumab (1)
29.11	IF patient is [being considered for] taking Panitumumab THEN Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR	Panitumumab (1)
29.12	IF patient is [being considered for] taking Panitumumab THEN In vitro assays and in vivo animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR	Panitumumab (1)
29.13	IF patient is [being considered for] taking Panitumumab THEN A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics Results suggest that age (21-88 years), gender, race (15% non-white), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab	Panitumumab (1)
29.14	IF patient is [being considered for] taking Panitumumab THEN Retrospective analyses as presented in Table 2 across seven randomized clinical trials suggest that anti-EGFR-directed monoclonal antibodies are not effective for the treatment of patients with mCRC containing KRAS mutations	Panitumumab (1)
29.4	IF patient is [being considered for] taking Panitumumab AND patients' tumors have KRAS mutations in codon 12 or 13 AND patient has colorectal cancer THEN use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations	Panitumumab (2)
59.1	IF the patient is taking Vectibix AND the patient has colorectal cancer AND the tumors have KRAS mutations in codon 12 or 13, THEN Vectibix is not recommended for the patient	Panitumumab (2)
60.1	IF the patient is taking Prasugrel AND patient is [being considered for] taking other drugs THEN the current treatment will not affect other drugs	Prasugrel
61.1	IF the patient is taking Primaquine AND the patient has G6PD deficiency OR the patient has a family or personal history of favism, THEN administration of Primaquine may result in hemolytic reactions	Primaquine
61.2	IF the patient is taking primaquine AND the patient is from Africa OR Southern Europe OR Mediterranean region OR Middle East OR South-East Asia, OR Oceania, THEN the patient is at higher risk for G6PD deficiency	Primaquine
61.3	IF the patient is taking primaquine AND the patient is from Africa OR Southern Europe OR Mediterranean region OR Middle East OR South-East Asia, OR Oceania, THEN the patient will have a greater chance of developing hemolytic anemia while receiving Primaquine and related drugs	Primaquine
61.4	IF the patient is taking primaquine AND (the patient has G6PD deficiency OR the patient has NADH methemoglobin reductase deficiency), THEN the patient should be observed closely for tolerance to primaquine AND primaquine should be discontinued if marked	Primaquine

	darkening of the urine OR (sudden decrease in hemoglobin concentration OR sudden decrease in leukocyte count) occurs	
8.1	IF patient is [being considered for] taking propafenone AND patient has CYP3A4 inhibition AND (patient has CYP2D6 deficiency OR patient has CYP2D6 inhibition) THEN simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events	Propafenone
8.2	IF patient is [being considered for] taking propafenone AND (patient is [being considered for] taking a CYP2D6 inhibitor OR patient is [being considered for] taking a CYP3A4 inhibitor) THEN simultaneous use with a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided	Propafenone
8.3	IF patient is [being considered for] taking propafenone AND patient is Caucasian THEN Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes, and approximately 6% of Caucasians in the U S population are naturally deficient in CYP2D6 activity	Propafenone
8.4	IF patient is [being considered for] taking propafenone AND patient is not Caucasian THEN Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes, and patient is less likely than Caucasian patients (6%) in the U S population to be naturally deficient in CYP2D6 activity	Propafenone
8.5	IF patient is [being considered for] taking propafenone AND patient is [currently] taking drug(s) that inhibit CYP2D6, CYP3A4, or CYP1A2 isoenzyme pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6, ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4, and amiodarone and tobacco smoke for CYP1A2) THEN these drugs can be expected to cause increased plasma levels of propafenone	Propafenone
8.6	IF patient is [currently] taking propafenone AND patient has CYP3A4 inhibition AND (patient has CYP2D6 deficiency OR patient has CYP2D6 inhibition) THEN increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity	Propafenone
8.7	IF patient is [currently] taking propafenone AND (patient is [being considered for] taking a CYP2D6 inhibitor OR patient is [being considered for] taking a CYP3A4 inhibitor) THEN simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided	Propafenone
8.8	IF patient is [being considered for] taking propafenone AND patient is [currently] taking drug(s) that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and CYP3A4 (such as ketoconazole, erythromycin, saquinavir, and grapefruit juice) THEN these drugs can be expected to cause increased plasma levels of propafenone	Propafenone
8.9	IF patient is [being considered for] taking propafenone AND patient has CYP3A4 inhibition AND (patient has CYP2D6 deficiency OR patient has CYP2D6 inhibition) THEN administration of propafenone may increase the risk of adverse reactions, including proarrhythmia, and simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided	Propafenone
8.10.	IF patient is [currently] taking quinidine AND patient is [being considered for] taking propafenone THEN Small doses of quinidine completely inhibit the CYP2D6 hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers	Propafenone
8.11	IF patient is [being considered for] taking quinidine AND patient is [being considered for] taking propafenone AND patient is an extensive metabolizer [of CYP2D6] THEN Concomitant administration of quinidine (50mg three times daily) with 150mg immediate-release propafenone three times daily decreased the clearance of propafenone by 60% in EM, making them PM Steady-state plasma concentrations increased by more that 2-fold for propafenone, and decreased 50% for 5OH-propafenone A 100 mg dose of quinidine increased steady state concentrations of propafenone 3-fold	Propafenone
8.12	IF patient is [currently] taking quinidine [a CYP2D6 inhibitor] AND patient is [being considered for] taking propafenone THEN Concomitant use of propafenone and quinidine should be avoided	Propafenone
8.13	IF patient is [being considered for] taking Propafenone THEN There are two genetically determined patterns of propafenone metabolism In over 90% of patients, the drug is	Propafenone

	rapidly and extensively metabolized with an elimination half-life from 2-10 hours These patients metabolize propafenone into two active metabolites 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2 In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed In these patients, the estimated propafenone elimination half-life ranges from 10-32 hours Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers	
8.14	IF patient is [being considered for] taking propafenone AND patient is a slow metabolizer THEN at daily doses of 850mg/day with slow metabolizers drug concentrations are about twice those of the extensive metabolizer At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers	Propafenone
8.15	IF patient is [being considered for] taking Propafenone AND patient is an extensive metabolizer THEN In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules	Propafenone
8.16	IF patient is [being considered for] taking Propafenone AND patient is a slow metabolizer THEN In slow metabolizers, propafenone pharmacokinetics is linear (linear increases in plasma levels following administration of RYTHMOL SR capsule)	Propafenone
8.17	IF patient is [being considered for] taking Propafenone AND patient is ANY metabolizer THEN Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients	Propafenone
8.18	IF patient is [being considered for] taking propafenone AND patient is an extensive metabolizer (of CYP2D6) THEN there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers, and a higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of RYTHMOL SR capsules	Propafenone
8.19	IF patient is [being considered for] taking propafenone AND patient is a poor metabolizer (of CYP2D6) THEN inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation	Propafenone
8.20.	IF patient is [being considered for] taking propafenone THEN in vitro and in vivo studies have shown that the R-isomer or propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6) This results in a higher ratio of S-propafenone to R-propafenone at steady state Both enantiomers have equivalent potency to block sodium channels, however, the S-enantiomer is a more potent β-antagonist than the R-enantiomer Following administration of RYTHMOL immediate release tablets or RYTHMOL SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1 7 The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg RYTHMOL SR are independent of dose In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time	Propafenone
9.1	IF patient is [being considered for] taking Propranolol THEN In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6 Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6 4-hydroxy propranolol is a weak inhibitor of CYP2D6	Propranolol
9.2	IF patient is [being considered for] taking Propranolol AND (patient is a CYP2D6 extensive metabolizer OR patient is a CYP2D6 poor metabolizer) THEN In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life Partial clearance to 4-hydroxy propranolol was significantly higher and to	Propranolol

	naphthyloxylactic acid was significantly lower in EMs than PMs	
9.3	IF patient is [being considered for] taking propranolol AND (patient is [being considered for] taking drugs that are metabolized by CYP2D6, 1A2 or 2C19 OR patient is [being considered for] taking drugs that affect the activity (induction or inhibition) of one or more of CYP2D6, 1A2 or 2C19 pathways) THEN these drugs may lead to clinically relevant drug interactions	Propranolol
9.4	IF patient is [being considered for] taking propranolol AND patient is [being considered for] taking substrates or inhibitors of CYP2D6, such as amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir THEN blood levels and/or toxicity of propranolol may be increased by coadministration with these drugs	Propranolol
9.5	IF patient is [being considered for] taking propranolol AND patient is [being considered for] taking drugs that have an effect on CYP2D6, 1A2 and/or 2C19 metabolic pathways THEN caution should be exercised with coadministration of propranolol with these drugs	Propranolol
9.6	IF patient is [being considered for] taking propranolol AND patient is [being considered for] taking drugs that have an effect on CYP2D6, 1A2 and/or 2C19 metabolic pathways THEN coadministration of propranolol with these drugs may lead to clinically relevant drug interactions and changes on its efficacy and/or toxicity	Propranolol
30.1	IF patient is [being considered for] taking Protriptyline AND patient is Caucasian THEN The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called poor metabolizers)	Protriptyline
30.2	IF patient is [being considered for] taking Protriptyline AND patient is in a population other than Caucasian THEN reliable estimates of the prevalence of reduced biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) among Asian, African, and other populations are not yet available	Protriptyline
30.3	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is a poor metabolizer [of CYP2D6] THEN Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses Depending on the fraction of drug metabolized be P450 2D6, the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA)	Protriptyline
30.4	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is [being considered for] taking a drug that are not metabolized by, but inhibits the activity of CYP2D6 (e g quinidine, cimetidine) THEN drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy	Protriptyline
30.5	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is [being considered for] taking a drug that is a substrate of and inhibits CYP2D6 (e g many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics, propafenone and flecainide) THEN drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy	Protriptyline
30.6	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is [being considered for] taking a selective serotonin reuptake inhibitor (SSRI) THEN While all the selective serotonin reuptake inhibitors (SSRIs), e g , fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved	Protriptyline
30.7	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is [being considered for] taking a selective serotonin reuptake inhibitor (SSRI) that inhibits P450 2D6 THEN Caution is indicated in the coadministration of TCAs with any of the SSRIs	Protriptyline
30.8	IF patient is [being considered for] switching from Protriptyline [a TCA] to a selective serotonin reuptake inhibitor (SSRI) that inhibits P450 2D6 OR patient [being considered for] switching from a SSRI that inhibits P450 2D6 to Protriptyline THEN Caution is indicated in switching from one class to the other	Protriptyline
30.9	IF patient is [being considered for] taking Protriptyline [a TCA] AND patient is [being	Protriptyline

	considered for] discontinuing fluoxetine THEN sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary)	
30.10.	IF patient is [being considered for] taking tricyclic antidepressants AND patient is [being considered for] taking drugs that can inhibit cytochrome P450 2D6 THEN lower doses than usually prescribed for either the tricyclic antidepressant or the other drug may be required	Protriptyline
30.11	IF patient is [being considered for] discontinuing tricyclic antidepressants OR patient is [being considered for] discontinuing drugs that can inhibit cytochrome P450 2D6 THEN whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required	Protriptyline
30.12	F patient is [being considered for] taking tricyclic antidepressants AND patient is [being considered for] taking an inhibitor of P450 2D6 THEN It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6	Protriptyline
31.1	IF patient is [being considered for] taking drugs for which cytochrome P45IID6 is an enzyme critical to its metabolism, notably including mexiletine, some phenothiazines, and most polycyclic antidepressants AND patient is Oriental THEN Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals Testing with debrisoquine is sometimes used to distinguish the P450IID6- deficient poor metabolizers from the majority-phenotype extensive metabolizers	Quinidine
31.2	IF patient is [being considered for] taking drugs for which cytochrome P45IID6 is an enzyme critical to its metabolism, notably including mexiletine, some phenothiazines, and most polycyclic antidepressants AND patient is American black THEN Constitutional deficiency of cytochrome P450IID6 is found in less than 2% of American blacks Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient poor metabolizers from the majority-phenotype extensive metabolizers	Quinidine
31.3	IF patient is [being considered for] taking drugs for which cytochrome P45IID6 is an enzyme critical to its metabolism, notably including mexiletine, some phenothiazines, and most polycyclic antidepressants AND patient is American white THEN Constitutional deficiency of cytochrome P450IID6 is found in less than 8% of American whites Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient poor metabolizers from the majority-phenotype extensive metabolizers	Quinidine
31.4	IF patient is [being considered for] taking drugs whose metabolism is P450IID6 dependent AND patient is a poor metabolizer of P450IID6 THEN the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers	Quinidine
31.5	IF patient is [being considered for] taking drugs whose metabolism is P450IID6-dependent AND patient is a poor metabolizer of P450IID6 THEN to obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced	Quinidine
31.6	IF patient is [being considered for] taking drugs whose metabolism is P450IID6-dependent AND patient is a poor metabolizer of P450IID6 AND its the actions of prodrugs that are mediated by P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively) THEN it may not be possible to achieve the desired clinical benefits in poor metabolizers	Quinidine
31.7	IF patient is [being considered for] taking Quinidine THEN Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers	Quinidine
31.8	IF patient is [being considered for] taking Quinidine AND patient is [being considered for] taking a drug metabolized by cytochrome P450II6 THEN Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6	Quinidine
32.1	IF patient is [being considered for] taking Rabeprazole AND patient is a poor metabolizer THEN In a clinical study in Japan evaluating rabeprazole in patients	Rabeprazole

	categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers This could be due to higher rabeprazole plasma levels in poor metabolizers	
32.2	IF patient is [being considered for] taking Rabeprazole AND patient is [being considered for] taking other drugs metabolized by CYP2C19 AND (patient is an extensive metabolizer OR patient is a poor metabolizer) THEN Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied	Rabeprazole
32.3	IF patient is [being considered for] taking Rabeprazole AND patient is a poor metabolizer [of CYP2C19] THEN In a study of CYP2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers	Rabeprazole
32.4	IF patient is [being considered for] taking Rabeprazole AND patient is Caucasian THEN In vitro studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole CYP2C19 exhibits a known genetic polymorphism due to its deficiency in 3 to 5% of Caucasians	Rabeprazole
32.5	IF patient is [being considered for] taking Rabeprazole AND patient is Asian THEN In vitro studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole CYP2C19 exhibits a known genetic polymorphism due to its deficiency in 17 to 20% of Asians	Rabeprazole
32.6	IF patient is [being considered for] taking Rabeprazole AND patient has a known genetic polymorphism in CYP2C19 leading to its deficiency THEN Rabeprazole metabolism is slow in this patient, therefore, they are referred to as poor metabolizers of the drug	Rabeprazole
62.1	IF the patient is taking ELITEX AND the patient has G6PD deficiency, THEN ELITEX can cause severe hemolysis	Rasburicase
62.2	IF the patient is taking ELITEK AND the patient is at higher risk for G6PD deficiency, THEN it's recommended that the patient be screened prior to starting ELITEK therapy	Rasburicase
62.3	IF the patient is taking ELITEX AND the patient has G6PD deficiency, THEN do not treat the patient with ELITEX	Rasburicase
63.1	IF the patient is taking isoniazid AND the patient is a "rapid inactivator" OR a "slow inactivator", THEN the effectiveness of isoniazid is not altered	Rifampin, *isoniazid*, and pyrazinamide
63.2	IF the patient is taking isoniazid AND the patient is a "slow inactivator", THEN higher blood levels of isoniazid may occur, and thus, increase toxic reactions	Rifampin, *isoniazid*, and pyrazinamide
63.3	IF the patient is taking isoniazid AND the patient is African American OR if the patient is Caucasian, THEN the patient has about a 50% probability of being a "slow inactivator" AND about a 50% probability of being a "rapid inactivator"	Rifampin, *isoniazid*, and pyrazinamide
63.4	IF the patient is taking isoniazid AND the patient is Eskimo OR if the patient is Asian, THEN the patient is more likely to be a "rapid inactivator" than a "slow inactivator"	Rifampin, *isoniazid*, and pyrazinamide
75.1	IF patient is [being considered for] taking Risperidone THEN Risperidone is metabolized to 9 hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs	Risperidone
75.2	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking a drug that reduces the metabolism of risperidone [by CYP2D6] to 9-hydroxyriperidone THEN Drug interactions would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone	Risperidone
75.3	IF patient is [being considered for] taking Risperidone AND (patient is a poor metabolizer [of CYP2D6] OR patient is an extensive metabolizer [of CYP2D6]) THEN Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects No comparison of effectiveness in the two groups has been made	Risperidone

75.4	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking a drug that is metabolized by CYP2D6 THEN studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6 Therefore, RISPERDAL is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway	Risperidone
75.5	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking donepezil THEN In drug interaction studies, RISPERDAL did not significantly affect the pharmacokinetics of donepezil, which is metabolized by CYP 2D6	Risperidone
75.6	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking galantamine THEN In drug interaction studies, RISPERDAL did not significantly affect the pharmacokinetics of galantamine, which is metabolized by CYP 2D6	Risperidone
75.7	IF patient is [being considered for] taking Risperidone THEN Risperidone is extensively metabolized in the liver The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6 AND The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone	Risperidone
75.8	IF patient is Caucasian AND patient is [being considered for] taking a drug metabolized by CYP2D6 (e g many neuroleptics, antidepressants, antiarrhythmics, and other drugs) THEN CYP 2D6 is subject to genetic polymorphism (in about 6% to 8% of Caucasians, have little or no activity and are poor metabolizers) and to inhibition by a variety of substrates and some non-substrates, notably quinidine	Risperidone
75.9	IF patient is Asian AND patient is [being considered for] taking a drug metabolized by CYP2D6 (e g many neuroleptics, antidepressants, antiarrhythmics, and other drugs) THEN CYP 2D6 is subject to genetic polymorphism (in a very low percentage of Asians, have little or no activity and are poor metabolizers) and to inhibition by a variety of substrates and some non-substrates, notably quinidine	Risperidone
75.10.	IF patient is [being considered for] taking Risperidone AND (patient is an extensive CYP2D6 metabolizer OR patient is a poor CYP2D6 metabolizer) THEN Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers	Risperidone
75.11	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking an inhibitor of CYP2D6 THEN inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers	Risperidone
75.12	IF patient is [being considered for] taking Risperidone AND (patient is a poor [CYP2D6] metabolizer OR patient is an extensive [CYP2D6] metabolizer) THEN The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given RISPERDAL do not suggest important differences between poor and extensive metabolizers	Risperidone
75.13	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking a known CYP2D6 inducer THEN co-administration of known enzyme inducers (e g , carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone	Risperidone
75.14	IF patient is [being considered for] taking Risperidone AND patient is [being considered for] taking a drug metabolized by CYP2D6 THEN It is possible for risperidone to interfere with metabolism of drugs metabolized by CYP 2D6 Relatively weak binding of risperidone to the enzyme suggests this is unlikely	Risperidone
33.1	IF patient is [being considered for] taking Sodium Phenylacetate and Sodium Benzoate AND patient is [being considered for] taking valproic acid AND patient has a urea cycle	Sodium Phenylacetate

	disorder THEN There have been reports that valproic acid can induce hyperammonemia through inhibition of the synthesis of N-acetylglutamate, a co-factor for carbamyl phosphate synthetase Therefore, administration of valproic acid to patients with urea cycle disorders may exacerbate their condition and antagonize the efficacy of AMMONUL	and Sodium Benzoate
33.2	IF patient is [being considered for] taking Sodium Phenylacetate and Sodium Benzoate AND patient is diagnosed with OTC, ASS, CPS, or a diagnosis categorized as other THEN Adverse events were reported with similar frequency in patients with OTC, ASS, CPS, and diagnoses categorized as other	Sodium Phenylacetate and Sodium Benzoate
33.3	IF patient is [being considered for] taking Sodium Phenylacetate and Sodium Benzoate AND patient is diagnosed with OTC or CPS THEN Nervous system disoiders were more frequent in patients with OTC and CPS, compared with patients with ASS and patients with other diagnoses	Sodium Phenylacetate and Sodium Benzoate
33.4	IF patient is [being considered for] taking Sodium Phenylacetate and Sodium Benzoate AND patient is diagnosed with OTC or CPS THEN Convulsions and mental impairment were reported in patients with OTC and CPS	Sodium Phenylacetate and Sodium Benzoate
33.5	IF patient is [being considered for] taking Sodium Phenylacetate and Sodium Benzoate AND patient has enzyme deficiencies occurring earlier in the urea cycle (i e , OTC and CPS) THEN there are reports in the literature that patients with enzyme deficiencies occurring earlier in the urea cycle (i e , OTC and CPS) tend to be more severely affected	Sodium Phenylacetate and Sodium Benzoate
34.1	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has a urea cycle disorder that involves deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (ASS) THEN BUPHENYL is indicated as adjunctive therapy in the chronic management of patient	Sodium Phenylbutyrate
34.2	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life) THEN BUPHENYL is indicated	Sodium Phenylbutyrate
34.3	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy THEN BUPHENYL is indicated	Sodium Phenylbutyrate
34.4	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has neonatal-onset disease AND patient has ornithine transcarbamylase deficiency THEN Patients with neonatal-onset disease have a high incidence of mental retardation Those who had IQ tests administered had an incidence of mental retardation as follows ornithine transcarbamylase deficiency, 100% (14/14 patients tested) Retardation was severe in the majority of the retarded patients	Sodium Phenylbutyrate
34.5	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has neonatal-onset disease AND patient has argininosuccinic acid synthetase deficiency THEN Patients with neonatal-onset disease have a high incidence of mental retardation Those who had IQ tests administered had an incidence of mental retardation as follows argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested) Retardation was severe in the majority of the retarded patients	Sodium Phenylbutyrate
34.6	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has neonatal-onset disease AND patient has carbamylphosphate synthetase deficiency THEN Patients with neonatal-onset disease have a high incidence of mental retardation Those who had IQ tests administered had an incidence of mental retardation as follows carbamoylphosphate synthetase deficiency, 57% (4/7 patients tested) Retardation was severe in the majority of the retarded patients.	Sodium Phenylbutyrate
34.7	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient has late-onset deficiency THEN In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98% However, compliance with the therapeutic regimen has not been adequately documented to allow evaluation of the potential for BUPHENYL and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonemic encephalopathy if carefully adhered to The majority of these patients tested (30/46 or 65%) have IQ's in the average to low average/borderline mentally retarded range Reversal of pre-existing neurologic impairment is not likely to	Sodium Phenylbutyrate

	occur with treatment and neurologic deterioration may continue in some patients	
34.8	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient is an infant AND (patient has neonatal-onset of CPS deficiency OR patient has neonatal-onset of OTC deficiency) THEN At the recommended dose of sodium phenylbutyrate, it is suggested that patient initially receive a daily dietary protein intake limited to approximately 1 6 g/kg/day for the first 4 months of life If tolerated, the daily protein intake may be increased to 1 9 g/kg/day during this period Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake	Sodium Phenylbutyrate
34.9	IF patient is taking Sodium Phenylbutyrate AND patient is 4 months to 1 year of age AND (patient has neonatal-onset of CPS deficiency OR patient has neonatal-onset of OTC deficiency) THEN it is recommended that the infant receive at least 1 4 g/kg/day, but 1 7 g/kg/day is advisable	Sodium Phenylbutyrate
34.11	IF patient is [being considered for] taking Sodium Phenylbutyrate AND (patient has neonatal-onset of carbamoylphosphate synthetase deficiency OR patient has neonatal-onset of ornithine transcarbamylase deficiency) AND patient is at least 6 months of age THEN it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids	Sodium Phenylbutyrate
34.12	IF patient is [being considered for] taking Sodium Phenylbutyrate AND (patient has argininosuccinic acid synthetase deficiency OR patient has late-onset disease (partial deficiencies, including females heterozygous for ornithine transcarbamylase)) THEN patient initially may receive a diet containing the age-determined minimal daily natural protein allowance The protein intake may be increased as tolerated and determined by plasma glutamine and other amino acid levels However, many patients with partial deficiencies avoid dietary protein	Sodium Phenylbutyrate
34.13	IF patient is [being considered for] taking Sodium Phenylbutyrate AND (patient is diagnosed with neonatal-onset deficiency of carbamoylphosphate synthetase OR patient is diagnosed with neonatal-onset deficiency of ornithine transcarbamylase) THEN Citrulline supplementation is required and recommended citrulline daily intake is recommended at 0 17 g/kg/day or 3 8 g/m^2/day	Sodium Phenylbutyrate
34.14	IF patient is [being considered for] taking Sodium Phenylbutyrate AND (patient is diagnosed with a milder form of carbamoylphosphate synthetase deficiency OR patient is diagnosed with a milder form of ornithine transcarbamylase deficiency) THEN The free-base form of arginine may be used instead of citrulline supplementation Daily intake is recommended at 0 17 g/kg/day or 3 8 g/m^2/day	Sodium Phenylbutyrate
34.15	IF patient is [being considered for] taking Sodium Phenylbutyrate AND patient is diagnosed with deficiency of argininosuccinic acid synthetase THEN Arginine supplementation is needed for patient arginine (free base) daily intake is recommended at 0 4-0 7 g/kg/day or 8 8-15 4 g/m^2/day	Sodium Phenylbutyrate
34.10.	IF patient is taking Sodium Phenylbutyrate AND patient is 1 to 3 years of age AND (patient has neonatal-onset of CPS deficiency OR patient has neonatal-onset of OTC deficiency) THEN From 1 to 3 years of age, the protein intake should not be less than 1 2 g/kg/day, 1 4 g/kg/day is advisable during this period	Sodium Phenylbutyrate
35.1	IF patient is [being considered for] taking Tamoxifen AND (patient has ER positive breast cancer OR patient has unknown breast cancer and positive nodes) THEN Among women with ER positive or unknown breast cancer and positive nodes who received about 5 years of treatment, overall survival at 10 years was 61 4% for NOLVADEX vs 50 5% for control (logrank 2p< 0 00001) The recurrence-free rate at 10 years was 59 7% for NOLVADEX vs 44 5% for control (logrank 2p< 0 00001) Among women with ER positive or unknown breast cancer and negative nodes who received about 5 years of treatment, overall survival at 10 years was 78 9% for NOLVADEX vs 73 3% for control (logrank 2p<0 00001) The recurrence-free rate at 10 years was 79 2% for NOLVADEX versus 64 3% for control (logrank 2p<0 00001)	Tamoxifen
35.2	IF patient is [being considered for] taking Tamoxifen AND (patient is a women with ER positive breast cancer OR patient has unknown breast cancer) THEN The effect of the scheduled duration of tamoxifen may be described as follows In women with ER positive or unknown breast cancer receiving 1 year or less, 2 years or about 5 years of NOLVADEX, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at 2p<0 003) The corresponding reductions in breast	Tamoxifen

	cancer recurrence were 21%, 29% and 47% (trend significant at 2p<0 00001)	
35.3	IF patient is [being considered for] taking Tamoxifen AND patient is a women with ER poor breast cancer THEN Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% (2p = 0 007) for all durations taken together, or 9% (2p = 0 02) if contralateral breast cancers are excluded The corresponding reduction in mortality was 6% (NS) The effects of about 5 years of NOLVADEX on recurrence and mortality were similar regardless of age and concurrent chemotherapy There was no indication that doses greater than 20 mg per day were more effective	Tamoxifen
35.4	IF patient is [being considered for] taking Tamoxifen THEN The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving NOLVADEX compared to placebo Data on contralateral breast cancer are available from 32,422 out of 36,689 patients in the 1995 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) In clinical trials with NOLVADEX of 1 year or less, 2 years, and about 5 years duration, the proportional reductions in the incidence rate of contralateral breast cancer among women receiving NOLVADEX were 13% (NS), 26% (2p = 0 004) and 47% (2p < 0 00001), with a significant trend favoring longer tamoxifen duration (2p = 0 008) The proportional reductions in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor Treatment with about 5 years of NOLVADEX reduced the annual incidence rate of contralateral breast cancer from 7 6 per 1,000 patients in the control group compared with 3 9 per 1,000 patients in the tamoxifen group	Tamoxifen
35.5	IF patient is [being considered for] taking Tamoxifen THEN For the primary endpoint, the incidence of invasive breast cancer was reduced by 43% among women assigned to NOLVADEX (44 cases - NOLVADEX, 74 cases - placebo, p=0 004, relative risk (RR)=0 57, 95% CI 0 39-0 84) No data are available regarding the ER status of the invasive cancers The stage distribution of the invasive cancers at diagnosis was similar to that reported annually in the SEER data base	Tamoxifen
35.6	IF patient is [being considered for] taking Tamoxifen AND patient has an ER positive tumor THEN NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors	Tamoxifen
35.7	IF patient is [being considered for] taking Tamoxifen AND patient has an ER negative tumor THEN NOLVADEX did not alter the incidence of estrogen receptor negative tumors or larger tumors	Tamoxifen
73.1	IF patient is [being considered for] taking Telaprevir THEN A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR)	Telaprevir
73.2	IF patient is [being considered for] taking Telaprevir AND (patient has rs12979860 CT genotype OR patient has rs12979860 TT genotype) THEN rs12979860 [IL28B] was genotyped in 454 of 1088 subjects in Study 108 (treatment-naive) and 527 of 662 subjects in Study C216 (previously treated) SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naive subjects receiving PR48 (Table 9) Among both treatment-naive and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with INCIVEK-containing regimens The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the substudy population relative to the overall trial population	Telaprevir
36.1	IF patient is [being considered for] taking Terbinafine THEN Terbinafine is an inhibitor of CYP4502D6 isozyme and has an effect on metabolism of desipramine, cimetidine, fluconazole, cyclosporine, rifampin, and caffeine	Terbinafine
36.2	IF patient is [being considered for] taking Terbinafine THEN In vivo studies have shown that terbinafine is an inhibitor of the CYP450 2D6 isozyme Drugs predominantly metabolized by the CYP450 2D6 isozyme include the following drug classes tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers, antiarrhythmics class 1C (e g , flecainide and propafenone) and monoamine oxidase inhibitors Type B	Terbinafine
36.3	IF patient is [being considered for] taking Lamisil (Terbinafine) AND patient is [being	Terbinafine

	considered for taking a drug predominantly metabolized by the CYP450 2D6 isozyme THEN Coadministration of Lamisil should be done with careful monitoring and may require a reduction in dose of the 2D6-metabolized drug	
36.4	IF patient is [being considered for] taking Terbinafine AND patient is [being considered for] taking desipramine THEN In a study to assess the effects of terbinafine on desipramine in healthy volunteers characterized as normal metabolizers, the administration of terbinafine resulted in a 2-fold increase in Cmax and a 5 fold increase in AUC In this study, these effects were shown to persist at the last observation at 4 weeks after discontinuation of Lamisil Tablets	Terbinafine
36.5	IF patient is [being considered for] taking Terbinafine AND patient is [being considered for] taking dextromethorphan THEN In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan, terbinafine increases the dextromethorphan/dextrorphan metabolite ratio in urine by 16- to 97-fold on average	Terbinafine
36.6	IF patient is [being considered for] taking Terbinafine AND (patient is [being considered for taking antipyrine OR patient is [being considered for taking digoxin) THEN In vivo drug-drug interaction studies conducted in healthy volunteer subjects showed that terbinafine does not affect the clearance of antipyrine or digoxin Terbinafine decreases the clearance of caffeine by 19% Terbinafine increases the clearance of cyclosporine by 15%	Terbinafine
37.1	IF patient is [being considered for] taking Tetrabenazine [a CYP2D6 inhibitor] THEN data suggest that inhibition of CYP2D6 in healthy subjects given a single 50 mg dose of tetrabenazine does not further increase the effect on the QTc interval	Tetrabenazine
37.2	IF patient is [being considered for] taking Tetrabenazine THEN Following oral administration of tetrabenazine, the extent of absorption is at least 75% After single oral doses ranging from 12 5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection because of the rapid and extensive hepatic metabolism of tetrabenazine to α-HTBZ and β-HTBZ α-HTBZ and β-HTBZ are metabolized principally by CYP2D6 Peak plasma concentrations (Cmax) of α-HTBZ and β-HTBZ are reached within 1 to 1/12, hours post-dosing α-HTBZ and β-HTBZ are subsequently metabolized to another major circulating metabolite, O-dealkylated-HTBZ, for which Cmax is reached approximately 2 hours post-dosing	Tetrabenazine
37.3	IF patient is [being considered for] taking Tetrabenazine THEN α-HTBZ and β-HTBZ, major circulating metabolites, have half-lives of 4-8 hours and 2-4 hours, respectively α-HTBZ and β-HTBZ are formed by carbonyl reductase that occurs mainly in the liver α-HTBZ is O-dealkylated by CYP450 enzymes, principally CYP2D6, with some contribution of CYP1A2 β-HTBZ is O-dealkylated principally by CYP2D6	Tetrabenazine
37.4	IF patient is [being considered for] taking Tetrabenazine THEN The results of in vitro studies do not suggest that tetrabenazine, α-HTBZ, or β HTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A	Tetrabenazine
37.5	IF patient is [being considered for] taking Tetrabenazine THEN In vitro studies suggest that neither tetrabenazine nor its α- or β-HTBZ metabolites is likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19	Tetrabenazine
37.6	IF patient is [being considered for] taking Tetrabenazine AND patient does not express the drug metabolizing enzyme CYP2D6 (poor metabolizers, PMs) THEN Although the pharmacokinetics of tetrabenazine and its metabolites in subjects who do not express the drug metabolizing enzyme CYP2D6 (poor metabolizers, PMs) have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased compared to subjects who express the enzyme (extensive metabolizers, EMs), with an increase similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively)	Tetrabenazine
37.7	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] a dose over 50 mg THEN Patients should be genotyped for CYP2D6 prior to treatment with daily doses of tetrabenazine over 50 mg	Tetrabenazine
37.8	IF patient is [being considered for] taking Tetrabenazine AND patient is a PM of CYP2D6 THEN Patients who are PMs should not be given daily doses greater than 50 mg	Tetrabenazine

37.9	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] taking paroxetine THEN α-HTBZ and β-HTBZ [metabolites of Tetrabenazine] are metabolized principally by CYP2D6 A strong CYP2D6 inhibitor (paroxetine) markedly increases exposure to these metabolites	Tetrabenazine
37.10.	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] a dose above 50 mg THEN Doses above 50 mg should not be given without CYP2D6 genotyping	Tetrabenazine
37.11	IF patient is taking Tetrabenazine AND patient has new onset depression AND patient requires antidepressants that are strong CYP2D6 inhibitors (such as paroxetine and fluoxetine) THEN the total dose of XENAZINE should be halved	Tetrabenazine
37.12	IF patient is taking Tetrabenazine AND patient is taking a antidepressant that is a strong CYP2D6 inhibitor (such as paroxetine and fluoxetine) AND depression or suicidality does not resolve THEN consideration should be given to discontinuing treatment with tetrabenazine	Tetrabenazine
37.13	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] taking an antidepressant that is a strong CYP2D6 inhibitor THEN Antidepressants that are strong CYP2D6 inhibitors significantly increase exposure to α- and β-HTBZ [metabolites of Tetrabenazine]	Tetrabenazine
37.14	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] a daily dose of greater than 50 mg THEN Before patients are given a daily dose of greater than 50 mg, they should be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs)	Tetrabenazine
37.15	IF patient is [being considered for] taking Tetrabenazine AND patient is a PM THEN When a dose of tetrabenazine is given to PMs, exposure will be substantially higher (about 3-fold for α-HTBZ and 9-fold foi β-HTBZ) than it would be in EMs The dosage should therefore be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers	Tetrabenazine
37.16	IF patient is [being considered for] taking Tetrabenazine THEN In vitro studies indicate that α-HTBZ and β-HTBZ are substrates for CYP2D6 The effect of CYP2D6 inhibition on the pharmacokinetics of tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine given after 10 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily There was an approximately 30% increase in Cmax and an approximately 3-fold increase in AUC for α-HTBZ in subjects given paroxetine prior to tetrabenazine compared to tetrabenazine given alone For β-HTBZ, the Cmax and AUC were increased 2 4- and 9-fold, respectively, in subjects given paroxetine prior to tetrabenazine given alone The elimination half-life of α-HTBZ and β-HTBZ was approximately 14 hours when tetrabenazine was given with paroxetine	Tetrabenazine
37.17	IF patient is already receiving a stable dose of Tetrabenazine AND patient is [being considered for] taking any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) THEN Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetiabenazine should be halved	Tetrabenazine
37.18	IF patient is [being considered for] taking Tetrabenazine AND patient is [being considered for] taking P450 inhibitors other than CYP2D6 inhibitors THEN Based on in vitro studies, a clinically significant interaction between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) is not likely	Tetrabenazine
37.19	IF patient is [being considered for] taking Tetrabenazine AND patient appears to require doses greater than 50 mg per day THEN Patients who appear to require doses greater than 50 mg per day should be genotyped for CYP2D6	Tetrabenazine
37.20.	IF patient is [being considered for] taking Tetrabenazine AND patient is a CYP2D6 poor metabolizer THEN In patients who are CYP2D6 poor metabolizers, dosing is similar to EMs except that the recommended maximum single dose is 25 mg, and the maximum recommended daily dose is 50 mg	Tetrabenazine
37.21	IF patient is already receiving a stable dose of Tetrabenazine AND patient is [being considered for] taking a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine,	Tetrabenazine

	quinidine) THEN Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine), to a patient already receiving a stable dose of tetrabenazine In patients receiving co-administered strong CYP2D6 inhibitors, the daily dose of tetrabenazine should be halved	
37.22	IF patient is initiating treatment with XENAZINE AND patient is on a stable dose of a strong CYP2D6 inhibitor THEN The dosing recommendations for the CYP2D6 poor metabolizers should be followed The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated	Tetrabenazine
2.1	IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine, and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy	Thioguanine
2.2	IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in the patient	Thioguanine
2.3	IF patient is [being considered for] taking thioguanine THEN prescribers should be aware that some laboratories offer testing for TPMT deficiency	Thioguanine
2.4	IF patient is [being considered for] taking thioguanine AND patient has bone marrow suppression THEN bone marrow suppression may be associated with factors other than TPMT deficiency	Thioguanine
2.5	IF patient is [being considered for] taking thioguanine AND patient has TPMT testing THEN TPMT testing may not identify if patient is at risk for severe toxicity AND close monitoring of clinical and hematologic parameters is important	Thioguanine
2.6	IF patient is [being considered for] taking thioguanine THEN prescribers should be aware that some laboratories offer testing for TPMT deficiency	Thioguanine
2.7	IF patient is [currently] taking thioguanine AND patient is [being considered for] aminosalicylate derivatives (e g olsalazine, mesalazine, or sulphasalazine) that inhibit the TPMT enzyme THEN aminosalicylate derivatives should be administered with caution	Thioguanine
2.8	IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine AND patient may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy AND substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in the patient	Thioguanine
2.9	IF patient is [being considered for] taking thioguanine THEN prescribers should be aware that some laboratories offer testing for TPMT deficiency	Thioguanine
38.1	IF patient is [being considered for] taking Thioridazine AND (patient is [being considered for] taking a reduced cytochrome P450 2D6 isozyme activity drugs that inhibit this isozyme (e g , fluoxetine and paroxetine) OR patient is [being considered for] taking certain other drugs (e g , fluvoxamine, propranolol, and pindolol)) THEN Reduced cytochrome P450 2D6 isozyme activity drugs that inhibit this isozyme (e g , fluoxetine and paroxetine) and certain other drugs (e g , fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias Therefore, thioridazine is contraindicated with these drugs	Thioridazine
38.2	IF patient is [being considered for] taking Thioridazine AND patient is [being considered for taking other agents that prolong the QTc interval THEN increased risk may result from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval Therefore, thioridazine is contraindicated with these drugs	Thioridazine
38.3	IF patient is [being considered for] taking Thioridazine AND patient has a genetic defect leading to reduced levels of activity of P450 2D6 THEN thioridazine is contraindicated in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6	Thioridazine

38.4	IF patient is [being considered for] taking Thioridazine AND patient has reduced activity of P450 2D6 THEN patient may be at increased risk of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interva	Thioridazine
38.5	IF patient is [being considered for] taking Thioridazine AND patient is taking a drug that may inhibit P450 2D6 THEN patient may be at increased risk of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval	Thioridazine
38.6	IF patient is [being considered for] taking Thioridazine AND patient is [being considered for] taking drugs that inhibit P450 2D6 isozyme activity THEN In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2 4-fold higher Cmax and a 4 5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450 2D6 isozyme activity Thus, this study suggests that drugs that inhibit P450 2D6 or the presence of reduced activity levels of this isozyme will produce elevated plasma levels of thioridazine	Thioridazine
38.7	IF patient is [being considered for] taking Thioridazine AND patient is [being considered for taking a drug that inhibits P450 2D6 THEN The coadministration of drugs that inhibit P450 2D6 with thioridazine is contraindicated	Thioridazine
38.8	IF patient is [being considered for] taking Thioridazine AND patient is known to have reduced activity of P450 2D6 THEN the use of thioridazine in patients known to have reduced activity of P450 2D6 is contraindicated	Thioridazine
39.1	IF patient is [being considered for] taking Timolol AND patient is [being considered for] taking quinidine THEN Potentiated systemic beta-blockade (e g , decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6	Timolol
40.1	IF patient is [being considered for] taking Tiotropium THEN In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administereddose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose	Tiotropium
40.2	IF patient is [being considered for] taking Tiotropium THEN In vitro studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4	Tiotropium
41.1	IF patient is [being considered for] taking Tolterodine THEN Tolterodine is extensively metabolized by the liver following oral dosing The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51% +- 14% and 29% +- 6 3% of the metabolites recovered in the urine, respectively	Tolterodine
41.2	IF patient is [being considered for] taking Tolterodine THEN A subset (about 7%) of the population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine The identified pathway of metabolism for these individuals (poor metabolizers) is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine The remainder of the population is referred to as extensive metabolizers	Tolterodine
41.3	IF patient is [being considered for] taking Tolterodine AND patient a poor metabolizer of CYP2D6 THEN Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers, this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite	Tolterodine
41.4	IF patient is [being considered for] taking Tolterodine AND patient is [being considered for] taking Fluoxetine THEN Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity In a study to assess the effect of fluoxetine on the	Tolterodine

	pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4 8-fold increase in tolterodine AUC There was a 52% decrease in Cmax and a 20% decrease in AUC of the 5-hydroxymethyl metabolite Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers The sums of unbound serum concentrations of tolterodine immediate release and the 5-hydroxymethyl metabolite are only 25% higher during the interaction	
41.5	IF patient is [being considered for] taking Tolterodine AND patient is [being considered for] taking Fluoxetine THEN No dose adjustment is required when DETROL and fluoxetine are coadministered	Tolterodine
41.6	IF patient is [being considered for] taking Tolterodine AND patient is [being considered for] taking other drugs metabolized by the major drug metabolizing CYP enzymes THEN Tolterodine immediate release does not cause clinically significant interactions with other drugs metabolized by the major drug metabolizing CYP enzymes	Tolterodine
41.7	IF patient is [being considered for] taking Tolterodine AND patient is [being considered for] taking other drugs metabolized by the major drug metabolizing CYP enzymes THEN In vivo drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole In vitro data show that tolterodine immediate release is a competitive inhibitor of CYP2D6 at high concentrations (Ki 1 05 uM), while tolterodine immediate release as well as the 5-hydroxymethyl metabolite are devoid of any significant inhibitory potential regarding the other isoenzymes	Tolterodine
41.8	IF patient is [being considered for] taking Tolterodine AND patient is a CYP2D6 poor metabolizer THEN Tolterodine's effect on QT interval was found to correlate with plasma concentration of tolterodine There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study	Tolterodine
41.9	IF patient is [being considered for] taking Tolterodine AND patient is a CYP2D6 poor metabolizer AND (patient has a known history of QT prolongation OR patient is taking Class IA or Class III antiarrhythmic medications) THEN In a study of the effect of tolterodine immediate release tablets on the QT interval , the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs) The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin However, the confidence intervals overlapped These observations should be considered in clinical decisions to prescribe DETROL for patients with a known history of QT prolongation or patients who are taking Class IA (e g , quinidine, procainamide) or Class III (e g , amiodarone, sotalol) antiarrhythmic medications	Tolterodine
72.1	IF patient is [being considered for] taking Tositumomab THEN Tositumomab is a murine IgG2a lambda monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes Tositumomab is produced in an antibiotic free culture of mammalian cells and is composed of two murine gamma 2a heavy chains of 451 amino acids each and two lambda light chains of 220 amino acids each The approximate molecular weight of Tositumomab is 150 kD	Tositumomab
72.2	IF patient is [being considered for] taking Tositumomab THEN Tositumomab binds specifically to the CD20 (human B-lymphocyte-restricted differentiation antigen, Bp 35 or B1) antigen This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes (Ref 2) The antigen is also expressed on >90% of B-cell non-Hodgkin&rsquo,s lymphomas (NHL) (Ref 3) The recognition epitope for Tositumomab is found within the extracellular domain of the CD20 antigen CD20 does not shed from the cell surface and does not internalize following antibody binding (Ref 4)	Tositumomab
72.3	IF patient is [being considered for] taking Tositumomab THEN Administration of the BEXXAR therapeutic regimen results in sustained depletion of circulating CD20 positive cells	Tositumomab

72.4	IF patient is [being considered for] taking Tositumomab THEN The impact of administration of the BEXXAR therapeutic regimen on circulating CD20 positive cells was assessed in two clinical studies, one conducted in chemotherapy naive patients and one in heavily pretreated patients The assessment of circulating lymphocytes did not distinguish normal from malignant cells Consequently, assessment of recovery of normal B cell function was not directly assessed At seven weeks, the median number of circulating CD20 positive cells was zero (range 0-490 cells/mm^3) Lymphocyte recovery began at approximately 12 weeks following treatment Among patients who had CD20 positive cell counts recorded at baseline and at 6 months, 8 of 58 (14%) chemotherapy naive patients had CD20 positive cell counts below normal limits at six months and 6 of 19 (32%) heavily pretreated patients had CD20 positive cell counts below normal limits at six months There was no consistent effect of the BEXXAR therapeutic regimen on post-treatment serum IgG, IgA, or IgM levels	Tositumomab
72.5	IF patient is [being considered for] taking Tositumomab AND patient has CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma (including patients with Rituximab-refractory non-Hodgkin's lymphoma) THEN Tositumomab is indicated for use Determination of the effectiveness of the BEXXAR therapeutic regimen is based on overall response rates in patients whose disease is refractory to chemotherapy alone or to chemotherapy and Rituximab The effects of the BEXXAR therapeutic regimen on survival are not known	Tositumomab
72.6	IF patient is [being considered for] taking Tositumomab AND patient has CD20 positive non-Hodgkin's lymphoma THEN The BEXXAR therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin's lymphoma	Tositumomab
42.1	IF patient is [being considered for] taking Tramadol and Acetaminophen THEN Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver Metabolite M1 (O-desmethyltramadol) is pharmacologically active in animal models Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response	Tramadol and Acetaminophen
42.2	IF patient is [being considered for] taking Tramadol and Acetaminophen AND patient has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 THEN Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 These individuals are poor metabolizers of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in poor metabolizers versus extensive metabolizers, while M1 concentrations were 40% lower	Tramadol and Acetaminophen
42.3	IF patient is [being considered for] taking Tramadol and Acetaminophen AND patient is [being considered for] taking inhibitors of CYP2D6 THEN In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite nor fluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown	Tramadol and Acetaminophen
42.4	IF patient is [being considered for] taking Tramadol and Acetaminophen AND patient is [being considered for] taking drugs which impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) THEN The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including ULTRACET, particularly with concomitant use ofs erotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, and triptans, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) This may occur within the recommended dose	Tramadol and Acetaminophen
42.5	IF patient is [being considered for] taking Tramadol and Acetaminophen AND (patient is [being considered for] taking a CYP2D6 inhibitor OR patient is [being considered for] taking a CYP3A4 inhibitor) THEN Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors, such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce	Tramadol and Acetaminophen

	metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome	
42.6	IF patient is [being considered for] taking Tramadol and Acetaminophen AND patient is [being considered for] taking Quinidine THEN Tramadol is metabolized to M1 by CYP2D6 Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1 The clinical consequences of these findings are unknown In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism	Tramadol and Acetaminophen
42.7	IF patient is [being considered for] taking Tramadol and Acetaminophen AND patient is [being considered for] taking inhibitors of CYP2D6 THEN In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol	Tramadol and Acetaminophen
64.1	IF the patient is taking Trastuzumab THEN, HER2 testing should be performed by laboratories with demonstrated proficiency prior to initiating therapy	Trastuzumab
64.2	IF the patient has HER2 protein overexpression, THEN the patient will benefit from Trastuzumab treatment	Trastuzumab
64.3	IF the patient has adjuvant breast cancer AND the tumor is HER2 overexpressing node positive or node negative, THEN treat patient with Herceptin	Trastuzumab
64.4	IF the patient has metastatic breast cancer AND the tumor is HER2-overexpressing, THEN treat the patient with both herceptin and paclitaxel for first-line treatment	Trastuzumab
64.5	IF the patient has metastatic breast cancer AND the tumor is HER2-overexpressing AND the patient has received one or more chemotherapy regimens, THEN treat the patient with herceptin as a single agent	Trastuzumab
64.6	IF improper assay performance occurs with the HER2 testing, THEN results may be unreliable	Trastuzumab
64.7	IF HER2 testing is being performed for a patient AND a commercial assay is being used, THEN users should refer to the package inserts of specific assay kits for information on the validation and performance the assay	Trastuzumab
65.1	IF the patient has APL, FAB classification M3 AND (the patient has the t(15,17) translocation OR the patient has the PML/RARα gene) AND are refractory to or who have relapsed from anthracycline chemotherapy OR antracycline-based chemotherapy is contraindicated for the patient, THEN treat the patient with tretinoin	Tretinoin
65.2	IF the patient is taking Tretinoin AND the patient is suspected of having APL AND the patient is negative for t(15,17), THEN PML/RARα fusion should be sought using molecular diagnostic techniques prior to Tretinoin therapy	Tretinoin
65.3	IF the patient is taking Tretinoin AND the patient is suspected of having APL, THEN confirmation of the disease should be sought by detection of the t(15,17) genetic marker by cytogenetic studies prior to Tretinoin therapy	Tretinoin
43.1	IF patient is taking Valproic acid AND patient is being considered for taking Depakote ER AND patient has a known urea cycle disorder THEN Depakote ER is contraindicated in patients with known urea cycle disorders (UCD) Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency	Valproic acid
44.1	IF patient is [being considered for] taking Venlafaxine AND patient is [being considered for] taking a drug that inhibits CYP2D6 THEN In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism and venlafaxine However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the	Venlafaxine

	two metabolizer groups	
44.2	IF patient is [being considered for] taking Venlafaxine AND patient is [being considered for] taking a drug that inhibits CYP2D6 THEN no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor	Venlafaxine
44.3	IF patient is [being considered for] taking Venlafaxine AND patient is [being considered for] taking Ketoconazole THEN A pharmacokinetic study with ketoconazole 100 mg b i d with a single dose of venlafaxine 50 mg in extensive metabolizers (EM, n = 14) and 25 mg in poor metabolizers (PM, n = 6) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desvenlafaxine (ODV) in most subjects following administration of ketoconazole Venlafaxine Cmax increased by 26% in EM subjects and 48% in PM subjects Cmax values for ODV increased by 14% and 29% in EM and PM subjects, respectively	Venlafaxine
44.4	IF patient is [being considered for] taking Venlafaxine AND patient is [being considered for] taking a CYP3A4 inhibitor THEN In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4 Because CYP3A4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A4-mediated metabolism and venlafaxine is small	Venlafaxine
44.5	IF patient is [being considered for] taking Venlafaxine AND (patient is [being considered for] taking a CYP2D6 inhibitor OR patient is [being considered for] taking a CYP3A4 inhibitor) THEN The concomitant use of venlafaxine with a drug treatment(s) that potently inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce potent simultaneous inhibition of these two enzyme systems	Venlafaxine
44.6	IF patient is [being considered for] taking Venlafaxine THEN In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6 These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine to that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan	Venlafaxine
44.7	IF patient is [being considered for] taking Venlafaxine AND patient is [being considered for] taking risperidone THEN Risperidone and Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone)	Venlafaxine
66.1	IF the patient is taking Voriconazole AND the patient is taking drug(s) as current treatment AND any of the drug(s) are inhibitors or inducers of enzymes CYP2C19 or CYP2C9 or CYP3A4 THEN the current treatment will increase or decrease exposure of Voriconazole in the patient	Voriconazole
66.2	IF the patient is taking Voriconazole THEN taking Voriconazole will increase or decrease exposure to other drugs the patient is taking that are inhibitors or inducers of enzymes CYP2C19 or CYP2C9 or CYP3A4	Voriconazole
66.3	IF the patient is taking Voriconazole AND the patient is Caucasian OR the patient is Black THEN the patient has a 3-5% probability of being a poor metabolizer of Voriconazole	Voriconazole
66.4	IF the patient is taking Voriconazole AND the patient is Asian THEN the patient has a 15-20% probability of being a poor metabolizer of Voriconazole	Voriconazole
10.1	IF patient [is being considered] for warfarin AND (patient has the variant allele CYP2C9*2 OR patient has variant allele CYP2C9*3) THEN the variant alleles CYP2C9*2 and CYP2C9*3 result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin	Warfarin (1)
10.2	IF patient [is being considered] for warfarin AND patient is Caucasian THEN The frequencies of CYP2C9*2 and CYP2C9*3 in Caucasians are approximately 11% and 7%, respectively	Warfarin (1)
10.3	IF patient [is being considered] for warfarin AND patient has one or more of variants CYP2C9*2 or CYP2C9*3 alleles THEN patient have decreased S-warfarin clearance	Warfarin (1)

10.4	IF patient is [being considered for] taking warfarin AND patient is African THEN Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry	Warfarin (1)
10.5	IF patient is [being considered for] taking warfarin AND patient is Caucasians THEN Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *9, and *11 alleles in Caucasians	Warfarin (1)
10.6	IF patient is [being considered for] taking warfarin AND patient is a carrier of either the CYP2C9*2 OR CYP2C9*3 alleles THEN A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele	Warfarin (1)
10.7	IF patient [is being considered] for warfarin AND patient is a carrier of either the CYP2C9*2 OR CYP2C9*3 alleles THEN In an observational study, the risk of achieving INR > 3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype The relative risk of over anticoagulation as measured by INR > 3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele	Warfarin (1)
74.1	IF the patient has changes in diet OR patient is taking other medications OR patient is taking botanicals OR patient has genetic variations in CYP2C9 enzymes OR patient has genetic variations is VKORC1 enzymes THEN Numerous factors, alone or in combination including changes in diet, medications, botanicals, and genetic variations in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin	Warfarin (1) (2)
74.2	IF patient is [being considered for] taking Warfarin AND patient has risk factors for bleeding OR (patient has CYP2C9 variants OR patient has VKORC1 variants) THEN Identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses	Warfarin (1) (2)
74.3	IF patient is [being considered for] taking Warfarin AND (patient's CYP2C9 genotype is unknown OR patient's VKORC1 genotype is unknown) THEN the patient's CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg per day Modify this dose based on consideration of patient-specific clinical factors	Warfarin (1) (2)
74.4	IF patient is [being considered for] taking Warfarin AND (patient's CYP2C9 genotype information is available AND patient's VKORC1 genotype is available) THEN The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants Consider these ranges in choosing the initial dose	Warfarin (1) (2)
74.5	IF patient is [being considered for] taking Warfarin AND (patient has genetic variations in the VKORC1 gene OR patient has genetic variations in CYP2C9) THEN In 201 Caucasian patients treated with stable warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses In this study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone, about 40% of the variance in warfarin dose could be attributed to variations in VKORC1 and CYP2C9 genes combined	Warfarin (1) (2)
74.6	IF patient is [being considered for] taking Warfarin AND patient is Caucasian THEN About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients	Warfarin (1) (2)
74.7	IF patient is [being considered for] taking Warfarin AND patient is Asian THEN About 55% of the variability in warfarin dose could be explained by the combination of	Warfarin (1) (2)

VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients Similar observations have been reported in Asian patients

73.1	IF patient is [being considered for] taking Warfarin THEN Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide The degree of depression is dependent upon the dosage administered and, in part, by the patient's VKORC1 genotype Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%	Warfarin (2)
73.2	IF patient is [being considered for] taking Warfarin AND patient has VKORC1 genotype information available THEN Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide The degree of depression is dependent upon the dosage administered and, in part, by the patient's VKORC1 genotype Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%	Warfarin (2)
73.3	IF patient is [being considered for] taking Warfarin THEN Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex	Warfarin (2)
73.4	IF patient is [being considered for] taking Warfarin AND patient has certain SNPs in VKORC1 gene(especially the -1639G>A allele) THEN Certain single nucleotide polymorphisms in the VKORC1 gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin	Warfarin (2)

APPENDIX 2: RULE PATTERN CLASSIFICATION LEGEND

Legend	Pre- or Post- Condition	Pre-/Post- Condition Rule Pattern
a	Pre-Condition (IF statement)	Drug
b	Pre-Condition (IF statement)	drug + current_condition/demographic_data/history_of_condition/history_of_meds
c	Pre-Condition (IF statement)	drug + genotype/phenotype/family_history
d	Pre-Condition (IF statement)	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds
e	Pre-Condition (IF statement)	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds + inpatient/outpatient_procedure
f	Pre-Condition (IF statement)	drug + genotype/phenotype/family_history + population
g	Pre-Condition (IF statement)	drug + population
h	Pre-Condition (IF statement)	drug1 + drug2/current_med_list
i	Pre-Condition (IF statement)	drug1 + drug2/current_med_list + current_condition/demographic_data/history_of_condition/history_of_meds
j	Pre-Condition (IF statement)	drug1 + drug2/current_med_list + genotype/phenotype/family_history
k	Pre-Condition (IF statement)	drug1 + drug2/current_med_list + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds
l	Pre-Condition (IF statement)	genotype/phenotype/family_history
m	Pre-Condition (IF statement)	genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds
n	Pre-Condition (IF statement)	genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds + inpatient/outpatient_procedure
o	Pre-Condition (IF statement)	genotype/phenotype/family_history + current_med_list
p	Pre-Condition (IF statement)	genotype/phenotype/family_history + inpatient/outpatient_procedure
q	Pre-Condition (IF statement)	other
aa	Post-Condition (THEN statement)	associated_clinical_outcomes
bb	Post-Condition (THEN statement)	patient_communications
cc	Post-Condition (THEN statement)	pharmacological_activity_with_involvement_of_gene/protein
dd	Post-Condition (THEN statement)	probability/frequency_of_clinical_outcome
ee	Post-Condition (THEN statement)	probability/frequency_of_having_variants_in_population
ff	Post-Condition (THEN statement)	recommend_use_caution
gg	Post-Condition (THEN statement)	recommended_testing
hh	Post-Condition (THEN statement)	recommended_treatment_protocol
ii	Post-Condition (THEN statement)	study_clinical_outcomes
jj	Post-Condition (THEN statement)	test_interpretation
kk	Post-Condition (THEN statement)	testing_is_available/test use
ll	Post-Condition (THEN statement)	toxicity/complications/change_in_pharmacological_activity

APPENDIX 3. RULE PATTERN CLASSIFICATIONS

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
45.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning		Warning
45.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning		Warning
45.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning		Warning
45.4	a	bb	Information related to treatment to relay to (or to be relayed from) the patient	Recommendation		Recommendation
45.5	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
45.6	d	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
45.7	d	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
12.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.4	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.5	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.6	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.7	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.8	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.9	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
12.10.	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to	Information only		Information only

Rule ID[F]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			coadministration of drugs			
12.12	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.13	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
12.14	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
12.15	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
12.16	j	ll	Treatment protocol Advice about drug dose	Recommendation		Recommendation
12.17	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
12.18	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
13.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
13.2	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
46.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
46.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
46.3	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
46.4	i	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
46.5	j	hh	Treatment protocol Advice about drug dose	Information only		Information only
46.6	k	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
46.7	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
46.8	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
47.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
47.2	o	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
47.3	o	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
47.4	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
47.5	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
47.6	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
48.1	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
3.1	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
3.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
49.1	l	ll	Advice related to testing How to interpret test results	Information only		Information only
49.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
49.3	g	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
49.4	g	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
49.5	g	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
49.6	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.7	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.8	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.9	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.10.	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.11	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
49.12	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
49.13	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
49.14	l	jj	Advice related to testing How to interpret test results	Information only		Information only
49.15	l	jj	Advice related to testing How to interpret test results	Information only		Information only
4.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
4.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
4.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
4.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
4.5	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
4.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
50.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
50.2	c	hh	Treatment protocol Appropriate patient monitoring requirements	Warning	Information only	Warning
50.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
50.4	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
50.5	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
50.6	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
50.7	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
50.8	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
52.1	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
52.2	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
52.3	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
14.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
14.2	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
14.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
14.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
15.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
15.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
15.3	c	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Recommendation	Warning	Warning
15.4	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
67.1	c	hh	Treatment protocol Other recommendation	Recommendation		Recommendation
5.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
5.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
5.3	e	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
5.4	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
5.5	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
5.6	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
5.7	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
5.8	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
5.9	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
5.10.	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
5.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
5.12	f	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a	Information only		Information only

Rule ID[Ŧ]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			population to which this patient belongs?			
5.13	f	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
5.14	c	jj	Advice related to testing How to interpret test results	Information only		Information only
5.15	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
5.16	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
5.17	d	ii	Treatment protocol Advice about drug dose	Information only		Information only
5.18	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
16.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
16.2	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation	Warning	Warning
16.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
16.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
16.5	h	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
16.6	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
16.7	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
53.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
53.2	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
53.3	h	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
53.4	c	bb	Information related to treatment to relay to (or to be relayed from) the patient	Recommendation		Recommendation

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
17.1	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
17.2	d	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
17.3	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
17.4	d	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Recommendation	Warning	Warning
17.5	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
17.6	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
17.7	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
17.8	a	bb	Information related to treatment to relay to (or to be relayed from) the patient	Recommendation		Recommendation
17.9	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
17.10.	d	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
17.11	d	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
54.1	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
54.2	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
18.1	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation	Warning	Warning
18.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
18.4	a	ll	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
18.5	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
18.6	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only

Rule ID[Ŧ]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
18.7	a	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
18.8	b	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
18.9	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
18.10.	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
18.11	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
18.12	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
18.13	h	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
18.14	h	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
18.15	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.16	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
18.17	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
18.18	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.19	ı	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
18.20.	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
18.21	h	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
18.22	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.23	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.25	a	cc	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
18.26	h	ff	Considerations before initiating treatment Who might have an altered response to	Recommendation		Recommendation

Rule ID[†]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			treatment or an altered risk for ADEs due to coadministration of drugs			
18.27	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
19.1	a	ll	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
19.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
19.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
19.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
19.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
20.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
20.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
20.3	a	ll	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
20.4	a	ll	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
20.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
20.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
20.7	i	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
20.8	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
21.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
21.2	a	ll	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to	Information only	Warning	Warning

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			coadministration of drugs			
22.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.4	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
22.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
22.7	h	hh	Treatment protocol Advice about drug dose	Information only		Information only
22.8	i	hh	Treatment protocol Advice about drug dose	Information only		Information only
22.9	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.10.	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
22.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
22.12	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
22.13	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
22.14	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
22.15	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
22.16	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
68.1	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
68.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
68.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
68.4	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
68.5	b	dd	What is the frequency of factors (genetic or	Information only		Information only

Rule ID[F]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			otherwise) relevant to treatment response in a population to which this patient belongs?			
68.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
68.7	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
68.8	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
68.9	b	hh	Information related to treatment to relay to (or to be relayed from) the patient	Recommendation		Recommendation
23.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
23.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
23.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
23.4	a	aa	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
23.5	a	cc	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only	Warning	Warning
23.6	h	ff	Treatment protocol Other recommendation	Recommendation		Recommendation
23.7	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
23.8	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
23.9	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
23.10.	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
23.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
23.12	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
23.13	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
23.14	c	ll	Considerations before initiating treatment	Information only		Information only

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history			
23.15	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
55.1	h	ff	Treatment protocol Other recommendation	Recommendation		Recommendation
55.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
55.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
55.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
55.5	a	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
69.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
69.2	b	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
24.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
24.2	a	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
24.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
56.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
56.2	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
56.3	e	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
56.4	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
25.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
25.2	n	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation	Warning	Warning
25.3	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
25.4	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
25.5	e	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
25.6	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
25.7	d	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation	Warning	Warning
25.8	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
25.9	d	ll	Treatment protocol Advice about drug dose	Warning	Information only	Warning
25.10.	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
25.11	e	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
25.12	d	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
25.13	e	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
25.14	e	ii	Treatment protocol Advice about drug dose	Information only		Information only
25.15	d	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
70.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
70.2	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
71.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
71.2	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
71.3	e	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
71.4	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
71.5	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
71.6	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
71.7	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
6.1	c	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
6.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
6.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Recommendation	Warning
6.4	c	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
6.5	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
6.6	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
6.7	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
6.8	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.9	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.10.	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.11	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.12	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.13	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
6.14	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
6.15	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
26.1	c	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
26.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
27.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
27.2	d	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
57.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
57.2	d	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
57.3	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
57.4	d	bb	Information related to treatment to relay to (or to be relayed from) the patient	Recommendation		Recommendation
58.1	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
58.2	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
58.3	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
1.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
1.2	a	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
1.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.5	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
1.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.7	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
1.8	c	hh	Treatment protocol Advice about drug dose	Information only	Warning	Warning
1.9	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.10.	b	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
1.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
1.12	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
1.13	b	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
1.14	l	jj	Advice related to testing How to interpret test results	Information only		Information only
1.15	l	jj	Advice related to testing How to interpret test results	Information only		Information only
1.16	l	kk	Advice related to testing What testing is	Information only		Information only

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			available prior to drug administration			
1.17	c	ff	Advice related to testing How to interpret test results	Information only		Information only
1.18	p	ff	Advice related to testing How to interpret test results	Information only		Information only
1.19	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation
1.20.	c	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.21	c	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.22	c	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.23	c	aa	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
1.24	c	hh	Treatment protocol Advice about drug dose	Information only		Information only
1.25	c	hh	Treatment protocol Advice about drug dose	Information only		Information only
1.26	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
11.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
11.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
11.3	j	cc	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
11.4	k	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
11.5	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
11.6	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
11.7	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
11.8	j	ll	Considerations before initiating treatment	Warning	Information only	Warning

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs			
28.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
28.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
28.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
28.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
28.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
28.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
51.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
51.2	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
51.3	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
51.4	d	dd	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
51.5	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Information only		Information only
51.6	a	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
51.7	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
51.8	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
51.9	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
51.10.	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
51.11	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
51.12	h	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
51.13	k	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
51.14	k	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
51.15	d	ii	Considerations before initiating treatment Who might have an altered response to	Information only		Information only

Rule ID[Ŧ]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			treatment or an altered risk for ADEs due to genotype/phenotype/family_history			
51.16	d	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
51.17	d	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
51.18	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Information only		Information only
7.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
7.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
7.3	a	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
29.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
29.2	d	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
29.3	d	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
29.5	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
29.6	c	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
29.7	c	jj	Advice related to testing How to interpret test results	Recommendation		Recommendation
29.8	b	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.9	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.10.	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.11	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.12	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.13	a	ii	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
29.14	a	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
29.4	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
59.1	d	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Recommendation		Recommendation
60.1	h	aa	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
61.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
61.2	g	ee	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
61.3	g	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Warning	Information only	Warning
61.4	c	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Recommendation		Recommendation
8.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
8.2	h	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation
8.3	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
8.4	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
8.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
8.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
8.7	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
8.8	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
8.9	c	hh	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to	Recommendation	Warning	Warning

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			coadministration of drugs			
8.10.	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only	Warning	Warning
8.11	j	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
8.12	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
8.13	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
8.14	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
8.15	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
8.16	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
8.17	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
8.18	c	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
8.19	c	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
8.20.	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
9.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
9.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
9.3	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
9.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warnmg	Information only	Warning
9.5	h	ff	Treatment protocol Other recommendation	Recommendation	Warning	Warning
9.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
30.1	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
30.2	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
30.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
30.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
30.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
30.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
30.7	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation
30.8	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation
30.9	h	hh	Treatment protocol Other recommendation	Recommendation		Recommendation
30.10.	h	hh	Treatment protocol Advice about drug dose	Information only	Warning	Warning
30.11	h	hh	Treatment protocol Advice about drug dose	Information only	Warning	Warning
30.12	h	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
31.1	g	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
31.2	g	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
31.3	h	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
31.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
31.5	c	hh	Treatment protocol Advice about drug dose	Information only		Information only
31.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
31.7	a	ll	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only

Rule ID[†]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
31.8	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation	Warning	Warning
32.1	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
32.2	j	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
32.3	c	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
32.4	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
32.5	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
32.6	c	jj	Advice related to testing How to interpret test results	Information only		Information only
62.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
62.2	c	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
62.3	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
63.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
63.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
63.3	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
63.4	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
75.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
75.2	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.3	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to	Information only		Information only

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			coadministration of drugs			
75.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.7	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
75.8	g	ee	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
75.9	g	ee	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
75.10.	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
75.11	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.12	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
75.13	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
75.14	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
33.1	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
33.2	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
33.3	d	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning

Rule ID[F]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
33.4	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
33.5	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
34.1	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
34.2	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
34.3	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
34.4	d	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
34.5	d	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
34.6	d	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
34.7	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
34.8	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
34.9	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
34.11	d	hh	Treatment protocol Other recommendation	Recommendation		Recommendation
34.12	d	hh	Treatment protocol Other recommendation	Recommendation		Recommendation
34.13	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
34.14	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
34.15	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
34.10.	d	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
35.1	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
35.2	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
35.3	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
35.4	a	ii	Considerations before initiating treatment	Information only		Information only

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			What considerations should be made when initiating therapy (other)			
35.5	a	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
35.6	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
35.7	d	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
73.1	a	kk	Advice related to testing Who should be screened prior to drug administration	Information only		Information only
73.2	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
36.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
36.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
36.3	h	ff	Treatment protocol Appropriate patient monitoring requirements	Recommendation	Warning	Warning
36.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
36.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
36.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
37.1	a	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
37.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
37.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
37.4	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
37.5	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
37.6	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
37.7	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
37.8	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
37.9	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
37.10.	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation	Warning	Warning
37.11	ı	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
37.12	ı	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
37.13	ı	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
37.14	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
37.15	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
37.16	a	ll	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
37.17	h	hh	Treatment protocol Advice about drug dose	Recommendation	Warning	Warning
37.18	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
37.19	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
37.20.	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
37.21	h	hh	Treatment protocol Advice about drug dose	Recommendation	Warning	Warning
37.22	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
2.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
2.2	c	hh	Treatment protocol Advice about drug dose	Warning	Information only	Warning
2.3	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
2.4	b	aa	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
2.5	c	jj	Advice related to testing How to interpret test results	Recommendation		Recommendation
2.6	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
2.7	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
2.8	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
2.9	a	kk	Advice related to testing What testing is available prior to drug administration	Information only		Information only
38.1	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation	Warning	Warning
38.2	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation	Warning	Warning
38.3	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation	Warning	Warning
38.4	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
38.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
38.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
38.7	h	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
38.8	c	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
39.1	h	aa	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
40.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
40.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
41.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
41.2	a	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
41.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
41.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
41.5	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
41.6	h	ll	Considerations before initiating treatment Who might have an altered response to	Information only		Information only

Rule ID[¥]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			treatment or an altered risk for ADEs due to coadministration of drugs			
41.7	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
41.8	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only	Warning	Warning
41.9	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Recommendation	Warning	Warning
72.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
72.2	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
72.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
72.4	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
72.5	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
72.6	d	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
42.1	a	cc	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs (other)	Information only		Information only
42.2	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
42.3	h	ii	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
42.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
42.5	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning
42.6	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
42.7	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Warning	Information only	Warning

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
64.1	a	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
64.2	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Information only		Information only
64.3	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
64.4	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
64.5	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
64.6	q	jj	Advice related to testing How to interpret test results	Information only		Information only
64.7	q	jj	Advice related to testing How to interpret test results	Recommendation		Recommendation
65.1	m	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
65.2	d	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
65.3	b	gg	Advice related to testing Who should be screened prior to drug administration	Recommendation		Recommendation
43.1	i	hh	Indication or contraindication of use/Who will or will not benefit from treatment	Recommendation		Recommendation
44.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
44.2	h	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
44.3	h	dd	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
44.4	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
44.5	h	ff	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Recommendation		Recommendation
44.6	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
44.7	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
66.1	h	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
66.2	a	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to	Warning	Information only	Warning

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
			coadministration of drugs			
66.3	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
66.4	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
10.1	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
10.2	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
10.3	c	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
10.4	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
10.5	g	ee	What is the frequency of factors (genetic or otherwise) relevant to treatment response in a population to which this patient belongs?	Information only		Information only
10.6	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
10.7	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
74.1	j	ll	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to coadministration of drugs	Information only		Information only
74.2	d	hh	Treatment protocol Appropriate patient monitoring requirements	Recommendation		Recommendation
74.3	c	hh	Treatment protocol Advice about drug dose	Recommendation		Recommendation
74.4	c	hh	Treatment protocol Advice about drug dose	Information only		Information only
74.5	c	ii	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Warning	Information only	Warning
74.6	g	ll	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
74.7	g	ll	What factors (genetic or otherwise) are relevant to clinical outcomes or treatment response?	Information only		Information only
73.1	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only

Rule ID[T]	Pre-cond.[§]	Post-cond.[§]	Type of question	UI type	2nd UI type	Resolved UI type
73.2	c	cc	Considerations before initiating treatment Who might have an altered response to treatment or an altered risk for ADEs due to genotype/phenotype/family_history	Information only		Information only
73.3	a	cc	What (or how) are genes/enzymes involved in a drugs' mechanism of action?	Information only		Information only
73.4	c	Hh	Treatment protocol Advice about drug dose	Warning	Information only	Warning

[T]See Appendix 1
[§]See Appendix 2

APPENDIX 4: AVAILABILITY OF DATA ELEMENTS

Data element category	Data element	y/n	Derived	Most recent date evaluated
Condition	acute coronary syndrome	y		9/1/11
Condition	acute lymphoblastic leukemia (ALL)	y		9/1/11
Condition	acute promyelocytic leukemia (APL)	y		9/1/11
Condition	acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant)	y		9/22/09
Condition	aggressive systemic mastocytosis (ASM)	y		9/1/11
Condition	Anemia	y	Derived	9/1/11
Condition	bone marrow suppression	n	Derived	9/1/11
Condition	bone marrow toxicity	n	Derived	9/1/11
Condition	breast cancer	y	Derived	9/1/11
Condition	cardiac disease	y	Derived	9/1/11
Condition	cardiovascular disease	y	Derived	9/1/11
Condition	Chills	y		9/1/11
Condition	Chronic Eosinophilic Leukemia (CEL)	y		9/1/11
Condition	chronic myelogenous leukema (CML)	y		9/22/09
Condition	colorectal cancer (CRC)	y		9/1/11
Condition	del 5q myelodysplastic syndromes	y		9/1/11
Condition	Depression	y	Derived	9/1/11
Condition	diarrhea	y	Derived	9/1/11
Condition	disease caused by low-or-Intermediate-1-risk myelodysplastic syndrome	y	Derived	9/22/09
Condition	disease progression	n		9/1/11
Condition	failure	n		9/1/11
Condition	favism	y		9/1/11
Condition	fever	y	Derived	9/1/11
Condition	French-American-British (FAB) classification M3 AML	y		9/1/11
Condition	gastrointestinal stromal tumors (GISTs)	y	Derived	9/1/11
Condition	healthy	n	Derived	9/1/11
Condition	hematologic malignancy	y	Derived	9/1/11
Condition	hemoglobin M	y		9/1/11
Condition	hepatic impairment	y	Derived	9/1/11
Condition	history of QT prolongation	y		9/1/11
Condition	HIV	y		9/22/09
Condition	hyperammonemic encephalopathy	y		9/1/11
Condition	Hypereosinophilic Syndrome (HES)	y		9/1/11
Condition	hypersensitivity	n		9/1/11
Condition	intolerant to previous treatment	n		9/1/11
Condition	Juvenile rheumatoid arthritis (JRA)	y	Derived	9/1/11
Condition	late-onset disease	n		9/1/11
Condition	life-threatening diseases associated with PDGFR protein tyrosine kinases	N	Derived	9/1/11

Data element category	Data element	y/n	Derived	Most recent date evaluated
Condition	Low- or Intermediate-1-risk myelodysplastic syndromes	y	Derived	9/1/11
Condition	Malignant	n		9/22/09
Condition	Metastatic	n		9/22/09
Condition	myelodysplastic diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements	n	Derived	9/1/11
Condition	myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements	n	Derived	9/1/11
Condition	myelosuppression	n	Derived	9/1/11
Condition	neonatal-onset disease	n	Derived	9/1/11
Condition	Neurotoxicity	n		9/1/11
Condition	Neutropenia	y		9/1/11
Condition	new onset/newly diagnosed disease	n		9/22/11
Condition	non-hematologic toxicity	n		9/1/11
Condition	non-Hodgkin's lymphoma	y	Derived	9/1/11
Condition	Postmenarchal	n		9/1/11
Condition	Postmenopausal	n		9/1/11
Condition	Pregnant	n		9/1/11
Condition	recurrent after previous treatment	n		9/1/11
Condition	refractory to previous treatment	n		9/1/11
Condition	relapsed from previous treatment	n		9/1/11
Condition	resistant to previous treatment	n		9/1/11
Condition	side effects	n		9/1/11
Condition	stomach pain	n		9/1/11
Condition	Stomatitis	y	Derived	9/1/11
Condition	Suicidality	y		9/1/11
Condition	systemic toxicity	y		9/1/11
Condition	Tolerated	y	Derived	9/22/09
Condition	transfusion dependent anemia	n	Derived	9/22/09
Condition	Tumor	n		9/1/11
Condition	Unresectable	y		9/22/09
Condition	urea cycle disorder (UCD)	y	Derived	9/1/11
Condition	Vomiting	y		9/1/11
Demographics	1 to 3 years of age	y	Derived	9/1/11
Demographics	4 months to 1 year of age	y	Derived	9/1/11
Demographics	70 kg body weight or below	y	Derived	9/1/11
Demographics	Adolescent	y	Derived	9/1/11
Demographics	Adult	y	Derived	9/1/11
Demographics	Africa	n		9/1/11
Demographics	African	n		9/1/11
Demographics	African American	y		9/1/11
Demographics	after the first month of life	y	Derived	9/1/11

Data element category	Data element	y/n	Derived	Most recent date evaluated
Demographics	American black	Y		9/1/11
Demographics	American white	Y		9/1/11
Demographics	Asian	Y		9/1/11
Demographics	at least 6 months of age	Y	Derived	9/1/11
Demographics	Between the ages of 10 and 17	Y	Derived	9/1/11
Demographics	Caucasian	Y		9/1/11
Demographics	Child	Y	Derived	9/1/11
Demographics	Eskimo	Y		9/1/11
Demographics	Female	Y		9/1/11
Demographics	Hong Kong	N		9/1/11
Demographics	Infant	Y	Derived	9/1/11
Demographics	Japan	N		9/1/11
Demographics	Korea	N		9/1/11
Demographics	Malaysia	N		9/1/11
Demographics	Male	Y		9/1/11
Demographics	Mediterranean region	N		9/1/11
Demographics	Middle East	N		9/1/11
Demographics	Neonatal	Y	Derived	9/1/11
Demographics	North China	N		9/1/11
Demographics	Oceania	N		9/1/11
Demographics	Oriental	Y		9/1/11
Demographics	Philippines	N		9/1/11
Demographics	South Asia	N		9/1/11
Demographics	South-East Asia	N		9/1/11
Demographics	Southern Europe	N		9/1/11
Demographics	Taiwan	n		9/1/11
Demographics	Thailand	n		9/1/11
Demographics	White	y		9/1/11
Demographics	within the first 28 days of life	y	Derived	9/1/11
Demographics	Women	y		9/1/11
Laboratory value	5q Chromosome	n		9/1/11
Laboratory value	arginase (ARG)	n		9/1/11
Laboratory value	argininosuccinate lyase (ASL)	n		9/1/11
Laboratory value	argininosuccinate synthetase (ASS)	n		9/1/11
Laboratory value	c-Kit/KIT	y	Derived	9/22/09
Laboratory value	carbamylphosphate synthetase (CPS)	n		9/1/11
Laboratory value	CCR5	y	Derived	9/22/09
Laboratory value	CD20 antigen	n		9/1/11
Laboratory value	CXCR4	n	Derived	9/22/09
Laboratory value	CYP2C19	n	Derived	9/22/09
Laboratory value	CYP2C9	n		9/1/11
Laboratory value	CYP2D6	y	Derived	9/22/09
Laboratory value	dihydropyrimidine dehydrogenase (DPD)	y	Derived	9/22/09

Data element category	Data element	y/n	Derived	Most recent date evaluated
Laboratory value	epidermal growth factor receptor (EGFR)	y	Derived	9/22/09
Laboratory value	evidence of viral replication (HIV)	y	Derived	9/22/09
Laboratory value	familial hypercholesterolemia	n	Derived	9/22/09
Laboratory value	FIP1L1-PDGFRα fusion kinase	y	Derived	9/23/09
Laboratory value	glucose-6 phosphate dehydrogenase (G6PD)	y	Derived	9/22/09
Laboratory value	Her2/neu	y	Derived	9/22/09
Laboratory value	HLA-B*1502	y	Derived	9/22/09
Laboratory value	HLA-B*5701	y	Derived	9/22/09
Laboratory value	IL-28b	n		9/1/11
Laboratory value	KRAS	y	Derived	9/22/09
Laboratory value	LDL receptor	n		9/1/11
Laboratory value	methemoglobin reductase	n		9/1/11
Laboratory value	N-acetylglutamate synthetase (NAGS)	n		9/1/11
Laboratory value	NADH methemoglobin reductase	n		9/1/11
Laboratory value	NAT1, NAT2	n		9/1/11
Laboratory value	ornithine transcarbamylase (OTC)	y	Derived	9/22/09
Laboratory value	PDGFR	y	Derived	9/1/11
Laboratory value	Ph1 chromosome	y	Derived	9/22/09
Laboratory value	PML/RARα	y	Derived	9/22/09
Laboratory value	t(15,17) translocation	y	Derived	9/22/09
Laboratory value	thiopurine methyltransferase (TPMT)	y	Derived	9/22/09
Laboratory value	UGT1A1	y	Derived	9/22/09
Laboratory value	urea cycle disorder (UCD)	n		9/1/11
Laboratory value	VKORC1	n		9/1/11
Medication	5- fluorouracil (5-FU)	y		9/1/11
Medication	abacavir	y		9/22/09
Medication	allopurinol	y		9/1/11
Medication	aminosalicylate derivatives	y	Derived	9/1/11
Medication	amiodarone	y		9/1/11
Medication	anthracycline chemotherapy	y	Derived	9/1/11
Medication	antiarrhythmics	y	Derived	9/1/11
Medication	antidepressants	y	Derived	9/1/11
Medication	antipyrine	y		9/1/11
Medication	antiretrovirals	y	Derived	9/1/11
Medication	apo B-lowering treatment	y		9/22/09
Medication	Aripiprazole	y		9/1/11
Medication	Arsenic Trioxide	y		9/1/11
Medication	Atazanavir Sulfate	y		9/1/11
Medication	atomoxetine	y		9/22/09
Medication	Atorvastatin	y		9/1/11
Medication	Azathioprine	y		9/1/11
Medication	Busulfan	y		9/1/11
Medication	Capecitabine	y		9/1/11

Data element category	Data element	y/n	Derived	Most recent date evaluated
Medication	carbamazepine	y		9/22/09
Medication	Carvedilol	y		9/1/11
Medication	celecoxib	y		9/22/09
Medication	Cetuximab	y		9/1/11
Medication	Cevimeline	y		9/1/11
Medication	Chloroquine	y		9/1/11
Medication	Cilostazol	y		9/1/11
Medication	Cimetidine	y		9/1/11
Medication	Class IA antiarrhythmic medications	y	Derived	9/1/11
Medication	Class III antiarrhythmic medications	y	Derived	9/1/11
Medication	clopidogrel	y		9/22/09
Medication	Clozapine	y		9/1/11
Medication	codeine	y		9/22/09
Medication	coumadin	y		9/22/09
Medication	CYP1A2 inducer	y	Derived	9/1/11
Medication	CYP1A2 inhibitor	y	Derived	9/1/11
Medication	CYP1A2 substrate	y	Derived	9/1/11
Medication	CYP2C19 inducer	y	Derived	9/1/11
Medication	CYP2C19 inhibitor	y	Derived	9/1/11
Medication	CYP2C19 substrate	y	Derived	9/1/11
Medication	CYP2C8 substrate	y	Derived	9/1/11
Medication	CYP2C9 inducer	y	Derived	9/1/11
Medication	CYP2C9 inhibitor	y	Derived	9/1/11
Medication	CYP2C9 substrate	y	Derived	9/1/11
Medication	CYP2D6 inducer	y	Derived	9/1/11
Medication	CYP2D6 inhibitor	y	Derived	9/1/11
Medication	CYP2D6 substrate	y	Derived	9/1/11
Medication	CYP3A inducer	y	Derived	9/1/11
Medication	CYP3A inhibitor	y	Derived	9/1/11
Medication	CYP3A3/4 inhibitor	y	Derived	9/1/11
Medication	CYP3A4 inducer	y	Derived	9/1/11
Medication	CYP3A4 inhibitor	y	Derived	9/1/11
Medication	CYP3A4 substrate	y	Derived	9/1/11
Medication	cytochrome P450 enzyme substrate	y	Derived	9/1/11
Medication	Dapsone	y		9/1/11
Medication	Dasatinib	y		9/1/11
Medication	delavudin	y		9/1/11
Medication	Depakote ER	y		9/1/11
Medication	Desipramine	y		9/1/11
Medication	Dextromethorphan	y		9/1/11
Medication	Dextromethorphan and Quinidine	y	Derived	9/1/11
Medication	Diazapam	y		9/1/11
Medication	Diazepam	y		9/1/11

Data element category	Data element	y/n	Derived	Most recent date evaluated
Medication	digoxin	y		9/1/11
Medication	donepezil	y		9/1/11
Medication	Doxepin	y		9/1/11
Medication	Drospirenone and Ethinyl Estradiol	y	Derived	9/1/11
Medication	drugs for which actions of prodrugs are mediated by CYP2D6-produced metabolites	y	Derived	9/1/11
Medication	drugs that have a narrow therapeutic index	n	Derived	9/1/11
Medication	drugs that prolong QT interval	n	Derived	9/1/11
Medication	drugs that prolong the QTc interval	n	Derived	9/1/11
Medication	elitex	y		9/22/09
Medication	encainide	y		9/1/11
Medication	Erbitux	y		9/22/09
Medication	Erlotinib	y		9/1/11
Medication	erythromycin	y		9/1/11
Medication	Esomeprazole	y		9/1/11
Medication	flecainide	y		9/1/11
Medication	fluconazole	y		9/22/09
Medication	fluoropyrimindine	y		9/1/11
Medication	Fluorouracil	y		9/1/11
Medication	fluoxetine	y		9/22/09
Medication	Fluoxetine and Olanzapine	y	Derived	9/1/11
Medication	fluoxetine HCL	y		9/22/09
Medication	fluvoxamine	y		9/1/11
Medication	Fulvestrant	y		9/1/11
Medication	galantamine	y		9/1/11
Medication	Gefitinib	y		9/1/11
Medication	gleevec	y		9/22/09
Medication	hydrocodone	y		9/1/11
Medication	hydromorphone	y		9/1/11
Medication	Imatinib	y		9/1/11
Medication	interferon-alpha treatment	y		9/1/11
Medication	irinotecan	y		9/22/09
Medication	isoniazid	y		9/22/09
Medication	Isosorbide and Hydralazine	y	Derived	9/1/11
Medication	Ketoconazole	y		9/1/11
Medication	Lapatinib	y		9/1/11
Medication	lenalidomide	y		9/22/09
Medication	leucovorin (LV)	y		9/1/11
Medication	lipid-lowering medications	y		9/22/09
Medication	lipitor	y		9/22/09
Medication	major drug metabolizing CYP enzyme substrates	n	Derived	9/1/11
Medication	Maraviroc	y		9/1/11
Medication	Mercaptopurine	y		9/1/11

Data element category	Data element	y/n	Derived	Most recent date evaluated
Medication	mesalazine	y		9/1/11
Medication	Metoprolol	y		9/1/11
Medication	mexiletine	y		9/1/11
Medication	morphine	y		9/22/09
Medication	Nelfinavir	y		9/1/11
Medication	neuroleptics	y	Derived	9/1/11
Medication	Nilotinib	y		9/1/11
Medication	olsalazine	y		9/1/11
Medication	Omeprazole	y		9/1/11
Medication	other drugs	y	Derived	9/1/11
Medication	Oxaliplatin	y		9/1/11
Medication	P450 inhibitor	y	Derived	9/1/11
Medication	Panitumumab	y		9/1/11
Medication	Pantoprazole	y		9/1/11
Medication	Paroxetine	y		9/1/11
Medication	Peginterferon alfa-2b	y		9/1/11
Medication	phenothiazines	y	Derived	9/1/11
Medication	pindolol	y		9/1/11
Medication	polycyclic antidepressants	n		9/1/11
Medication	prasugrel	y		9/22/09
Medication	primaquine	y		9/22/09
Medication	Propafenone	y		9/1/11
Medication	Propranolol	y		9/1/11
Medication	Quinidine	y		9/1/11
Medication	Rabeprazole	y		9/1/11
Medication	Rasburicase	y		9/1/11
Medication	retinoid and anthracycline chemotherapy	y	Derived	9/1/11
Medication	revlimid	y		9/22/09
Medication	Rifampin, isoniazid, and pyrazinamide	y	Derived	9/1/11
Medication	Risperidone	y		9/1/11
Medication	risperidone	y		9/1/11
Medication	ritonavir	y		9/1/11
Medication	Rituximab	y		9/1/11
Medication	saquinavir	y		9/1/11
Medication	selective seratonin reuptake inhibitor (SSRI)	y	Derived	9/22/11
Medication	selezentry	y		9/22/09
Medication	sertraline	y		9/1/11
Medication	Sodium Phenylacetate and Sodium Benzoate	y	Derived	9/1/11
Medication	Sodium Phenylbutyrate	y		9/1/11
Medication	sprycel	y		9/22/09

Data element category	Data element	y/n	Derived	Most recent date evaluated
Medication	strattera	y		9/22/09
Medication	sulphasalazine	y		9/1/11
Medication	Tamoxifen	y		9/1/11
Medication	Telaprevir	y		9/1/11
Medication	Terbinafine	y		9/1/11
Medication	Tetrabenazine	y		9/1/11
Medication	Thioguanine	y		9/1/11
Medication	thioridazine	y		9/22/09
Medication	Timolol	y		9/1/11
Medication	Tiotropium	y		9/1/11
Medication	Tolterodine	y		9/1/11
Medication	Tositumomab	y		9/1/11
Medication	TPMT inhibitor	n	Derived	9/1/11
Medication	Tramadol and Acetominophen	y	Derived	9/1/11
Medication	trastuzumab	y		9/22/09
Medication	Tretinoin	y		9/1/11
Medication	tretionin	y		9/22/09
Medication	tricyclic antidepressants	y	Derived	9/22/11
Medication	Type 1C antiarrhythmics	y	Derived	9/1/11
Medication	UGT1A1 substrate	n	Derived	9/1/11
Medication	Valproic acid	y		9/1/11
Medication	vectibix	y		9/22/09
Medication	Venlafaxine	y		9/1/11
Medication	Venlafazine XR	y		9/1/11
Medication	voriconazole	y		9/22/09
Medication	warfarin	y		9/22/09
Medication	xeloda	y		9/22/09
Medication	ziagen	y		9/22/09
Medication	anthracycline chemotherapy	y		9/22/09
Medication	chemotherapy regimen	y		9/22/09
Medication	Maraviroc	y		9/22/09
Procedure	(blood) transfusion	y		9/1/11
Procedure	percutaneous coronary intervention	y		9/1/11
Procedure	resection	n		9/22/09
Procedure	stem cell transplant	y		9/1/11

APPENDIX 5: AVAILABILITY OF DATA ELEMENTS FOR APPROXIMATE DECISION SUPPORT RULES

FDA Drug label	Rule IDs, no derivation needed[Ŧ]	Rule IDs, simple derivation needed[Ŧ]	Rule IDs, complex derivation needed[Ŧ]	Other Rule IDs[Ŧ]
Abacavir	45 4, 45 5	45 1, 45 2, 45 3, 45,6, 45 7		
Aripiprazole	12 3,12 4,12 9,12 10,12 11,12 12,12 13,12 14,12 15	12 1,12 2,12 5,12,6,12 7, 12 8,12 16,12 17,12 18,		
Arsenic Trioxide		13 1	13 2	
Atomoxetine		46 3	46 1,46 2,46 4,46 5,46 6, 46 7,46 8	
Atorvastatin				47 1,47 2,47 3,47 4,47 5, 47 6
Azathioprine				
Busulfan		48 1		
Capecitabine		3 2		3 1
Carbamazepine		49 1,49 2,49 11,49 12,49 13,49 14,49 15		49 3,49 4,49 5,49 6,49 7, 49 8,49 9,49 10
Carvedilol		4 1,4 2,4 3,4 4,4 5		4 6
Celecoxib	50 8	50 1,50 2,50 3,50 4,50 5, 50 6,50 7		
Cetuximab (1)				52 1,52 2,52 3
Cetuximab (2)*	14 3	14 4		14 1,14 2
Cevimeline	15 1,15 4	15 2,15 3		
Chloroquine		67 1		
Clopidogrel	5 1,5 15,5 4	5 6,5 7,5 8,5 9,5 10,5 16		5 12,5 13,5 14,5 15,5 17, 5 18,5 2,5 3,5 5
Clozapine	16 1	16 2,16 3,16 4,16 5,16 6, 16 7		
Codine sulfate		53 1,53 2,53 3,53 4		
Dapsone	17 3,17 8,17 9	17 5,17 7,17 10	17 2,17 4	17 6,17 11
Dasatinib		54 1		54 2
Dextromethorphan and Quinidine	18 4,18 5,18 6,18 14,18 15,18 16,18 17,18 18,18 19,18 21,18 22,18 25	18 2,18 3,18 7,18 10,18 11,18 12,18 13,18 20,18 23,18 26,18 27	18 1,18 9	18 8
Diazepam	19 1	19 2,19 3,19 4,19 5		
Doxepin	20 1,20 3,20 4	20 2,20 5,20 6,20 7	20 8	
Drospirenone and Ethinyl Estradiol	21 1,21 2			
Erlotinib				
Esomeprazole	22 2,22 3,22 4,22 9,22 10,22 11,22 12,22 13,22 14, 22 15	22 1,22 5,22 6,22 7,22 8		22 16
Fluorouracil	68 2	68 1,68 3,68 4,68 6,68 7, 68 8		68 5,68 9
Fluoxetine and Olanzapine	23 1,23 11,23 12,23 13,23 3 3,23 4,23 5,23 9,23 10	23 2,23 6,23 7,23 8,23 14 ,23 15,		
Fluoxetine HCL	55 2,55 5	55 1,55 3,55 4		

FDA Drug label	Rule IDs, no derivation needed[Ŧ]	Rule IDs, simple derivation needed[Ŧ]	Rule IDs, complex derivation needed[Ŧ]	Other Rule IDs[Ŧ]
Fulvestrant	69.1			69.2
Gefitinib	24.1,24.2,24.3			
Imatinib (1)		56.1,56.2,56.3,56.4		
Imatinib (2)*		25.1,25.4,25.8,25.9,25.10,25.12		25.2,25.3,25.5,25.6,25.7,25.11,25.13,25.14,25.15
Imatinib (3)*			70.1,70.2	
Imatinib (4)*	71.1,71.2,71.3	71.4,71.5,71.6,71.7		
Irinotecan	6.3,6.15	6.1,6.2,6.4,6.5,6.6,6.7,6.8,6.9,6.10,6.11,6.12,6.13,6.14		
Isosorbide and Hydralazine	26.2			26.1
Lapatinib	27.1	27.2		
Lenalidomide	57.4,57.2,57.3			57.1
Maraviroc	58.1		58.3	58.2
Mercaptopurine	1.1,1.2,1.5,1.7,1.11,1.19,1.26	1.3,1.4,1.6,1.8,1.9,1.12,1.14,1.15,1.16,1.17,1.18,1.20,1.21,1.22,1.23,1.24,1.25		1.10,1.13
Metoprolol	11.5,11.6,11.7	11.1,11.2,11.4,11.8		11.3
Nelfinavir	28.1,28.2	28.3,28.4,28.5,28.6		
Nilotinib (1)*	51.6	51.15,51.16,51.17,51.18		51.1,51.2,51.3,51.4,51.5,51.7,51.8,51.9,51.10,51.11,51.12,51.13,51.14
Nilotinib (2)		7.1,7.2,7.3		
Panitumumab (1)*	29.5,29.9,29.10,29.11,29.12,29.13,29.14	29.6,29.7		29.1,29.2,29.3,29.8
Panitumumab (2)	59.1	29.4		
Peginterferon alfa-2b				
Prasugrel		60.1		
Primaquine		61.1,61.4		61.2,61.3
Propafenone	8.3,8.4,8.10,8.11,8.12,8.13,8.20	8.1,8.2,8.5,8.6,8.7,8.8,8.9,8.14,8.15,8.16,8.17,8.18,8.19		
Propranolol	9.1	9.2,9.3,9.4,9.5,9.6		
Protriptyline	30.1,30.2,30.9	30.3,30.4,30.5,30.6,30.7,30.8,30.10,30.11,30.12		
Quinidine	31.7	31.4,31.5,31.6,31.8		31.1,31.2,31.3
Rabeprazole		32.4,32.5		32.1,32.2,32.3,32.6
Rasburicase		62.1,62.2,62.3		
Rifampin, isoniazid, and pyrazinamide	63.3,63.4	63.1,63.2		
Risperidone	75.1,75.5,75.6,75.7,75.8	75.2,75.3,75.4,75.9,75.10,75.11,75.12,75.13,75.14		
Sodium Phenylacetate and Sodium Benzoate	33.1			33.2,33.3,33.4,33.5

FDA Drug label	Rule IDs, no derivation needed[Ŧ]	Rule IDs, simple derivation needed[Ŧ]	Rule IDs, complex derivation needed[Ŧ]	Other Rule IDs[Ŧ]
Sodium Phenylbutyrate				34 1,34 2,34 3,34 4,34 5, 34 6,34 7,34 8,34 9,34 10 ,34 11,34 12,34 13,34 14, 34 15
Tamoxifen	35 4,35 5	35 1,35 2,35 3,35 6,35 7		
Telaprevir	73 1			73 2
Terbinafine	26 1,36 2	36 3,36 4,36 5,36 6		
Tetrabenazine	37 1,37 2,37 3,37 4,37 5, 37 7,37 9,37 10,37 14,37 16,37 19	37 6,37 8,37 12,37 13,37 15,37 17,37 18,37 20,37 21,37 22		37 11
Thioguanine	2 3,2 6,2 9	2 1,2 2,2 5,2 7,2 8		2 4
Thioridazine		38 1,38 3,38 4,38 5,38 6, 38 7,38 8		38 2
Timolol	39 1			
Tiotropium	40 1,40 2			
Tolterodine	41 1,41 4,41 5,41 2	41 3,41 8,41 9	41 6,41 7	
Tositumomab	72 1,72 2,72 3,72 4			72 5,72 6
Tramadol and Acetominophen	42 1,42 6	42 2,42 3,42 4,42 5,42 7		
Trastuzumab	64 1	64 2,64 3,64 6,64 7		64 4,64 5
Tretinoin	65 3	65 1,65 2		
Valproic acid		43 1		
Venlafaxine	44 3,44 6,44 7	44 1,44 2,44 4,44 5		
Voriconazole	66 2,66 3,66 4	66 1		
Warfarin (1)	10 2,10 4,10 5			10 1,10 3,10 6,10 7
Warfarin (1)(2)	74 6,74 7			74 1,74 2,74 3,74 4,74 5
Warfarin (2)	73 1,73 3	73 2,73 4		

[Ŧ]See

APPENDIX 6: APROXIMATE PHARMACOGENOMICS DECISION SUPPORT RULE PATTERN CLASSIFICATIONS LEGEND

Class ID	Pre condition (IF statement)	Post condition (THEN statement)	Rule IDs[Ŧ]
1	drug	test_interpretation	23 4
2	drug	patient_communications	45 4, 17 8
3	drug	pharmacological_activity_with_involvement_of_gene/protein	12 13, 12 14, 13 1, 4 3, 14 3, 15 1, 15 4, 5 1, 6 1,18 25, 20 1, 21 1, 22 13, 22 2, 22 3, 22 4, 22 9, 68 2, 23 12, 23 13, 23 3, 23 5, 69 1, 24 1, 24 3, 26 2, 27 1, 1 1, 28 1, 28 2, 29 11, 29 12, 29 9, 29 10 , 8 13, 8 20 , 9 1, 32 13, 32 7, 36 1, 36 2, 37 2, 37 3, 37 4, 37 5, 40 1, 40 2, 41 1, 72 1, 72 2, 72 3, 72 4, 42 1, 44 6, 73 1, 73 3, 11 5
4	drug	probability/frequency_of_having_variants_in_population	55 5, 1 2, 41 2
5	drug	recommended_testing	45 5, 17 1, 17 3, 17 9, 58 1, 29 5, 37 14, 37 19, 37 7, 37 10 , 64 1
6	drug	study_clinical_outcomes	24 2, 51 6, 7 3, 29 13, 29 14, 35 4, 35 5, 37 1
7	drug	testing_is_available/test use	5 15, 5 4, 6 15, 1 26, 1 5, 1 7, 73 1, 2 3, 2 6, 2 9
8	drug	toxicity/complications/change_in_pharmacological_activity	18 4, 18 7, 19 1, 20 3, 20 4, 21 2, 31 7, 37 16, 66 2
9	drug + current_condition/demographic_data/history_of_condition/history_of_meds	associated_clinical_outcomes	2 4
10	drug + current_condition/demographic_data/history_of_condition/history_of_meds	pharmacological_activity_with_involvement_of_gene/protein	69 2, 29 8
11	drug + current_condition/demographic_data/history_of_condition/history_of_meds	probability/frequency_of_clinical_outcome	68 5
12	drug + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_testing	18 8, 1 13, 1 10 , 65 3
13	drug + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_treatment_protocol	68 9
14	drug + genotype/phenotype/family_history	associated_clinical_outcomes	1 23
15	drug + genotype/phenotype/family_history	patient_communications	53 4
16	drug + genotype/phenotype/family_history	pharmacological_activity_with_involvement_of_gene/protein	6 1, 26 1, 8 19, 73 2
17	drug + genotype/phenotype/family_history	probability/frequency_of_clinical_outcome	6 4, 1 21, 1 22, 1 20
18	drug + genotype/phenotype/family_history	recommend_use_caution	1 17
19	drug +	recommended_testing	29 6, 62 2

Class ID	Pre condition (IF statement)	Post condition (THEN statement)	Rule IDs[₮]
	genotype/phenotype/family_history		
20	drug + genotype/phenotype/family_history	recommended_treatment_protocol	47 6, 49 12, 49 13, 50 2, 50 6, 50 7, 14 2, 15 3, 67 1, 5 5, 53 2, 68 1, 68 4, 6 14, 1 24, 1 25, 1 8, 51 18, 61 4, 8 17, 8 9, 31 5, 62 3, 37 15, 37 8, 37 20 , 2 2, 38 3, 38 8, 74 3, 74 4, 73 4
21	drug + genotype/phenotype/family_history	study_clinical_outcomes	6 5, 6 6, 6 7, 8 18, 32 1, 32 18, 32 3, 32 9, 33 5, 73 2, 10 6, 10 7, 74 5
22	drug + genotype/phenotype/family_history	test_interpretation	5 14, 29 7, 32 6, 2 5
23	drug + genotype/phenotype/family_history	toxicity/complications/change_in_pharmacological_activity	45 1, 45 2, 45 3, 12 17, 12 18, 46 1, 46 2, 47 1, 3 2, 49 2, 4 2, 4 4, 4 5, 4 6, 50 3, 14 1, 14 4, 5 16, 5 18, 5 2, 16 3, 17 5, 17 7, 18 2, 18 23, 18 20 , 20 8, 22 16, 68 3, 68 6, 68 7, 68 8, 23 14, 55 3, 55 4, 6 2, 1 3, 1 4, 1 6, 1 9, 61 1, 8 1, 8 14, 8 15, 8 16, 8 6, 9 2, 30 3, 31 4, 31 6, 32 16, 62 1, 63 1, 63 2, 37 6, 2 1, 2 8, 38 4, 41 3, 41 8, 41 9, 42 2, 10 3, 10 1
24	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	patient_communications	57 4
25	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	pharmacological_activity_with_involvement_of_gene/protein	25 12, 27 2, 51 16, 51 17
26	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	probability/frequency_of_clinical_outcome	51 4, 29 2, 34 4, 34 5, 34 6
27	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_testing	45 7, 45 6, 17 11, 17 10 , 65 2
28	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_treatment_protocol	46 8, 47 4, 47 5, 3 1, 50 4, 50 5, 52 2, 52 3, 17 2, 17 4, 54 1, 54 2, 56 2, 56 4, 25 4, 25 6, 25 7, 71 2, 71 4, 71 5, 71 6, 71 7, 57 2, 57 3, 51 8, 51 9, 29 4, 59 1, 34 1, 34 11, 34 12, 34 13, 34 14, 34 15, 34 2, 34 3, 34 8, 34 9, 34 10 , 72 5, 72 6, 74 2
29	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	study_clinical_outcomes	5 17, 25 15, 70 2, 51 15, 29 3, 33 2, 33 3, 33 4, 34 7, 35 1, 35 2, 35 3, 35 6, 35 7
30	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	toxicity/complications/change_in_pharmacological_activity	48 1, 52 1, 17 6, 25 8, 25 9, 25 10 , 33 1
31	drug + genotype/phenotype/family_history + current_condition/demographic_data/hi	recommended_treatment_protocol	56 3, 25 5, 71 3

Class ID	Pre condition (IF statement)	Post condition (THEN statement)	Rule IDs[Ŧ]
	story_of_condition/history_of_meds + inpatient/outpatient_procedure		
32	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds + inpatient/outpatient_procedure	study_clinical_outcomes	25 11, 25 13, 25 14
33	drug + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds + inpatient/outpatient_procedure	toxicity/complications/change_in_pharmacological_activity	5 3
34	drug + genotype/phenotype/family_history + population	probability/frequency_of_having_variants_in_population	5 12, 5 13
35	drug + population	probability/frequency_of_having_variants_in_population	63 4, 61 3, 12 15, 46 3, 49 11, 49 6, 49 7, 49 8, 49 9, 49 10 , 18 5, 18 6, 22 14, 22 15, 11 6, 11 7, 61 2, 8 3, 8 4, 30 1, 30 2, 32 14, 32 15, 32 4, 32 5, 63 3, 66 3, 66 4, 10 2, 10 4, 10 5
36	drug + population	recommended_testing	49 3, 49 4, 49 5
37	drug + population	testing_is_available/test use	31 1, 31 2
38	drug + population	toxicity/complications/change_in_pharmacological_activity	74 6, 74 7
39	drug1 + drug2/current_med_list	associated_clinical_outcomes	60 1, 39 1
40	drug1 + drug2/current_med_list	pharmacological_activity_with_involvement_of_gene/protein	18 14, 18 21
41	drug1 + drug2/current_med_list	probability/frequency_of_clinical_outcome	44 3
42	drug1 + drug2/current_med_list	recommend_use_caution	16 2, 16 6, 16 7, 18 26, 23 6, 55 1, 1 19, 9 5, 30 7, 30 8, 31 8, 36 3, 2 7, 44 5
43	drug1 + drug2/current_med_list	recommended_treatment_protocol	12 12, 12 4, 12 5, 12 6, 12 10 , 46 7, 50 8, 5 6, 5 9, 16 5, 53 3, 18 1, 18 11, 18 12, 18 13, 18 16, 18 17, 18 27, 18 9, 22 12, 22 7, 23 7, 23 8, 51 11, 51 10 , 8 12, 8 2, 8 7, 30 11, 30 12, 30 9, 30 10 , 37 17, 37 21, 37 22, 38 1, 38 2, 38 7, 41 5, 44 2
44	drug1 + drug2/current_med_list	study_clinical_outcomes	51 12, 42 3
45	drug1 + drug2/current_med_list	testing_is_available/test use	31 3
46	drug1 + drug2/current_med_list	toxicity/complications/change_in_pharmacological_activity	12 1, 12 11, 12 2, 12 3, 12 7, 12 8, 12 9, 4 1, 50 1, 15 2, 5 11, 5 7, 5 8, 5 10 , 16 4, 53 1, 18 15, 18 18, 18 22, 18 3, 18 10 , 19 2, 19 3, 19 4, 19 5, 20 2, 20 5, 20 6, 22 1, 22 11, 22 5, 22 6, 22 10 , 23 1, 23 11, 23 15, 23 2, 23 9, 23 10 , 55 2, 6 3, 1 11, 1 12, 11 1, 11 2, 28 3, 28 4, 28 5, 28 6, 7 1, 7 2, 8 5, 8 8, 8 10 , 9 3, 9 4, 9 6, 30 4, 30 5, 30 6, 32 11, 32 12, 32 17, 32 19, 32 8, 32 10 , 32 20 , 36 4,

Class ID	Pre condition (IF statement)	Post condition (THEN statement)	Rule IDs[Ŧ]
			36 5, 36 6, 37 18, 37 9, 38 5, 38 6, 41 4, 41 6, 41 7, 42 4, 42 5, 42 6, 42 7, 44 1, 44 4, 44 7, 66 1
47	drug1 + drug2/current_med_list + current condition/demographic_data/history_of_condition/history_of_meds	pharmacological_activity_with_involvement_of_gene/protein	18 19
48	drug1 + drug2/current_med_list + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_treatment_protocol	46 4, 20 7, 22 8, 37 11, 37 12, 43 1
49	drug1 + drug2/current_med_list + current_condition/demographic_data/history_of_condition/history_of_meds	toxicity/complications/change_in_pharmacological_activity	37 13
50	drug1 + drug2/current_med_list + genotype/phenotype/family_history	pharmacological_activity_with_involvement_of_gene/protein	11,3
51	drug1 + drug2/current_med_list + genotype/phenotype/family_history	recommended_treatment_protocol	46 5
52	drug1 + drug2/current_med_list + genotype/phenotype/family_history	study_clinical_outcomes	6 11, 6 12, 6 13, 6 8, 6 9, 6 10 , 8 11, 32 2
53	drug1 + drug2/current_med_list + genotype/phenotype/family_history	toxicity/complications/change_in_pharmacological_activity	12 16, 11 8, 74 1
54	drug1 + drug2/current_med_list + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	pharmacological_activity_with_involvement_of_gene/protein	11 4
55	drug1 + drug2/current_med_list + genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_treatment_protocol	46 6, 51 13, 51 14
56	genotype/phenotype/family_history	test_interpretation	49 14, 49 15, 1 14, 1 15
57	genotype/phenotype/family_history	testing_is_available/test use	1 16
58	genotype/phenotype/family_history	toxicity/complications/change_in_pharmacological_activity	49 1
59	genotype/phenotype/family_history + current_condition/demographic_data/history_of_condition/history_of_meds	recommended_treatment_protocol	13 2, 56 1, 25 1, 25 3, 70 1, 71 1, 57 1, 58 2, 58 3, 51 1, 51 2, 51 3, 51 5, 51 7, 29 1, 64 2, 64 3, 64 4, 64 5, 65 1, 25 2, 47 2, 47 3
60	genotype/phenotype/family_history + inpatient/outpatient_procedure	recommend_use_caution	1,18
61	other		64 6, 64 7

[Ŧ]See Appendix 1

APPENDIX 7: PHARMACOGENOMICS DECISION SUPPORT RULE PATTERN REQUIREMENTS

Taxonomy elements	PGx rule classes[Δ]	Strategy for class assignment
Triggers		
Order entered	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37,38,39,40,41,42,43,44,45,46,47,48,49, 50,51,52,53,54,55,57,60	drug IF statement + 2 testing IF statements (57 & 60)
Lab result stored	14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29, 30,31,32,33,34,50,51,52,53,54,55,56,57,58,59,60	genotype IF statement
Outpatient encounter	31,32,33,60	procedure IF statement
User request (no automatic trigger but user requests)	1,2,3,4,6,7,8,9,10,11,14,15,16,17,21,23,24,25,26,29,30,32,33,34,35,37,38,39,40,41,44,45,46,47,49,50,52,53,54,57,58	THEN statements that don't include "recommend" or "interpretation"
Time		no clear classes fit
Admission	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	current_condition IF statement
Problem entered	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	current_condition IF statement
Enter allergies		no clear classes that fit
Enter weight		no clear classes that fit
Intervention		
Notify	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37,38,39,40,41,42,43,44,45,46,47,48,49, 50,51,52,53, 54,55,56,57,58,59,60,61	All rules (note offered choices are children of "notify"
Log		no clear classes that fit
Provide defaults/ pick lists	5,7,12,13,19,20,27,28,31,36,37,43,45,48,51, 55,57,59	THEN statement includes "recommend_testing," "recommend_treatment" or "testing_is_available"
Show Guidelines	5,12,13,19,20,27,28,31,36,42,43,48,51,55,59	THEN statement includes "recommend_testing," "recommend_treatment"
Collect free text	5,12,13,19,20,27,28,31,36,42,43,48,51,55,59	THEN statement includes "recommend_testing," "recommend_treatment"
Get approval		no clear classes that fit
Show data entry template		no clear classes that fit
Offered choice		
Write order	5,7,12,13,19,20,27,28,31,36,37,43,45,48,51, 55,57,59	THEN statement includes "recommend_testing," "recommend_treatment" or "testing_is_available"
Defer warning		no clear classes that fit
Override rule/ keep order	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37,38,39,40,41,42,43,44,45,46,47,48,49, 50,51,52,53,54,55,57,60	drug IF statement (without patient_communication THEN statements) + 2 testing IF statements (57 & 60)
Cancel existing order	1,3,4,5,6,7,8,9,10,11,12,13,14,16,17,18,19, 20, 21,22,23,25,26,27,28,29,30,31,32,33,34,35,36,	drug IF statement (without patient_communication THEN

	37,38,39,40,41,42,43,44,45,46,47,48,49,50,51, 52,53, 54,55	statements)
Cancel current order	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37,38,39,40,41,42,43,44,45,46,47,48,49, 50,51,52,53,54,55,57,60	drug IF statement (without patient_communication THEN statements) + 2 testing IF statements (57 & 60)
Edit current order	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37,38,39,40,41,42,43,44,45,46,47,48,49, 50,51,52,53,54,55,57,60	drug IF statement (without patient_communication THEN statements) + 2 testing IF statements (57 & 60)
Edit existing order	1,3,4,5,6,7,8,9,10,11,12,13,14,16,17,18,19, 20, 21,22,23,25,26,27,28,29,30,31,32,33,34,35,36, 37,38,39,40,41,42,43,44,45,46,47,48,49,50,51, 52,53, 54,55	drug IF statement (without patient_communication THEN statements)
Set allergies		no clear classes that fit
Write letter	15,17,22,23,24,26,30,33,34,53,56,58	IF statement includes genotype & THEN statement is test_interpretation, patient_communications, probability/frequency_of_clinical _outcome, or toxicity/complications/change_in_ pharmacological_activity
Write note	15,17,22,23,24,26,30,33,34,53,56,58	IF statement includes genotype & THEN statement is test_interpretation, patient_communications, probability/frequency_of_clinical _outcome, or toxicity/complications/change_in_ pharmacological_activity
Edit problem list		no clear classes that fit
***Enter weight**		no clear classes that fit
***Enter height**		no clear classes that fit
***Enter age**		no clear classes that fit
***Enter lab value status**	2	1 rule with patient_communications THEN statement
Data element		
Lab result/ observation *A single genomic marker from a single gene test result	14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29, 30,31,32,33,34,50,51,52,53,54,55,56,57,58,59,60	genotype IF statement
Lab result/ observation *A single genomic marker filtered from high throughput test results	14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29, 30,31,32,33,34,50,51,52,53,54,55,56,57,58,59,60	genotype IF statement
Lab result/ observation *Multiple genomic markers from multiple gene test results or high throughput test results.		no clear classes that fit
Drug list	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37, 38,39,40,41,42,43,44,45,46,47,48,49, 50, 51,52,53, 54,55	drug IF statement

Hospital Unit	31,32,33,60	procedure IF statement
Diagnosis/Problem	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	current_condition IF statement
Age	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	demographic_data IF statement
Non-drug orders	57,60	2 test order IF statements
Gender	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	demographic_data IF statement
Family history	14,15,16,17,18,19,20,21,22,23,24,25,26,27, 28,29, 30,31,32,33,34,50,51,52,53,54,55,56,57, 58,59,60	family_history IF statement
Allergy list		no clear classes that fit
Weight	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	current_condition or demographic_data IF statement
Surgical history	31,32,33,60	procedure IF statement
Reason for admission		no clear classes that fit
Prior visit types		no clear classes that fit
Race	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	demographic_data IF statement
Patient medical history	9,10,11,12,13,24,25,26,27,28,29,30,31,32, 33,47,48,49,54,55,59	history_of_condition or history_of_meds IF statement
Language		no clear classes that fit
Place of birth	34,35,36,37,38	population IF statement

[Δ]See Appendix 6

APPENDIX 8: OTHER DATA ELEMENTS

FDA Drug label	Other data elements
Abacavir	Previously tolerated Abacavir
Atorvastatin	Received an adequate trial of diet therapy where LDL-C remains >= 190 mg/dL or LDL-C remains >= 160 mg/dL,
	Family history of premature CV,
	Two or more other CVD risk factors are present
Carbamazepine	Genetically at-risk for having HLA-B*1502,
	Of ancestry in populations in which HLA-B*1502 may be present
Carvedilol	Debrisoquin, a marker for CYP2D6 (poor metabolizer)
	Poor metabolizer of S-mephenytoin (deficient in cytochrome P450 2C19)
Dapsone	"at risk",
	Predisposition to increased hemolytic effect with dapsone (e g G6PD deficiency)
Dextromethorphan and Quinidine	At risk of significant toxicity due to quinidine
Fluoxetine and Olanzapine	Has taken Fluoxetine in the previous 5 weeks
Imatinib (2)	Risk factors for cardiac failure,
	Blast crisis,
	Accelerated phase
Imatinib (4)	Demonstrates an insufficient response to therapy,
	Patient has not experienced any adverse drug reactions
Mercaptopurine	Phenotypic testing to determine level of thiopurine nucleotides or TPMT activity in erythrocytes
Nilotinib (1)	Resistant to prior therapy that included imatinib,
	Intolerant to prior therapy that included imatinib
Primaquine	Family history of favism
Propafenone	Grapefruit juice,
	Tobacco smoke
Rasburicase	Higher risk for G6PD deficiency
Risperidone	Drug that reduces the metabolism of risperidone [by CYP2D6] to 9-hydroxyriperidone,
Trastuzumab	Improper assay performance,
	Adjuvant breast cancer
Warfarin (1)(2)	Risk factors for bleeding

APPENDIX 9: RESOURCES CONFIGURED FOR OPENINFOBUTTON MEDICATION ORDER ENTRY CONTEXT

Pharmacogenomics Knowledge Resource Details (Medication order entry context) [F]	Content subsection
Resource CDC Summaries of EGAPP Recommendation Statements (US Centers for Disease Control and Prevention) Base URL http //www cdc gov/genomics/gtesting/EGAPP/recommend/ Concept of interest Irinotecan Subtopic Should UGT1A1 Genotyping Be Used to Predict Response to Irinotecan Chemotherapy? EGAPP Recommendation	Drug Genomic Biomarker Clinical Evidence
Resource PLoS Currents Evidence on Genomic Tests (PLoS Currents Evidence on Genomic Tests [Internet]) Base URL http //www ncbi nlm nih gov/pmc/ Concept of interest Clopidogrel Subtopic Evidence on Genomic Tests - Clopidogrel Concept of interest Mercaptopurine Subtopic Evidence on Genomic Tests - Mercaptopurine Concept of interest Tamoxifen Subtopic Evidence on Genomic Tests - Tamoxifen Concept of interest Thioguanine Subtopic Evidence on Genomic Tests - Thioguanine Concept of interest Warfarin Subtopic Evidence on Genomic Tests - Warfarin	Drug Genomic Biomarker Clinical Evidence
Resource Clinical Pharmacogenetics Implementation Consortium Guidelines (Relling & Klein, 2011) Base URL https //courses washington edu/pgxkb/pdfs/cpic/ *(NOTE URL was active only for this study)* Concept of interest Clopidogrel Subtopic Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy Concept of interest Mercaptopurine Subtopic Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing Concept of interest Thioguanine Subtopic Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing	Drug Genomic Biomarker Clinical Evidence
Resource eMedicine Genomic Medicine Articles (eMedicine Genomic Medicine Articles [Internet]) Base URL http //emedicine medscape com/article/ Concept of interest Clopidogrel Subtopic Clopidogrel Dosing and CYP2C19 Concept of interest Irinotecan Subtopic Irinotecan Toxicity and UGT1A Concept of interest Mercaptopurine Subtopic Azathioprine Metabolism and TPMT Concept of interest Tamoxifen	Drug Genomic Biomarker Clinical Evidence

Pharmacogenomics Knowledge Resource Details (Medication order entry context) [T]	Content subsection
Subtopic Tamoxifen Metabolism and CYP2D6	
Concept of interest Thioguanine	
Subtopic Azathioprine Metabolism and TPMT	
Concept of interest Warfarin	
Subtopic Warfarin Dosing and VKORC1/CYP2C9	
Resource DailyMed {National Library of Medicine (US), DailyMed Web site [database on the Internet]}	FDA Drug Label Resources
Base URL http://dailymed.nlm.nih.gov/dailymed/rxcui.cfm?	
Concept of interest FDA Drug Label (RxCUI used to search for the drug label of any medication)	
Subtopic N/A	
Resource PharmGKB – Clinical PGx (Pharmacogenomics Knowledge Base, PharmGKB)	FDA Drug Label Resources
Base URL http://www.pharmgkb.org/clinical/	
Concept of interest Capecitabine	
Subtopic Pharmacogenomic Information in the Context of the FDA Approved Drug Label	
Concept of interest Carvedilol	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Clopidogrel	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Irinotecan	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Mercaptopurine	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Metoprolol	
Subtopic Pharmacogenomic Information in the Context of the FDA Approved Drug Label	
Concept of interest Nilotinib	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Propafenone	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Tamoxifen	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Thioguanine	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	
Concept of interest Warfarin	
Subtopic Pharmacogenomic Information in the Context of the FDA-Approved Drug Label	

Pharmacogenomics Knowledge Resource Details (Medication order entry context) [Ŧ]	Content subsection
Resource ePKgene (University of Washington, Department of Pharmaceutics)	Metabolism and Pharmacogenetics
Base URL https //courses washington edu/pgxkb/pdfs/cpic/	
Concept of interest Clopidogrel	
Subtopic Clopidogrel Drug Summary	
Concept of interest Irinotecan	
Subtopic Irinotecan Drug Summary	
Concept of interest Tamoxifen	
Subtopic Tamoxifen Drug Summary	
Concept of interest Warfarin	
Subtopic Warfarin Drug Summary	
Resource PharmGKB - Pathways (Pharmacogenomics Knowledge Base, PharmGKB)	Metabolism and Pharmacogenetics
Base URL http //www pharmgkb org/do/serve?objCls=Pathway&objId=	
Concept of interest Capecitabine	
Subtopic Fluoropyrimidine Pathway, Pharmacokinetics	
Concept of interest Clopidogrel	
Subtopic Antiplatelet Drug Clopidogrel Pathway (PK)	
Concept of interest Irinotecan	
Subtopic Irinotecan Pathway, Pharmacokinetics	
Concept of interest Mercaptopurine	
Subtopic Thiopurine Pathway	
Concept of interest Tamoxifen	
Subtopic Anti-estrogen Pathway (Tamoxifen PK)	
Concept of interest Thioguanine	
Subtopic Thiopurine Pathway	
Concept of interest Warfarin	
Subtopic Warfarin Pathway, Pharmacokinetics	
Resource PubMed Clinical Queries – Find Systematic Reviews (US National Library of Medicine)	Search for Articles
Base URL http //www ncbi nlm nih gov/pubmed?	
Concept of interest Clopidogrel	
Subtopic Find Systematic Reviews	
Concept of interest Irinotecan	
Subtopic Find Systematic Reviews	
Concept of interest Mercaptopurine	
Subtopic Find Systematic Reviews	
Concept of interest Metoprolol	
Subtopic Find Systematic Reviews	
Concept of interest Tamoxifen,	
Subtopic Find Systematic Reviews	
Concept of interest Warfarin	
Subtopic Find Systematic Reviews	
Concept of interest Capecitabine	
Subtopic Medical Genetics Search	

Pharmacogenomics Knowledge Resource Details (Medication order entry context) [Ŧ]		Content subsection
Concept of interest	Carvedilol	
Subtopic	Medical Genetics Search	
Concept of interest	Clopidogrel	
Subtopic	Medical Genetics Search	
Concept of interest	Irinotecan	
Subtopic	Medical Genetics Search	
Concept of interest	Mercaptopurine	
Subtopic	Medical Genetics Search	
Concept of interest	Metoprolol	
Subtopic	Medical Genetics Search	
Concept of interest	Nilotinib	
Subtopic	Medical Genetics Search	
Concept of interest	Propafenone	
Subtopic	Medical Genetics Search	
Concept of interest	Tamoxifen	
Subtopic	Medical Genetics Search	
Concept of interest	Thioguanine	
Subtopic	Medical Genetics Search	
Concept of interest	Warfarin	
Subtopic	Medical Genetics Search	

[Ŧ]See Appendix 11 for screenshots of resources

eMedicine: Genomic Medicine Articles [Internet]. Retrieved September 9, 2011 from http://emedicine.medscape.com/genomics/articles

Pharmacogenomics Knowledge Base (PharmGKB) Clinical Pharmacogenomics [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/clinical/index.jsp

Pharmacogenomics Knowledge Base (PharmGKB) Pathways [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/search/browse/pathways.action

PLoS Currents: Evidence on Genomic Tests [Internet]. (2010). Retrieved September 9, 2011 from http://knol.google.com/k/plos/plos-currents-evidence-on-genomic-tests/28qm4w0q65e4w/50

Relling, M. V., & Klein, T. E. (2011). CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*, *89*(3), 464-467.

University of Washington, Department of Laboratory Medicine. UW Online Laboratory Test Guide [Internet]. Retrieved September 9, 2011 from http://menu.labmed.washington.edu/bcard/search.asp

University of Washington, Department of Pharmaceutics. ePKgene, Impact of Genetics on Drug Exposure [Internet]. Retrieved September 9, 2011 from http://www.pharmacogeneticsinfo.org

US Centers for Disease Control and Prevention. CDC Summaries of EGAPP Recommendation Statements [internet resource], last updated January 13, 2011. Retrieved September 9, 2011 from http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/

US National Library of Medicine. DailyMed Web site [database on the Internet]. Retrieved September 9, 2011 from http://dailymed.nlm.nih.gov/dailymed/about.cfm

US National Library of Medicine. PubMed Web site [database on the Internet]. Retrieved September 9, 2011 from http://www.ncbi.nlm.nih.gov/pubmed

APPENDIX 10: RESOURCES CONFIGURED FOR OPENINFOBUTTON LABORATORY REVIEW CONTEXT

Pharmacogenomics Knowledge Resource Details (Laboratory review context)[F]	Category of evidence
Resource ePKgene (University of Washington, Department of Pharmaceutics)	Gene Specific Resources
Base URL https //courses washington edu/pgxkb/images/ *(NOTE URL was active only for this study)*	
Concept of interest CYP2C19	
Subtopic CYP2C19 Gene Summary	
Concept of interest CYP2C9	
Subtopic CYP2C9 Gene Summary	
Concept of interest CYP2D6	
Subtopic CYP2D6 Gene Summary	
Concept of interest UGT1A1	
Subtopic UGT1A1 Gene Summary	
Resource PharmGKB Gene Details (Pharmacogenomics Knowledge Base, PharmGKB)	Gene Specific Resources
Base URL http //www pharmgkb org/search/annotatedGene/	
Concept of interest CYP2C19	
Subtopic Annotated PGx Gene Information for CYP2C19	
Subtopic Important Variant Information for CYP2C19	
Subtopic Important Haplotype Information for CYP2C19	
Concept of interest CYP2C9	
Subtopic Annotated PGx Gene Information for CYP2C9	
Subtopic Important Variant Information for CYP2C9	
Subtopic Important Haplotype Information for CYP2C9	
Concept of interest CYP2D6	
Subtopic Annotated PGx Gene Information for CYP2D6	
Subtopic Important Variant Information for CYP2D6	
Subtopic Important Haplotype Information for CYP2D6	
Concept of interest DPYD	
Subtopic Annotated PGx Gene Information for DPYD	
Subtopic Important Variant Information for DPYD	
Concept of interest TPMT	
Subtopic Annotated PGx Gene Information for TPMT	
Subtopic Important Variant Information for TPMT	
Subtopic Important Haplotype Information for TPMT	
Concept of interest UGT1A1	
Subtopic Annotated PGx Gene Information for UGT1A1	
Subtopic Important Variant Information for UGT1A1	
Subtopic Important Haplotype Information for UGT1A1	
Resource UW Online Laboratory Test Guide (University of Washington, Department of Laboratory Medicine)	Gene Specific Resources
Base URL http //menu labmed washington edu/search/	

Concept of interest	CYP2C19
Subtopic	Cytochrome P450 2C19 Genotype (performed at Mayo)
Concept of interest	CYP2D6
Subtopic	Cytochrome P450 2D6 Genotyping for Tamoxifen Therapy
Concept of interest	TPMT
Subtopic	Thiopurine Methyltransferase, RBC (TPMT)
Concept of interest	UGT1A1
Subtopic	UDP-Glycuronosyl Transferase 1A1 TA Repeat Genotype

[T]See Appendix 11 for screenshots of resources

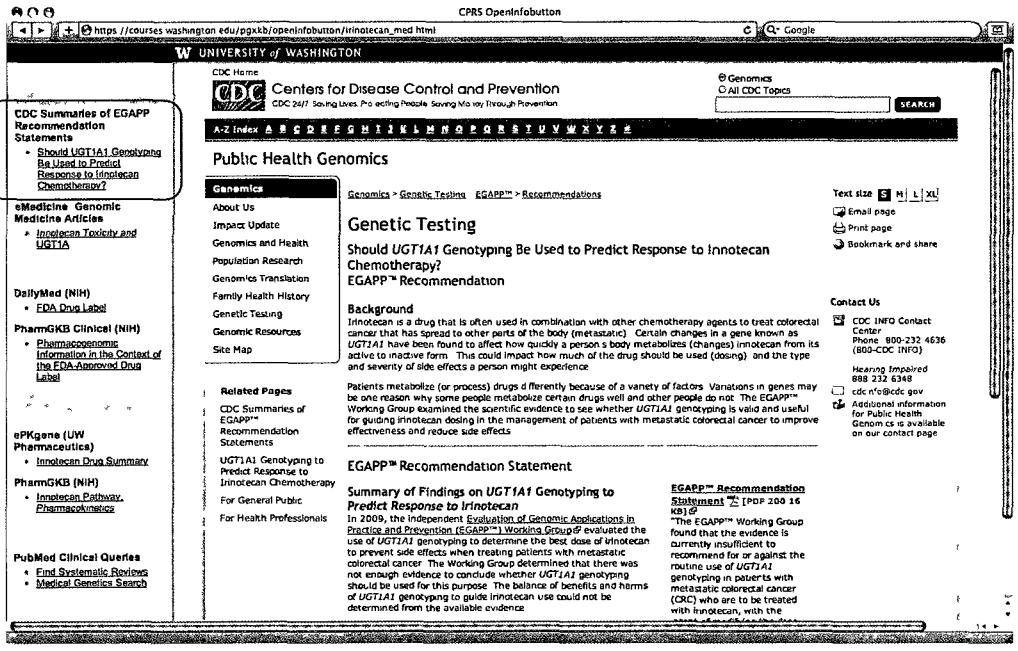
Pharmacogenomics Knowledge Base (PharmGKB) Annotated PGx Genes [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/search/browseVip.action?browseKey=annotatedGenes

University of Washington, Department of Laboratory Medicine. UW Online Laboratory Test Guide [Internet]. Retrieved September 9, 2011 from http://menu.labmed.washington.edu/bcard/search.asp

University of Washington, Department of Pharmaceutics. ePKgene, Impact of Genetics on Drug Exposure [Internet]. Retrieved September 9, 2011 from http://www.pharmacogeneticsinfo.org

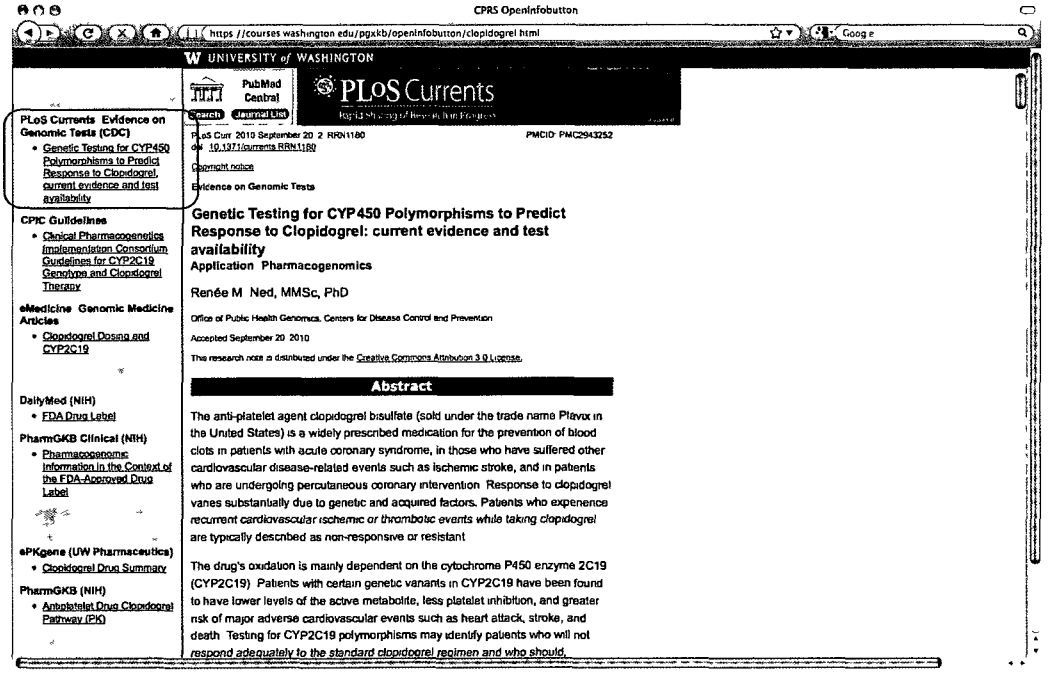
APPENDIX 11. SCREENSHOTS OF RESOURCES CONFIGURED FOR OPENINFOBUTTON

CDC Summaries of EGAPP Recommendation Statements



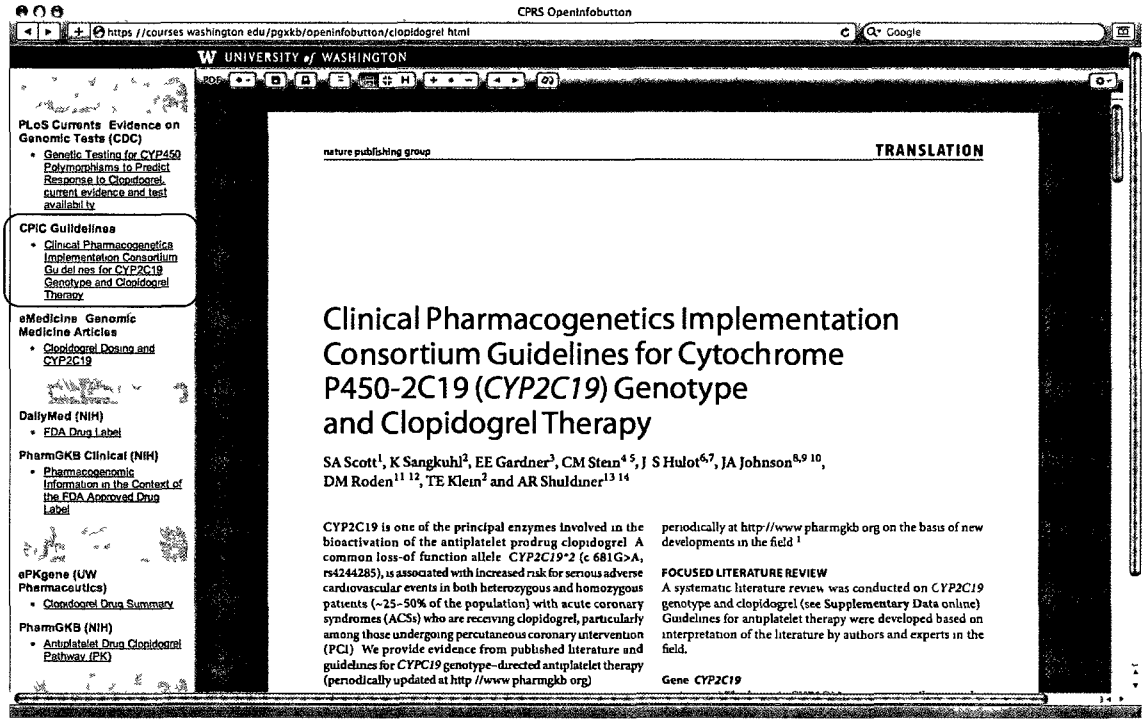
(US Centers for Disease Control and Prevention)

PLoS Currents: Evidence on Genomic Tests



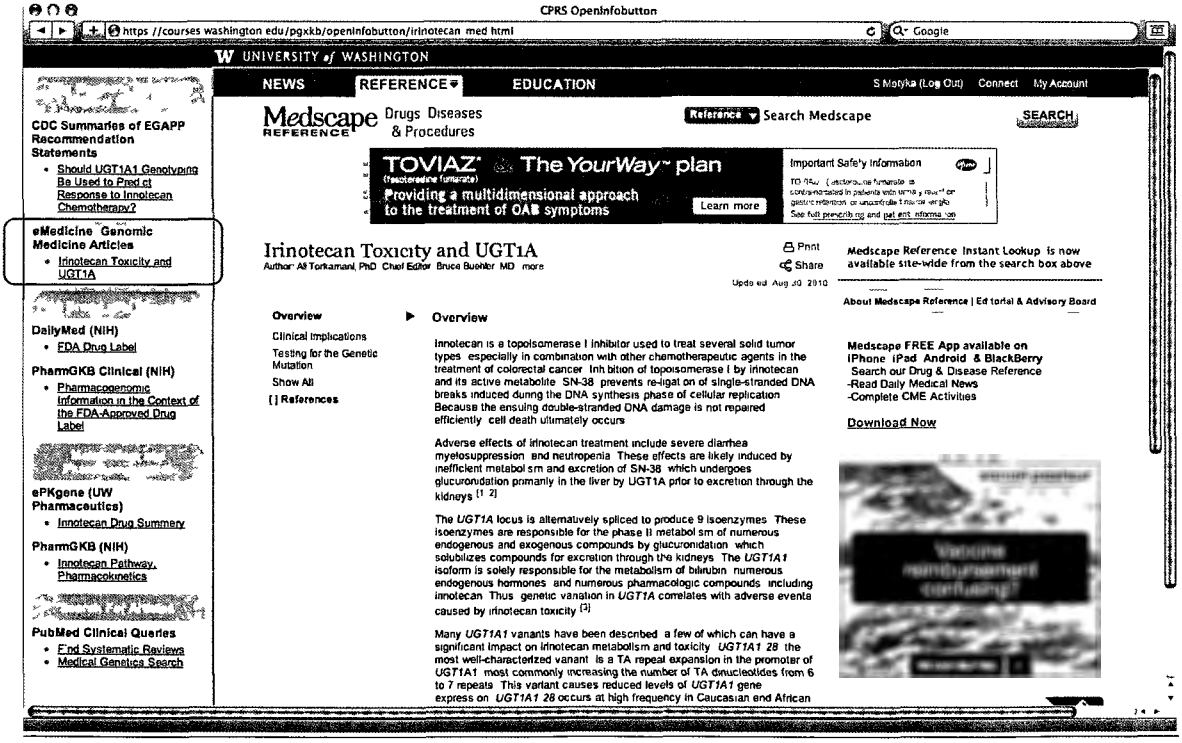
(PLoS Currents: Evidence on Genomic Tests [Internet])

Clinical Pharmacogenetics Implementation Consortium Guidelines



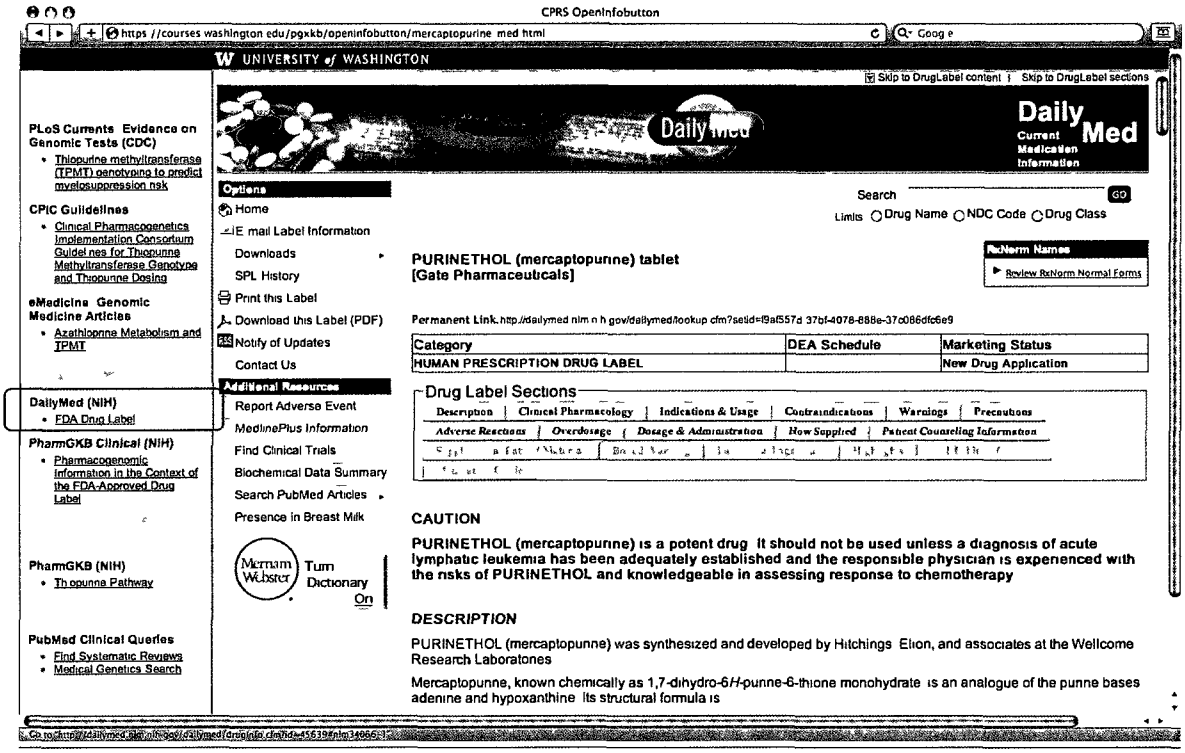
(Relling & Klein, 2011)

eMedicine: Genomic Medicine Articles



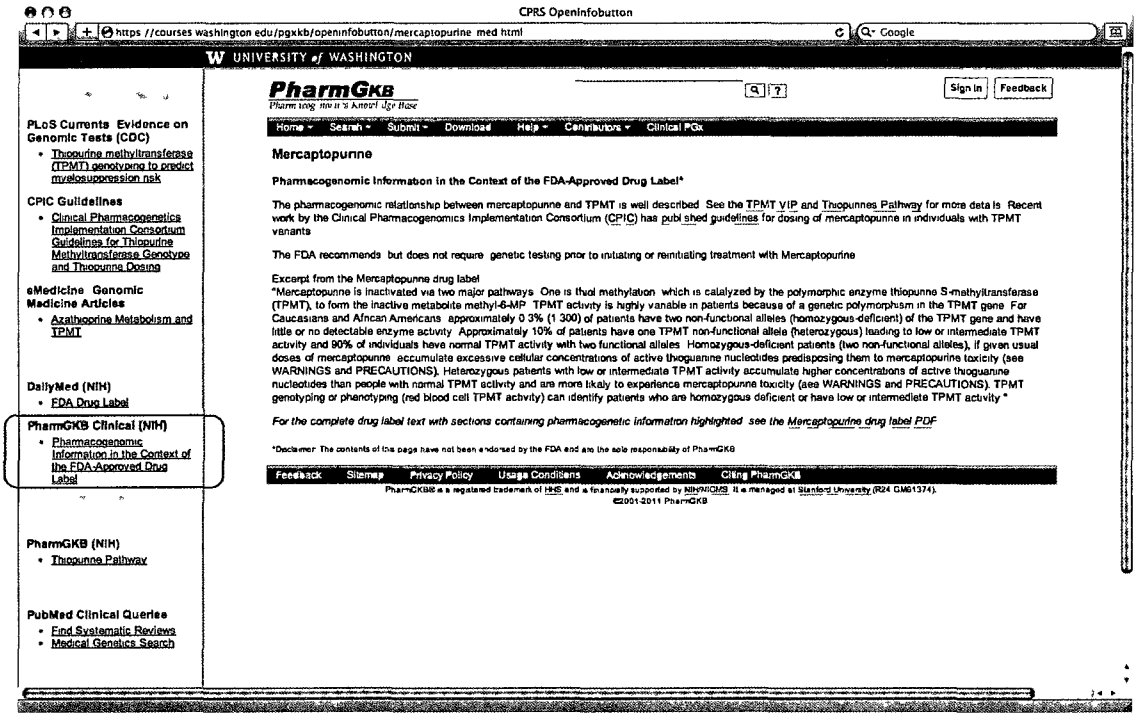
(eMedicine: Genomic Medicine Articles [Internet])

DailyMed



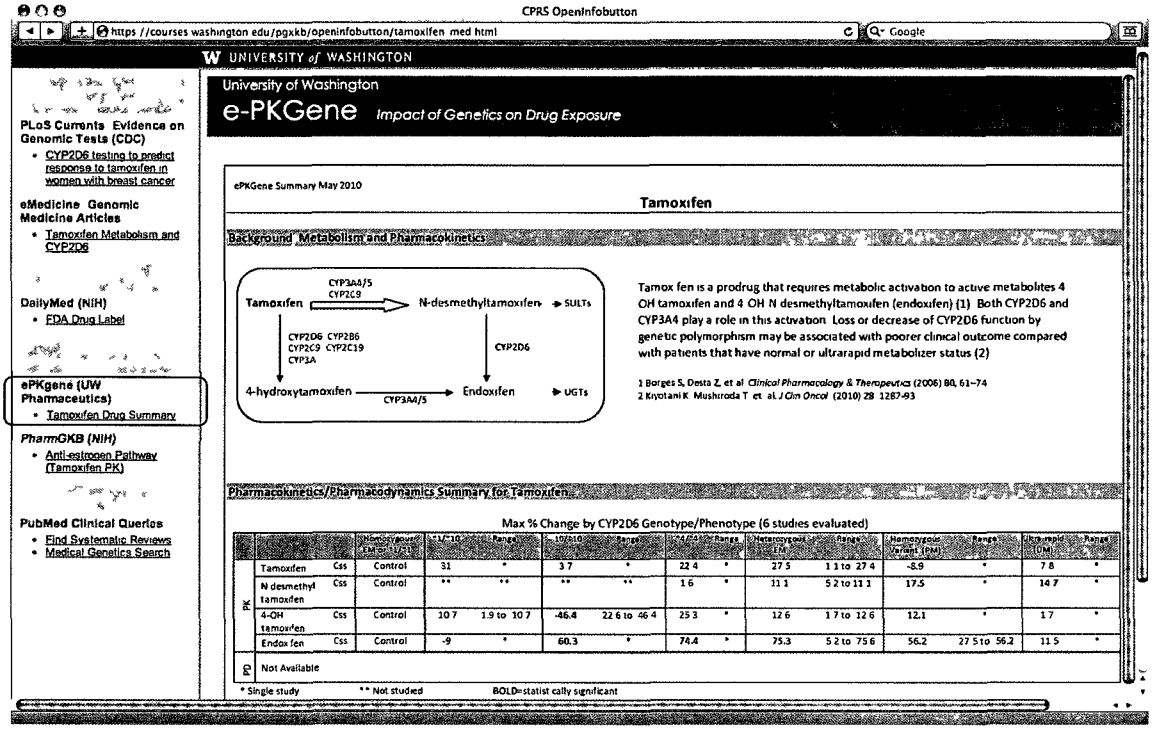
(US National Library of Medicine)

PharmGKB – Clinical PGx



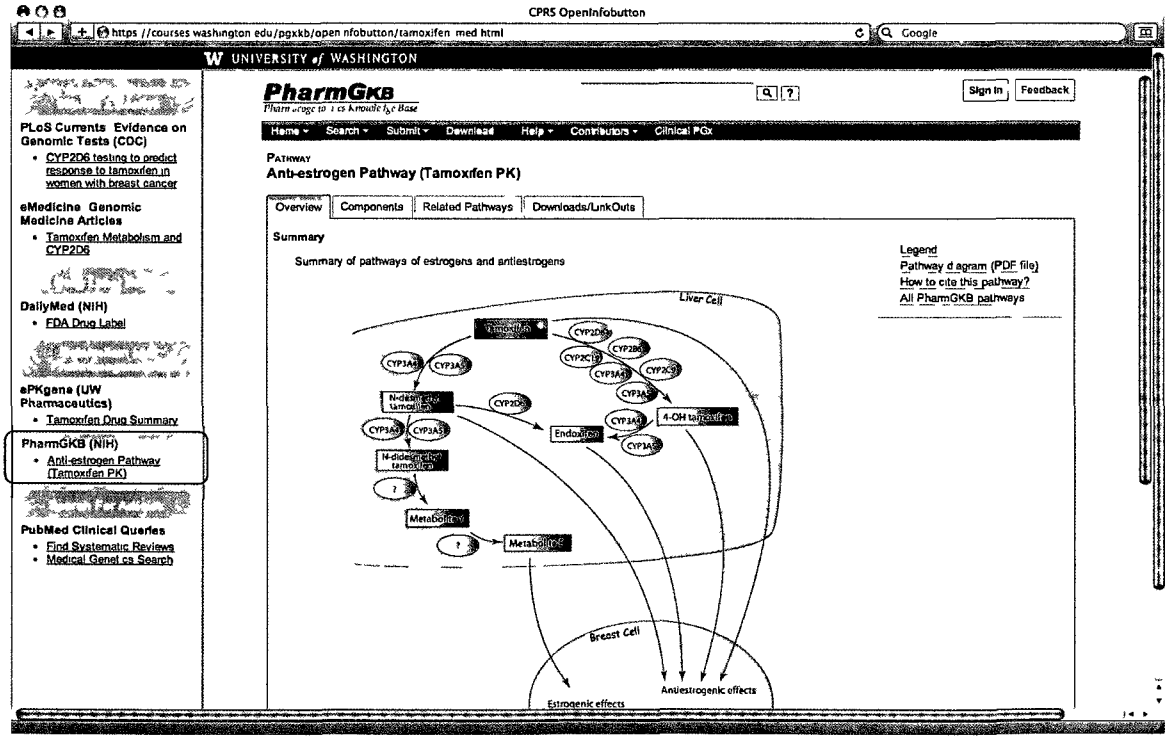
(Pharmacogenomics Knowledge Base, PharmGKB)

ePKgene – Drug summary



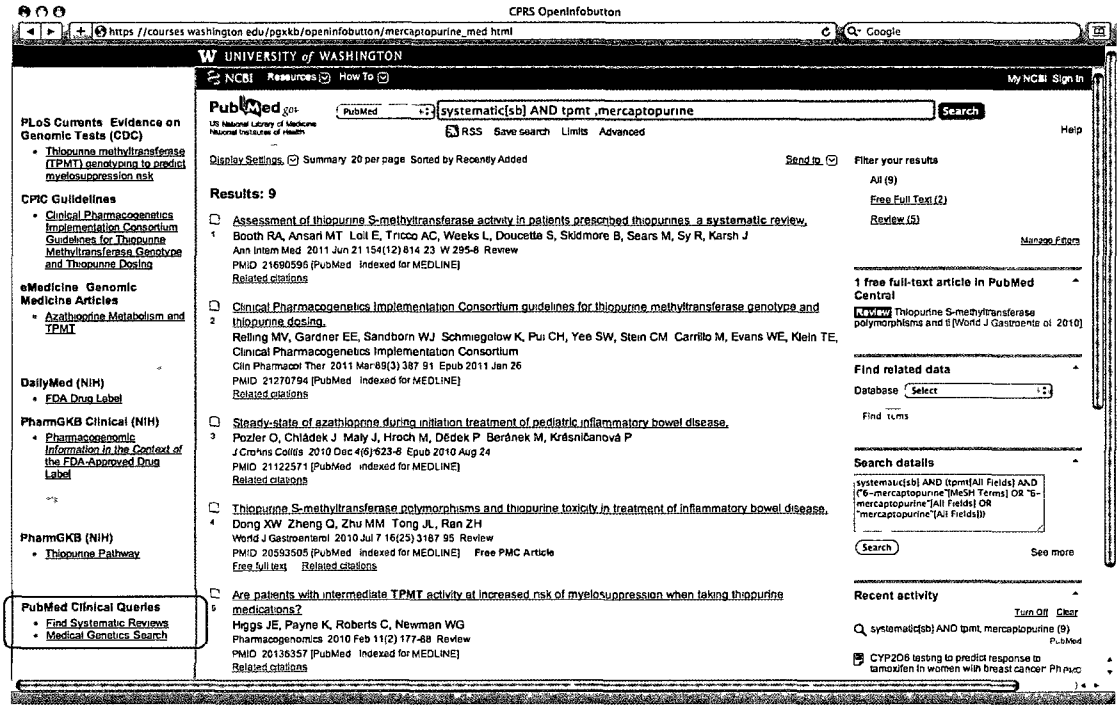
(University of Washington, Department of Pharmaceutics)

PharmGKB - Pathways



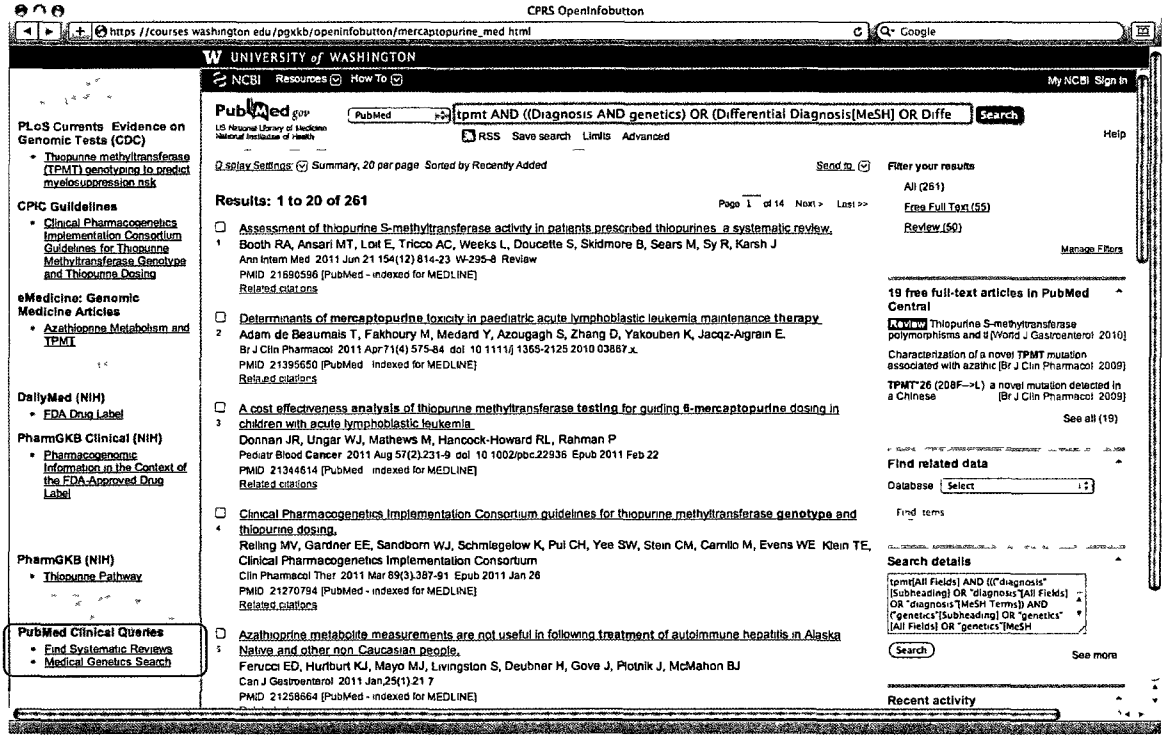
(Pharmacogenomics Knowledge Base, PharmGKB)

PubMed Clinical Queries – Find Systematic Reviews



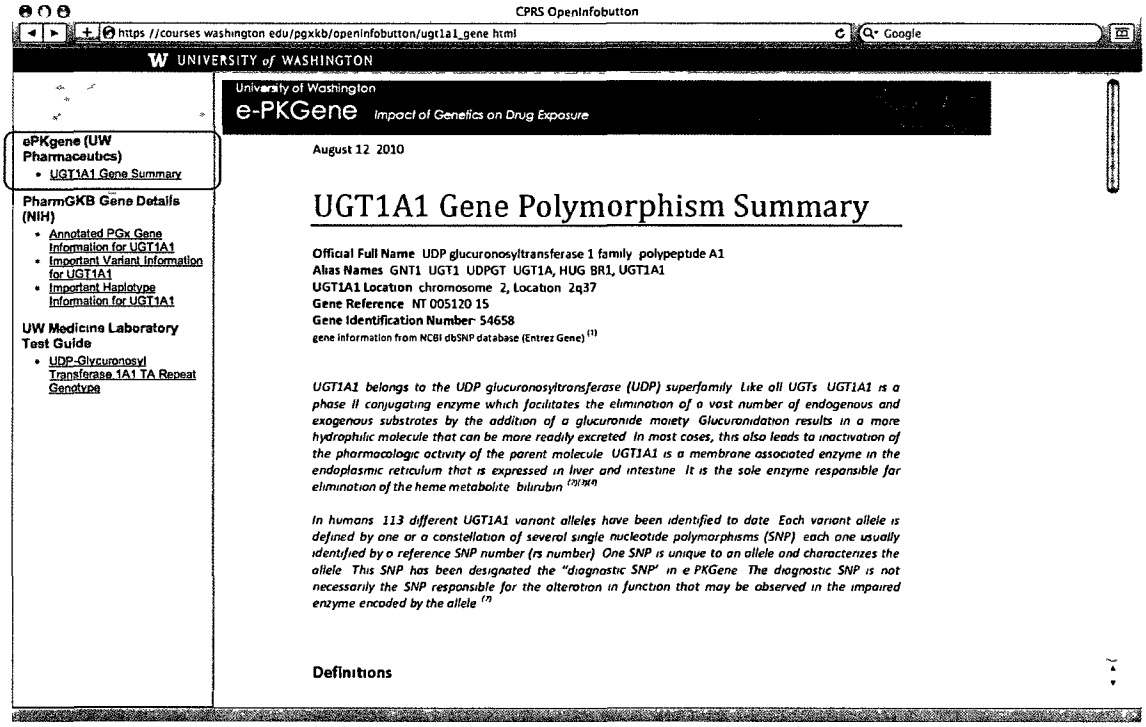
(US National Library of Medicine)

PubMed Clinical Queries – Medical Genetics Search



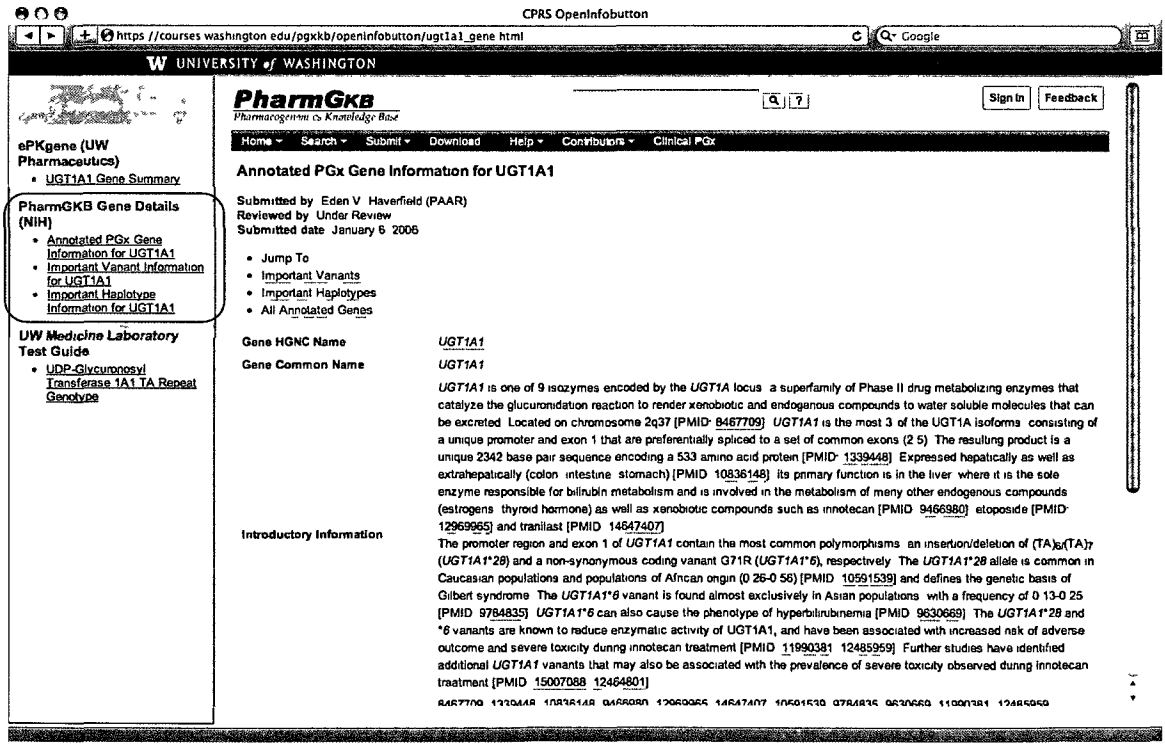
(US National Library of Medicine)

ePKgene – Gene summary



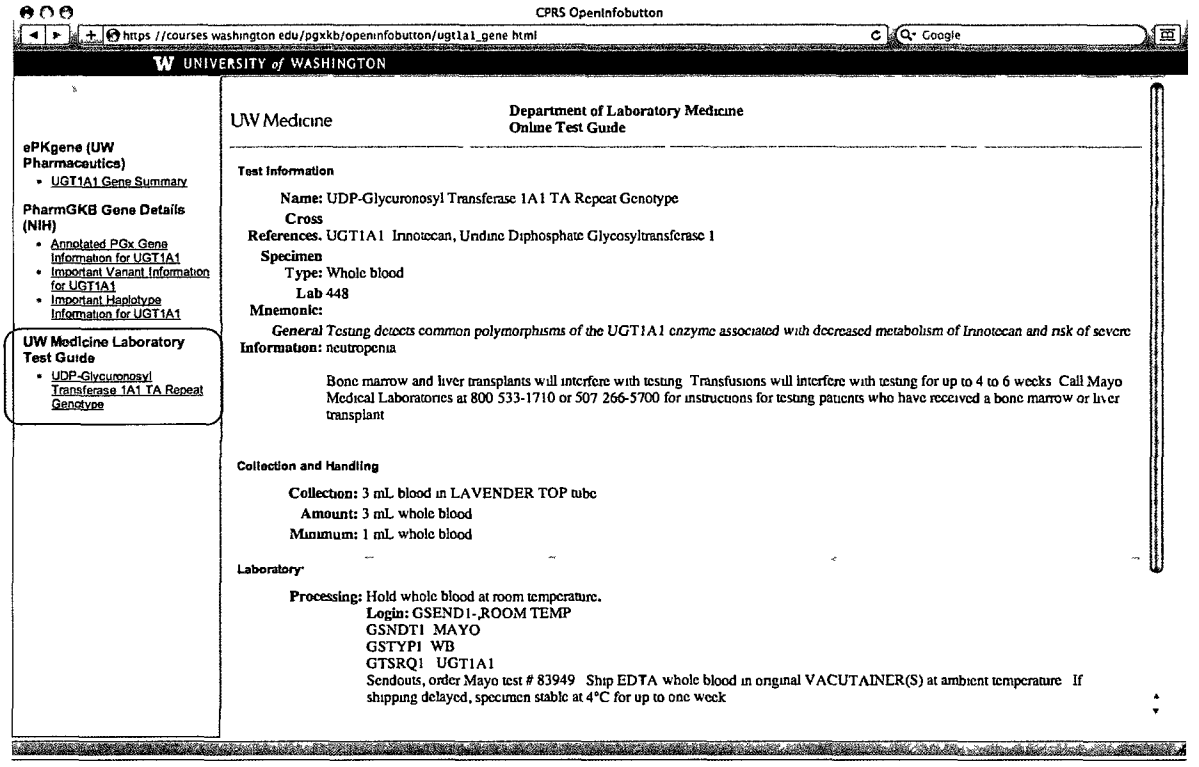
(University of Washington, Department of Pharmaceutics)

PharmGKB Gene Details



(Pharmacogenomics Knowledge Base, PharmGKB)

UW Online Laboratory Test Guide



(University of Washington, Department of Laboratory Medicine.)

eMedicine: Genomic Medicine Articles [Internet]. Retrieved September 9, 2011 from http://emedicine.medscape.com/genomics/articles

Pharmacogenomics Knowledge Base (PharmGKB) Annotated PGx Genes [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/search/browseVip.action?browseKey=annotatedGenes

Pharmacogenomics Knowledge Base (PharmGKB) Clinical Pharmacogenomics [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/clinical/index.jsp

Pharmacogenomics Knowledge Base (PharmGKB) Pathways [Internet]. Retrieved September 9, 2011 from http://www.pharmgkb.org/search/browse/pathways.action

PLoS Currents: Evidence on Genomic Tests [Internet]. (2010). Retrieved September 9, 2011 from http://knol.google.com/k/plos/plos-currents-evidence-on-genomic-tests/28qm4w0q65e4w/50

Relling, M. V., & Klein, T. E. (2011). CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*, *89*(3), 464-467.

University of Washington, Department of Laboratory Medicine. UW Online Laboratory Test Guide [Internet]. Retrieved September 9, 2011 from http://menu.labmed.washington.edu/bcard/search.asp

University of Washington, Department of Pharmaceutics. ePKgene, Impact of Genetics on Drug Exposure [Internet]. Retrieved September 9, 2011 from http://www.pharmacogeneticsinfo.org

US Centers for Disease Control and Prevention. CDC Summaries of EGAPP Recommendation Statements [internet resource], last updated January 13, 2011. Retrieved September 9, 2011 from http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/

US National Library of Medicine. DailyMed Web site [database on the Internet]. Retrieved September 9, 2011 from http://dailymed.nlm.nih.gov/dailymed/about.cfm

US National Library of Medicine. PubMed Web site [database on the Internet]. Retrieved September 9, 2011 from http://www.ncbi.nlm.nih.gov/pubmed

APPENDIX 12: ALERT MESSAGES FOR ONCOLOGY MEDICATIONS

Scenario	Alert messages	Approximate decision support rules
Medication Capecitabine Genomic Information DPYD*2A (deficient DPD activity)	Low actionable alert message **Patient has DPD deficiency** This patient has deficiency of dihydropyrimidine dehydrogenase (DPD) activity Rarely, unexpected, severe toxicity (e g stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to DPD deficiency A link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be excluded High actionable alert message **Patient has DPD deficiency** This patient has known dihydropyrimidine dehydrogenase (DPD) deficiency Capecitabine (XELODA) is contraindicated in this patient	Low actionable rule(s) • Rule 3 2 IF patient is [being considered for] taking capecitabine AND patient has deficiency of dihydropyrimidine dehydrogenase (DPD) activity THEN rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to DPD deficiency AND a link between decreased levels of DPD and increased, potential fatal toxic effects of 5-fluorouracil therefore cannot be excluded High actionable rule(s) • Rule 3 1 IF patient is [being considered for] taking XELODA AND (patient has known hypersensitivity to capecitabine or to any of its components OR patient has a known hypersensitivity to 5-fluorouracil OR patient has known dihydropyrimidine dehydrogenases (DPD) deficiency OR patient has severe renal impairment) THEN XELODA is contraindicated in patient
Medication Irinotecan Genomic Information UGT1A1*1/*28 (slow extensive metabolizer (ePKgene, 2010b))	Low actionable alert message **Patient has a UGT1A1*28 polymorphism** This patient has a UGT1A1*28 polymorphism UGT1A1 activity is reduced in this patient and patient is at increased risk for neutropenia following initiation of irinotecan (CAMPTOSAR) treatment The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver In vitro studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC) do not inhibit cytochrome P-450 isozymes SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite	Low actionable rule(s) • Rule 6 1 IF patient is [being considered for] taking irinotecan AND patient has a genetic polymorphism that leads to reduced enzyme activity such as the UGT1A1*28 polymorphism THEN The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver In vitro studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite UGT1A1 activity is reduced in this patient

Scenario	Alert messages	Approximate decision support rules
	High actionable alert message	High actionable rule(s)
	Patient has a UGT1A1*28 polymorphism This patient is homozygous for the UGT1A1*28 allele A reduction in the starting dose by at least one level of irinotecan (CAMPTOSAR) should be considered However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment	• Rule 6 14 IF patient is [being considered for] taking irinotecan AND patient is homozygous for the UGT1A1*28 allele THEN a reduction in the starting dose by at least one level of CAMPTOSAR should be considered However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment
Medication Nilotinib	Low actionable alert message	Low actionable rule(s)
	Patient has a UGT1A1*28 polymorphism This patient has a UGT1A1*28 polymorphism	• Rule 7 3 IF patient is [being considered for] taking Nilotinib AND patient has UGT1A1 (TA)7/(TA)7 genotype THEN Tasigna can increase bilirubin levels A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients
Genomic Information UGT1A1*28/*28 (intermediate metabolizer (ePKgene, 2010b))	A pharmacogenetics analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment In that study, the UGT1A1*28/*28 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the UGT1A1*1/*1 and UGT1A1*1/*28 genotypes However, the largest increases in bilirubin were observed in the UGT1A1*28/*28 genotype patients	
	High actionable alert message	High actionable rule(s)
	• None	• None
Medication Mercaptopurine	Low actionable alert message	Low actionable rule(s)
	Patient is TPMT homozygous-deficient This patient is TPMT homozygous-deficient (two non-functional alleles) and is unusually sensitive to myelosuppressive effects of mercaptopurine At usual doses of mercaptopurine this patient will accumulate excessive cellular concentrations of active thioguanine nucleotides	• Rule 1 3 IF patient is [being considered for] taking mercaptopurine AND patient is TPMT homozygous-deficient (two non-functional alleles) AND patient is given usual doses of mecaptopurine THEN patient will accumulate excessive cellular concentrations of active thioguanine nucleotides AND patient will be predisposed to PURINETHOL toxicity
Genomic Information TPMT*3A/*3A (homozygous variant, mutant, low, or deficient activity (Relling et al , 2011))	This patient will be predisposed to mercaptopurine (PURINETHOL) toxicity, and is prone to developing rapid bone marrow suppression following the initiation of treatment	• Rule 1 6 IF patient is [being considered for] taking mercaptopurine AND patient is homozygous for an inherited defect

Scenario	Alert messages	Approximate decision support rules
		in the TPMT (thiopurine-S-methyltransferase) gene THEN patient is unusually sensitive to myelosuppressive effects of mercaptopurine and patient is prone to developing rapid bone marrow suppression following the initiation of treatment
	High actionable alert message **Patient is TPMT homozygous-deficient** This patient is homozygous-TPMT deficient (two non functional alleles) Substantial dose reductions are generally required to avoid the development of life threatening bone marrow suppression following the initiation of treatment	High actionable rule(s) • Rule 1 8 IF patient is [being considered for] taking mercaptopurine AND patient is homozygous-TPMT deficient (two non-functional alleles) THEN substantial dose reductions are generally required to avoid the development of life threatening bone marrow suppression • Rule 1 23 IF patient is [being considered for] taking mercaptopurine AND patient has inherited little or no thiopurine S-methyltransferase (TPMT) activity THEN patient is at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally requires substantial dose reduction • Rule 1 24 IF patient is [being considered for] taking mercaptopurine AND patient is homozygous deficient for TPMT THEN the optimal starting dose has not been established
Medication Tamoxifen	Low actionable alert message • None High actionable alert message	Low actionable rule(s) • None High actionable rule(s)
Genomic Information CYP2D6*4/*4 (poor metabolizer (ePKgene, 2010a))	• None	• None
Medication Thioguanine	Low actionable alert message **Patient has an inherited deficiency of TPMT**	Low actionable rule(s) • Rule 2 1 IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine, and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy
Genomic Information TPMT*1/*3C (heterozygote or intermediate activity (Relling et al , 2011))	This patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) This patient may be unusually sensitive to the myelosuppressive effects of thioguanine and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy	

Scenario	Alert messages	Approximate decision support rules
	Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in the patient High actionable alert message **Patient has an inherited deficiency of TPMT** This patient has TPMT test results that indicate an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) This patient may be unusually sensitive to the myelosuppressive effects of thioguanine and may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in this patient However, TPMT testing may not identify if patient is at risk for severe toxicity, and close monitoring of clinical and hematologic parameters is important	• Rule 2 2 IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in the • Rule 2 8 IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine AND patient may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy AND substantial dosage reductions may be required to avoid the development of life threatening bone marrow suppression in the patient High actionable rule(s) • Rule 2 5 IF patient is [being considered for] taking thioguanine AND patient has TPMT testing THEN TPMT testing may not identify if patient is at risk for severe toxicity AND close monitoring of clinical and hematologic parameters is important • Rule 2 8 IF patient has an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) AND patient is [being considered for] taking thioguanine THEN patient may be unusually sensitive to the myelosuppressive effects of thioguanine AND patient may be prone to developing rapid bone marrow suppression following initiation of thioguanine therapy AND substantial dosage reductions may be required to avoid the development of life threatening bone marrow suppression in the patient

APPENDIX 13: ALERT MESSAGES FOR CARDIOLOGY MEDICATIONS

Scenarios	Alert messages	Approximate decision support rules
Medication:	Low actionable alert message	Low actionable rule(s)
Carvedilol	**Patient is a CYP2D6 poor metabolizer**	• Rule 4 4 IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin (a marker for cytochrome P450 2D6) THEN 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers
Genomic Information: **CYP2D6*4/*4 (poor metabolizer (ePKgene, 2010a))**	This patient is a poor metabolizer of debrisoquin (a marker for cytochrome P450 2D6) Poor metabolizers have 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers Plasma levels of S(-)carvedilol are increased only about 20% to 25% indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol	• Rule 4 5 IF patient is [being considered for] taking carvedilol AND patient is a poor metabolizer of debrisoquin THEN plasma levels of S(-)carvedilol are increased only about 20% to 25%, indicating this enantiomer is metabolized to a lesser extent by cytochochrome P450 2D6 than R(+)-carvedilol High actionable rule(s) • None
	High actionable alert message • None	
Medication:	Low actionable alert message	Low actionable rule(s)
Clopidogrel	**Patient is a CYP2C19 poor metabolizer**	• Rule 5 2 IF patient is [being considered for] taking Plavix AND patient is a CYP2C19 poor metabolizer THEN Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patient
Genomic Information: **CYP2C19*2/*2 (poor metabolizer (ePKgene, 2011a))**	This patient is a CYP2C19 poor metabolizer Copidogrel (Plavix) at recommended doses forms less of that metabolite and has a smaller effect on platelet function in this patient Study results • The majority of published cohort studies show that patients of this status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers, and in only one cohort study, the increased event rate was observed only in poor metabolizers • A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups When poor metabolizers	• Rule 5 16 IF patient [is being considered] for clopidogrel AND patient is a poor metabolizer of CYP2C19 THEN A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen • Rule 5 18 IF patient is [being considerd for] taking Plavix AND (patient is an intermediate metabolizer of CYP2C19 OR patient is a poor metabolizer of CYP2C19) THEN the majority of published cohort studies show that

Scenarios	Alert messages	Approximate decision support rules
	received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen High actionable alert message **Patient is a CYP2C19 poor metabolizer** This patient is a poor metabolizer of CYP2C19 Consider alternative treatment or treatment strategies in patient An appropriate dose regimen for this patient population has not been established in clinical outcome trials	patients of this status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers, and in only one cohort study, the increased event rate was observed only in poor metabolizers High actionable rule(s) • Rule 5 5 IF patient is [being considered for] taking Plavix AND patient is identified as a CYP2C19 poor metabolizer THEN consider alternative treatment or treatment strategies in patient • Rule 5 17 IF patient [is being considered] for clopidogrel AND patient is a poor metabolizer of CYP2C19 THEN an appropriate dose regimen for this patient population has not been established in clinical outcome trials
Medication: **Metoprolol** **Genomic Information:** **CYP2D6*1/*17 (slow extensive metabolizer (ePKgene, 2010a))**	Low actionable alert message • None High actionable alert message • None	Low actionable rule(s) • None High actionable rule(s) • None
Medication: **Propafenone** **Genomic Information:** **CYP2D6*10/*10 (slow extensive metabolizer (ePKgene, 2010a))**	Low actionable alert message **Patient is a slow metabolizer of CYP2D6** This patient is a slow metabolizer of CYP2D6 At daily doses of 850mg/day with slow metabolizers, drug concentrations are about twice those of the extensive metabolizer At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers Propafenone pharmacokinetics is linear (linear increases in plasma levels following administration of propafenone (RYTHMOL SR) capsule) High actionable alert message **Patient is a slow metabolizer of CYP2D6** This patient is a slow metabolizer of	Low actionable rule(s) • Rule 8 14 IF patient is [being considered for] taking propafenone AND patient is a slow metabolizer THEN at daily doses of 850mg/day with slow metabolizers drug concentrations are about twice those of the extensive metabolizer At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers • Rule 8 16 IF patient is [being considered for] taking propafenone AND patient is a slow metabolizer THEN propafenone pharmacokinetics is linear (linear increases in plasma levels following administration of RYTHMOL SR capsule) High actionable rule(s) • Rule 8 17 IF patient is [being considered for] taking propafenone AND patient is ANY metabolizer THEN Because the difference decreases at high doses and is

Scenarios	Alert messages	Approximate decision support rules
	CYP2D6 Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of propafenone (RYTHMOL SR) is the same for all patients	mitigated by the lack of the active 5-hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients
Medication:	Low actionable alert message	Low actionable rule(s)
Warfarin **Genomic Information:** **CYP2C9*2/*3 (intermediate metabolizer (ePKgene, 2011b))** **VKORC1 GG (Normal)**	**Patient has a CYP2C9*2 or CYP2C9*3 variant** This patient has a CYP2C9*2 or CYP2C9*3 variant allele and will have decreased S-warfarin clearance The variant alleles CYP2C9*2 and CYP2C9*3 result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin Study results • A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients In this meta-analysis, 3 studies assessed bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele • In an observational study, the risk of achieving INR > 3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype The relative risk of over anticoagulation as measured by INR > 3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who wer homozygous for the *1	• Rule 10 1 IF patient [is being considered] for warfarin AND (patient has the variant allele CYP2C9*2 OR patient has variant allele CYP2C9*3) THEN the variant alleles CYP2C9*2 and CYP2C9*3 result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin • Rule 10 3 IF patient [is being considered] for warfarin AND patient has one or more of variants CYP2C9*2 or CYP2C9*3 alleles THEN patient have decreased S-warfarin clearance • Rule 10 6 IF patient is [being considered for] taking warfarin AND patient is a carrier of either the CYP2C9*2 OR CYP2C9*3 alleles THEN A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for theCYP2C9*1 allele For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele • Rule 10 7 IF patient [is being considered] for warfarin AND patient is a carrier of either the CYP2C9*2 OR CYP2C9*3 alleles THEN In an observational study, the risk of achieving INR > 3 during the first 3 weeks of

<table>
<tr><th>Scenarios</th><th>Alert messages</th><th>Approximate decision support rules</th></tr>
<tr><td></td><td>allele

High actionable alert message
Patient has CYP2C9 genotype information available

Certain genetic variations in CYP2C9 and VKORC1 in this patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses

Patient CYP2C9 and VKORC1 genotype information can assist in selection of the starting dose

See table below for the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants Consider these ranges in choosing the initial dose

<table><tr><th>Variants</th><th colspan="6">CYP2C9</th></tr><tr><th>VKORC1</th><th>*1/*1</th><th>*1/*2</th><th>*1/*3</th><th>*2/*2</th><th>*2/*3</th><th>*3/*3</th></tr><tr><td>GG</td><td>5-7 mg</td><td>5-7 mg</td><td>3 4 mg</td><td>3 4 mg</td><td>3-4 mg</td><td>0 5 2 mg</td></tr><tr><td>AG</td><td>5-7 mg</td><td>3-4 mg</td><td>3-4 mg</td><td>0 5-2 mg</td><td>0 5-2 mg</td><td>0 5-2 mg</td></tr><tr><td>AA</td><td>3-4 mg</td><td>3-4 mg</td><td>0 5-2 mg</td><td>0 5 2 mg</td><td>0 5-2 mg</td><td>0 5-2 mg</td></tr></table></td><td>warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype The relative risk of over anticoagulation as measured by INR > 3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele
High actionable rule(s)
• Rule 74 2 IF patient is [being considered for] taking Warfarin AND patient has risk factors for bleeding OR (patient has CYP2C9 variants OR patient has VKORC1 variants) THEN Identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses
• Rule 74 4 IF patient is [being considered for] taking Warfarin AND (patient's CYP2C9 genotype information is available AND patient's VKORC1 genotype is available) THEN The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants Consider these ranges in choosing the initial dose</td></tr>
</table>

ePKgene. (2011a). CYP2C19 Gene Polymorphism Summary. Retrieved March 2nd, 2011 from www.pharmacogeneticsinfo.org

ePKgene. (2011b). CYP2C9 Gene Polymorphism Summary. Retrieved May 9th, 2011 from www.pharmacogeneticsinfo.org

ePKgene. (2010a). CYP2D6 Gene Polymorphism Summary. Retrieved Marcy 2nd, 2011 from www.pharmacogeneticsinfo.org

APPENDIX 14: PRE- EXPERIMENT PHARMACOGENOMICS KNOWLEDGE QUESTIONNAIRE

1. Please select all that characterize your experience with the following in clinical practice:

	Unaware of use	Aware of use
1a How aware are you of patient constitutional genetics (e g genotypes of drug metabolizing enzymes)? NOTE host genetics, NOT tumor genetics	☐	☐
1b How aware are you of decision support aids (e g clinical guidelines, dose adjustment calculator, etc)?	☐	☐

2. Please select all that characterize your experience with the following in clinical practice:

	Never use	Use sometimes	Use often
2a How often do you use patient constitutional genetics (e g genotypes of drug metabolizing enzymes)? NOTE host genetics, NOT tumor genetics	☐	☐	☐
2b How often do you use decision support aids (e g clinical guidelines, dose adjustment calculator, etc)?	☐	☐	☐

3. Please indicate your view on the usefulness of the following functionalities:

	Excellent/ Extremely useful	Good/ Very useful	Fair/ Useful	Poor/ Not very useful	No benefit/ Not at all useful
3a. How useful is providing electronic access to FDA drug labels?	☐	☐	☐	☐	☐
3b. How useful is the patients' constitutional genetics information?	☐	☐	☐	☐	☐
3c. How useful are prescribing-related alert messages embedded in patient electronic health records?	☐	☐	☐	☐	☐
3d. How useful are decision support aids specific to the patients' constitutional genetics and medication of interest?	☐	☐	☐	☐	☐

4. Please indicate your level of agreement with the following statements:

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
4a. The patients' constitutional genetics should be used to adjust drug dose	☐	☐	☐	☐	☐
4b. Decision aids improve the quality of my prescribing decisions	☐	☐	☐	☐	☐

5. Have you used patient constitutional genetic profile information to make prescribing decisions?

Yes ☐
No ☐

6. Any additional comments:

APPENDIX 15: POST- EXPERIMENT PHARMACOGENOMICS KNOWLEDGE QUESTIONNAIRE

1. Please indicate your general view on the usefulness of the following functionalities:

	Excellent/ Extremely useful	Good/ Very useful	Fair/ Useful	Poor/ Not very useful	No benefit/ Not at all useful/ Did not use
1a. How useful is providing electronic access to resources relevant to genetic laboratory results?	☐	☐	☐	☐	☐
1b. How useful is the patients' constitutional genetics information?	☐	☐	☐	☐	☐
1c. How useful are prescribing-related alert messages embedded in patient electronic health records?	☐	☐	☐	☐	☐
1d. How useful are decision support aids specific to the patients' constitutional genetics and medication of interest ("EVIDENCE")?	☐	☐	☐	☐	☐

2. Please indicate your level of agreement with the following statements:

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
2a. The patients' constitutional genetics should be used to adjust drug dose	☐	☐	☐	☐	☐
2b. Decision aids improve the quality of my prescribing decisions	☐	☐	☐	☐	☐

APPENDIX 16: LABORATORY SESSION TASK DEFINITIONS

Task 1 - Login

Sign into the Catalyst Survey using your UW NetID You will be presented your first clinical scenario

Please remember to think a-loud as you read through the clinical scenario and perform tasks

Click "End Task" once you have had a chance to read the clinical case

Task 1a - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the Catalyst Survey, next to the laboratory value, click the "i" icon to orient yourself to resources relevant to the genetic laboratory results

Another window will open with electronic resources

Spend some time familiarizing yourself with each resource

Close that window and click the "End Task" button when you are finished

Task 1b - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the PowerChart application select **Links and Reports**

Under "Web Links," are there any resources you regularly use to inform your prescribing decisions? (Please remember to think aloud)

Click the "End Task" button when you are finished

Task 1c - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the PowerChart application, select **Orders**

Click the "End Task" button when you are finished

Task 1d - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the **Orders** pane, click the **Add** button to begin a new order

Click the "End Task" button when you are finished

Task 1e - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

Find and select the drug you wish to prescribe

Click the "End Task" button when you are finished

Task 1f - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the **Ordering Physician** pop-up box, enter your name "LAST_NAME, FIRST_NAME" as the ordering physician

Click the **OK** button when finished with the pop-up box

Click the "End Task" button when you are finished with this task

Task 1g - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the **Order Sentences** pop-up box, select an existing order sentence and click the **OK** button when finished

NOTE A dummy alert message will appear The subsequent alert messages will include real clinical information

Assuming this alert message were real, how do you find out more information about it? (Please remember to think aloud)

Let the session facilitator know when you are finished thinking about this Click "End Task" after they show you where you can go

Task 1h - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

Click the "EVIDENCE" button within the alert message

Spend some time familiarizing yourself with the resources available to you (Please remember to think aloud)

Click the "End Task" button when you are finished

Task 1i - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

In the **Add Order** pop-up box, click the **Done** button

Click the "End Task" button when you are finished

Task 1j - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

Change the frequency for this order to be "BID before meals "

DO NOT SIGN YOUR ORDER

Click the "End Task" button when you are finished

Task 1k - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

Remove the drug from the "Orders for Signature "

Click the "End Task" button when you are finished

Task 1l - Orientation to CPOE and knowledge resources (Clinical Case Scenario 1)

How do you think you would close this patients' record? (Please remember to think aloud)

DO NOT CLOSE THE PATIENT RECORD

Let the session facilitator know when you are finished thinking about this, and they will provide you with information on how to close the patient record

Click the "End Task" button after closing the patient record

Task 1m - Clinical Case Scenario 2 - Part 1 [See Appendix 17]

In the Catalyst Survey,click "Next" to proceed with the next clinical scenario

A new clinical case scenario will be displayed

Please complete all questions for this clinical case scenario

Click the "End Task" button when you are finished

Task 2 - Clinical Case Scenario 2 - Part 2 [See Appendix 18]

In the Catalyst Survey,click "Next" to proceed with this clinical scenario

Laboratory values will be available for this clinical scenario

Spend some time reviewing the laboratory values

Click the "End Task" button when you are finished

Task 2a - Clinical Case Scenario 2 - Part 2

In the PowerChart application, complete all steps to order the drug you wish to prescribe

DO NOT SIGN YOUR ORDER

Click the "End Task" button when you are finished

Task 2e - Clinical Case Scenario 2 - Part 2

Click the "x" on the medical record tab to close this test patients' profile

Task 2f - Clinical Case Scenario 2 - Post clinical case questions [See Appendix 20]

In the Catalyst Survey,click "Next" to proceed with survey questions about the clinical case scenario

Please complete all questions

Click the "End Task" button when you are finished

Task 2g - Clinical Case Scenario 3 - Part 1 [See Appendix 17]

In the Catalyst Survey,click "Next" to proceed with the next clinical scenario

A new clinical case scenario will be displayed

Please complete all questions for this clinical case scenario

Click the "End Task" button when you are finished

Task 3 - Clinical Case Scenario 3 - Part 2 [See Appendix 18]

In the Catalyst Survey,click "Next" to proceed with this clinical scenario

Laboratory values will be available for this clinical scenario

Spend some time reviewing the laboratory values

Click the "End Task" button when you are finished

Task 3a - Clinical Case Scenario 3 - Part 2

In the PowerChart application, complete all steps to order the drug you wish to prescribe

DO NOT SIGN YOUR ORDER

Click the "End Task" button when you are finished

Task 3e - Clinical Case Scenario 3 - Part 2

Click the "x" on the medical record tab to close this test patients' profile

Task 3f - Clinical Case Scenario 3 - Post clinical case questions [See Appendix 20]

In the Catalyst Survey,click "Next" to proceed with survey questions about the clinical case scenario

Please complete all questions

Click the "End Task" button when you are finished

Task 3g - Clinical Case Scenario 4 - Part 1 [See Appendix 17]

In the Catalyst Survey,click "Next" to proceed with the next clinical scenario

A new clinical case scenario will be displayed

Please complete all questions for this clinical case scenario

Click the "End Task" button when you are finished

Task 4 - Clinical Case Scenario 4 - Part 2 [See Appendix 18]

In the Catalyst Survey,click "Next" to proceed with this clinical scenario

Laboratory values will be available for this clinical scenario

Spend some time reviewing the laboratory values

Click the "End Task" button when you are finished

Task 4a - Clinical Case Scenario 4 - Part 2

In the PowerChart application, complete all steps to order the drug you wish to prescribe

DO NOT SIGN YOUR ORDER

Click the "End Task" button when you are finished

Task 4e - Clinical Case Scenario 4 - Part 2

Click the "x" on the medical record tab to close this test patients' profile

Task 4f - Clinical Case Scenario 4 - Post clinical case questions [See Appendix 20]

In the Catalyst Survey,click "Next" to proceed with survey questions about the clinical case scenario

Please complete all questions

Click the "End Task" button when you are finished

Task 4g - Clinical Case Scenario 5 - Part 1 [See Appendix 17]

In the Catalyst Survey,click "Next" to proceed with the next clinical scenario

A new clinical case scenario will be displayed

Please complete all questions for this clinical case scenario

Click the "End Task" button when you are finished

Task 5 - Clinical Case Scenario 5- Part 2 [See Appendix 18]

In the Catalyst Survey,click "Next" to proceed with this clinical scenario

Laboratory values will be available for this clinical scenario

Spend some time reviewing the laboratory values

Click the "End Task" button when you are finished

Task 5a - Clinical Case Scenario 5 - Part 2

In the PowerChart application, complete all steps to order the drug you wish to prescribe

DO NOT SIGN YOUR ORDER

Click the "End Task" button when you are finished

Task 5e - Clinical Case Scenario 5 - Part 2

Click the "x" on the medical record tab to close this test patients' profile

Task 5f - Clinical Case Scenario 5 - Post clinical case questions [See Appendix 20]

In the Catalyst Survey,click "Next" to proceed with survey questions about the clinical case scenario

Please complete all questions

Click the "End Task" button when you are finished

Task 6 - Post-Laboratory Questionnaires [See Appendix 15]

In the Catalyst Survey,click "Next" to proceed with two post-laboratory session surveys

Please complete both questionnaires You DO NOT need to think aloud

Click the "End Task" button when you are finished

APPENDIX 17: EXPERIMENTAL SURVEY INSTRUMENT - BASELINE SURVEY QUESTIONS (WITHOUT ACCESS TO PGX KNOWLEDGE)

Example Clinical Case Scenario - Nilotinib

45 year old Asian female with imatinib-resistant chronic phase chronic myeloid leukemia. Patient has no history of cardiovascular disease or arrhythmias. All laboratory values, including complete blood count, electrolytes, and liver function tests, are within normal limits. Patient is not taking any other medications. You chose to prescribe nilotinib.

1. What is your preferred starting dose for carvedilol?

Dose: ☐

Frequency: ☐

Duration: ☐

2. Please indicate your level of confidence in your prescribing decision:

	Very confident	Confident	Neutral	Have doubts	Not at all confident
How confident are you in your prescribing decision in this case?	☐	☐	☐	☐	☐

APPENDIX 18: EXPERIMENTAL SURVEY INSTRUMENT – PRESCRIBING TASKS WITH ACCESS TO PGX KOWLEDGE (LABORATYORY SESSION ONLY)

Example Clinical Case Scenario – Nilotinib

45 year old Asian female with imatinib-resistant chronic phase chronic myeloid leukemia. Patient has no history of cardiovascular disease or arrhythmias. All laboratory values, including complete blood count, electrolytes, and liver function tests, are within normal limits. Patient is not taking any other medications. You chose to prescribe nilotinib.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
UGT1A1	*(TA)^{7}TAA*	*UGT1A1*28/*28*	*Intermediate Metabolizer*	

Perform tasks to order carvedilol for this patient using the PowerChart application.

See Appendix 16: Task 2a, Task 3a , Task 4a, and Task 5a

APPENDIX 19: EXPERIMENTAL SURVEY INSTRUMENT – PRESCRIBING QUESTIONS WITH ACCESS TO PGX KNOWLEDGE (WEB-BASED EXPERIMENT ONLY)

Example Clinical Case Scenario - Nilotinib

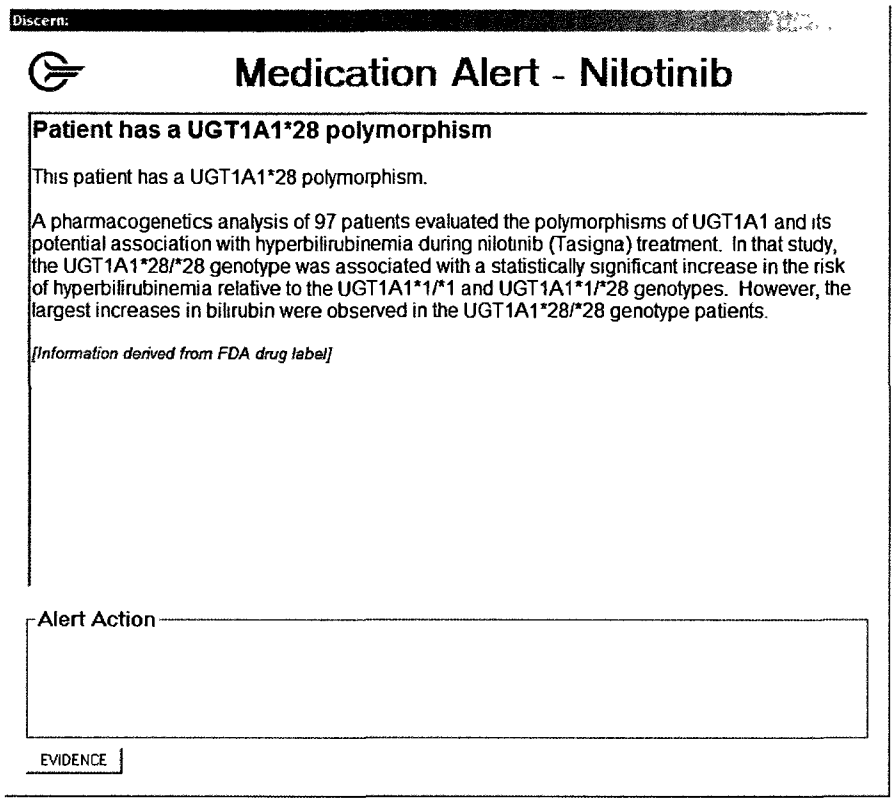
45 year old Asian female with imatinib-resistant chronic phase chronic myeloid leukemia. Patient has no history of cardiovascular disease or arrhythmias. All laboratory values, including complete blood count, electrolytes, and liver function tests, are within normal limits. Patient is not taking any other medications. You chose to prescribe nilotinib.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
UGT1A1	*(TA)^{7}TAA*	*UGT1A1*28/*28*	*Intermediate Metabolizer*	

CPOE alert message

(In a real CPOE environment this alert message would be triggered by the order entered on the previous page and by patient genetic laboratory values)



1. Indicate your alert action:

- ○ CANCEL order
- ○ OVERRIDE order
- ○ MODIFY order

2. What is your preferred starting dose for nilotinib? *[NOTE: This question was only shown if "OVERIDE alert" of "MODIFY order" was selected in the previous question]*

Dose: _____

Frequency: _____

Duration: _____

APPENDIX 20: EXPERIMENTAL SURVEY INSTRUMENT - FOLLOW-UP QUESTIONS

Example Clinical Case Scenario – Nilotinib

1. Please indicate your level of confidence in your prescribing decision:

	Very confident	Confident	Neutral	Have doubts	Not at all confident
How confident are you in your prescribing decision in this case?	☐	☐	☐	☐	☐

2. Please indicate your view on the usefulness of the following functionalities in this scenario:

	Excellent/ Extremely useful	Good/ Very useful	Fair/ Useful	Poor/ Not very useful	No benefit/ Not at all useful/ Did not use
2a. How useful were this patients' genetic laboratory results?	☐	☐	☐	☐	☐
2b. How useful were the resources relevant to the genetic laboratory results?	☐	☐	☐	☐	☐
2c. How useful was the prescribing-related alert message?	☐	☐	☐	☐	☐
2d. How useful were the "EVIDENCE" resources relevant to the medication you were prescribing?	☐	☐	☐	☐	☐

APPENDIX 21: ONCOLOGY CLINICAL CASE SCENARIOS WITH GENETIC LABORATORY VALUES

Capecitabine Clinical Case Scenario

A 50 year old Caucasian male has metastatic colon cancer. His ECOG performance status is 0. Past medical history is significant for hypertension, which is currently well controlled with diuretics. Patient is not taking any other medications. All laboratory values, including complete blood count, renal function tests, and liver function tests, are within normal limits. The patient has a creatinine clearance of 100 ml/min/ 1.73m^2. Because the patient lives 200 miles away, you have chosen a convenience regimen for his initial chemotherapy of capecitabine and oxaliplatin (CAPEOX).

Laboratory value(s):

Gene name	Variant(s)	Variant Common Name	Predicted Consequence	
DPYD	*IVS14+1G>A*	*DPYD*2A*	*Deficient DPD activity*	

Irinotecan Clinical Case Scenario

A 48 year old Caucasian male with a 40 pack year history of smoking is diagnosed with extensive stage small cell lung cancer. Past medical history is noncontributory and all laboratory values are within normal limits. He will be treated with cisplatin and irinotecan for 4-6 cycles.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
UGT1A1	*(TA)$_7$TAA*	*UGT1A1*1/*28*	*Slow Extensive Metabolizer*	

Mercaptopurine Clinical Case Scenario

A 22 year old Caucasian male is admitted to receive cycle 2 of induction of the augmented Berlin-Frankfurt-Munster (BFM) regimen to treat lymphoblastic lymphoma. Patient is otherwise healthy and is not taking any other medications. Cycle 2 of induction includes cyclophosphamide intravenously (IV), cytarabine IV, 6-mercaptopurine orally, and intrathecal methotrexate.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Likely phenotype (Source: Clinical Pharmacogentics Implementation Consortium)	
TPMT	*615G>A*	*TPMT*3A/*3A*	*Homozygous variant, mutant, low, or deficient activity*	

Nilotinib Clinical Case Scenario

45 year old Asian female with imatinib-resistant chronic phase chronic myeloid leukemia. Patient has no history of cardiovascular disease or arrhythmias. All laboratory values, including complete blood count, electrolytes, and liver function tests, are within normal limits. Patient is not taking any other medications. You chose to prescribe nilotinib.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
UGT1A1	*(TA)^{7}TAA*	*UGT1A1*28/*28*	*Intermediate Metabolizer*	

Tamoxifen Clinical Case Scenario

68 year old postmenopausal Caucasian female diagnosed with metastatic ER positive, PR positive, HER2 receptor negative breast cancer. Bone scan shows positive uptake in the spine and right scapula. Brain MRI and abdominal CT scans are negative for metastatic breast cancer. All laboratory values, including complete blood count and liver function tests, are within normal limits. Currently taking gabapentin for musculoskeletal pain due to fibromyalgia. Patient is not taking any other medications. You chose to prescribe tamoxifen.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
CYP2D6	*1846G>A*	*CYP2D6*4/*4*	*Poor Metabolizer*	

Thioguanine Clinical Case Scenario

A 22 year old African American male is admitted to receive cycle 2 of induction of the augmented Berlin-Frankfurt-Munster (BFM) regimen to treat lymphoblastic lymphoma. Patient is otherwise healthy and is not taking any other medications. Cycle 2 of induction includes cyclophosphamide intravenously (IV), cytarabine IV, 6-thioguanine orally, and intrathecal methotrexate.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Likely phenotype (Source: Clinical Pharmacogentics Implementation Consortium)	
TPMT	*615G>A*	*TPMT*1/*3C*	*Heterozygote or intermediate activity*	

APPENDIX 22: CARDIOLOGY CLINICAL CASE SCENARIOS WITH GENETIC LABORATORY VALUES

Carvedilol Clinical Case Scenario

A 45 year old Caucasian male with stable chronic heart failure (NYHA IIb) presents with worsening shortness of breath and fluid retention. He has now been diuresed and is doing well. His current regimen includes an oral nitrate, an ACE inhibitor, and a loop diuretic agent. You now plan to add carvedilol to his existing regimen.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)
CYP2D6	*1846G>A*	*CYP2D6*4/*4*	*Poor Metabolizer*

Clopidogrel Clinical Case Scenario

A 59 year old Caucasian male presents with acute coronary syndrome. His past medical history includes hypercholesterolemia, GERD, and hypertension for which he receives pravastatin, omeprazole, and atenolol. Patient has already undergone PCI after having received his loading dose of clopidogrel. You now want to start a maintenance dose of clopidogrel.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)
CYP2C19	*681G>A*	*CYP2C19*2/*2*	*Poor Metabolizer*

Metoprolol Clinical Case Scenario

A 37 year old African American male has primary hypertension. His thiazide dose has already been optimized. You now want to add metoprolol.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
CYP2D6	*1023C>T*	*CYP2D6*1/*17*	*Slow Extensive Metabolizer*	

Propafenone Clinical Case Scenario

A 68 year old Asian female has been diagnosed with a supraventricular tachyarrhythmia. Amiodarone is contraindicated due to her history of pulmonary fibrosis and thyroid disease. You plan to initiate propafenone therapy.

Laboratory value(s):

Gene name	Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)	
CYP2D6	*100C>T*	*CYP2D6*10/*10*	*Slow Extensive Metabolizer*	

Warfarin Clinical Case Scenario

A 75 year old Caucasian male with a previous TIA presents with atrial fibrillation. He weighs 65 kg. You plan to start the patient on warfarin for chronic anticoagulation.

Laboratory value(s):

Gene name	Genomic Variant(s)	Genotype Common Name	Assigned Phenotype Classification (Source: e-PKgene)
CYP2C9	*430C>T, 1075A>C*	*CYP2C9*2/*3*	*Intermediate Metabolizer*

Gene name	Genomic Variant(s)	Genotype	Predicted consequence
VKORC1	*None identified*	*VKORC1 GG*	*Normal*

VITA

Casey Lynnette Overby, with the assistance of her undergraduate advisor Dr. David States, defined the requirements for an undergraduate Bioinformatics Individual Concentration Program at the University of Michigan in Ann Arbor, MI. In 2000, Casey graduated with her Bachelor of Science in Bioinformatics. In 2006, Casey completed her Masters of Biotechnology at the University of Pennsylvania in Philadelphia, PA. During and following her Masters program, she worked at the University of Pennsylvania in the Biomedical Informatics Core Facility (BMIF) led by Dr. David Fenstermacher. There she assisted with developing software tools for researchers, participated on Cancer Biomedical Informatics Grid (caBIG^{TM}) projects, and participated in project management and technical support activities for BMIF projects. These experiences confirmed her interest in pursuing a research career in Biomedical and Health Informatics. In preparation for her doctoral program in Biomedical and Health Informatics at the University of Washington, Casey participated in the NIH-NSF Bioengineering & Bioinformatics Summer Institute at the University of Pittsburgh in Pittsburgh, PA. The program provided a review of courses important for conducting research, opportunities to participate in journal club, and the opportunity to complete a research project that aligned with her interests. In 2011, Casey graduated with a Doctor in Philosophy in Biomedical & Health Informatics from the University of Washington School of Medicine, and a Certificate in Public Health Genetics from the University of Washington School of Public Health. Casey's dissertation work, pursued with Dr. Peter Tarczy-Hornoch as her primary advisor, predominantly involved techniques used to implement clinical decision support tools (knowledge acquisition, knowledge representation, inferencing, and explanation) in the context of drug therapy individualization as a microcosm of personalized medicine. The common thread between Casey's research activities prior to and during the pursuit of her doctorate was her focus on providing informatics solutions to support the clinical decision-making needs of various users of technology. This is reflective of her general research interest in using informatics techniques to translate new findings (genomics information and otherwise) into clinical practice; particularly through the discovery of new knowledge and its application to clinical decision-making.