User-centered design and evaluation of a pharmacogenomics information portal to support clinical decision-making

by

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PREFACE

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"Go confidently in the direction of your dreams. Live the life you have imagined."

– paraphrased from Henry David Thoreau

ABSTRACT

Pharmacogenomics, the interaction of genes and medications that effect medication-related phenotypes such as efficacy, toxicity, and sensitivity reactions, is playing an increasing role in medication decision making as we seek more personalized medical care. As key experts in supporting medication-decision making, pharmacists are well-positioned to support the incorporation of pharmacogenomics into clinical care. Pharmacists desire trustworthy information resources that efficiently impart clinically relevant pharmacogenomics information to help them make informed recommendations. Clinical interpretation of pharmacogenomics genotypes and phenotypes is difficult, and clinicians feel that current resources do not adequately support pharmacogenomics-related decision making. We aim to develop information resources that provide pharmacists with comprehensive, usable, and actionable pharmacogenomic information that that they trust.

We assert that our project is *significant* in three ways. *First,* we developed a detailed and clinically relevant pharmacogenomics semantic model to annotate FDA product labels. *Second,* we demonstrate the effectiveness of using qualitative methods to design clinically relevant pharmacogenomics information resources that are highly usable by clinicians. *Third,* we demonstrate that our information resource based on our semantic model allows

pharmacists to use FDA-approved pharmacogenomics information more efficiently to answer questions faster, more correctly, and more easily in terms of usability than the FDA Table of Pharmacogenomics Biomarkers in Product Labeling and the FDA Drug Labeling section of PharmGKB.org

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1.0 INTRODUCTION

Pharmacogenomics, the interaction between gene variants and medications, has the potential to revolutionize the way medications are prescribed[1]. At the time of this writing, pharmacogenomics research has identified over 130 gene variants that can alter the safety and/or effectiveness of drug treatments[2]. Some hospitals have begun using genotype information to inform drug and dose selection for several drugs including warfarin[3,4] and clopidogrel[5,6]. As genotyping becomes more common, more pharmacists and physicians will encounter pharmacogenomic information. To use this information effectively, clinicians will need clear, relevant information that will help them interpret complex interactions between patient genotypes, resulting phenotypes, and medications, and avoid adverse events and improve patient outcomes[7,8].

At the time of this writing, the FDA recognizes 47 distinct genes that affect medications, resulting in different phenotypes when a patient takes an affected medication. These phenotypes can be grouped into categories, such as pharmacokinetic and pharmacodynamic phenotypes. For instance, some genes affect metabolism. A patient with one variant of a metabolism gene might metabolize the drug faster than normal, while another patient with a

different variant of the same gene might metabolize it slower. Other genes affect the way the drug impacts the body. Certain patients experience an increased risk of a hypersensitivity reaction, and for others, a medication may be ineffective for them because they do not have the necessary receptor.

The introduction of pharmacogenomics into clinical practice is important for many reasons related to drug safety, efficacy and effectiveness, including reducing the risk of adverse drug events related to drug response variability[1]. Adverse drug events account for approximately 31% (36,397 out of 117320) unplanned hospital admissions[9] in the United States. The adverse drug event problem is multi-faceted: many factors play a role in causing medication injuries, including clinical reasons and information gaps in care. Clinical factors include drug-drug interactions[10] and variability of patient response to medications[11], while information gaps include lack of dissemination of drug knowledge and lack of patient data[12]. Identifying patients with variable medication responses could reduce some ADEs by using genetic information to ensure the right drug goes to the right patient in the right dose.

A substantial portion of response variability can be explained by genetic variants identified by advances in genomics[11]. An example of this drug response variability is warfarin, which has a narrow therapeutic window that varies widely among patients. Depending on the patient's genotype, a physician might choose a starting dose as low as 0.5 mg or as high as 7 mg (Table 1)[13] . To prescribe the appropriate dose, a physician needs the patient's genotype results for two different biomarker tests, and he or she must understand how to interpret the results. This information is in addition to other factors that affect warfarin dosing such as age,

weight, and concomitant medications. The complexities of genotype interpretation with warfarin dosing increase the risk of adverse events for the patient: an overdose could result in a bleeding episode that could cause unplanned hospital admissions or even death, and an insufficient dose could result in ineffective anticoagulation, possibly causing a heart attack, stroke, or death.

Table 1: Three Ranges of Expected Maintenance Warfarin Daily Doses Based on CYP2C9 and VKORC1 Genotypes[13]

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

With the help of genetic tests, clinicians can ideally prescribe the right dose of the right drug at the right time to the right patient. In some cases, such as warfarin[3] and clopidogrel[5], genotyping already informs drug and dose selection in select hospitals[3,5]. However, medication-related genetic testing is still in its nascent phase[14], and consensus does not yet exist on the usefulness of pharmacogenomics versus other methods to determine drug choice or dosage[4,15–17], further complicating how to use genetic information. Effective presentation of risk information is still an obstacle[18]. As pharmacogenomics becomes more integrated into standard practice, clinicians have an ever greater need for clinically relevant, effectively presented, searchable information that supports accurate interpretation and adoption of treatment recommendations[19].

1.1 SIGNIFICANCE

1.1.1 Pharmacogenomics Implications

Pharmacogenomics presents a complex picture involving interactions between genes, medication exposure, and patient factors to produce phenotypes[20]. Specifically, variations in genes can impact drug effects, such as response, efficacy, and risk of adverse effects in many therapeutic areas [21]. Each combination presents a unique set of considerations [22,23]. These variants can be used to predict who will most likely and least likely benefit from a drug, which dose is optimal, or who is at greatest risk of experiencing an unintended adverse drug events such as toxicity or failed efficacy[24,25]. Applying this information to individual patients presents multiple challenges, including unfamiliar and potentially confusing notation for describing gene variants and phenotypes, and interpreting the impact of the gene variants on prescribing decisions. When presented with a patient with a genotype that might influence the efficacy or safety of a medication under consideration, the prescriber must incorporate information about the gene, the gene variant, how the transcribed protein interacts with any particular drug, and other typical patient clinical variables like age, weight, comorbidities, and concomitant medications to determine the best course of action[26].

Gene variants can affect a patient's risk of adverse drug events in two ways: drug exposure and drug response[27]. Drug exposure is how much of the drug the patient receives, which can be influenced by the dose and the pharmacokinetics profile (absorption, distribution, metabolism, and excretion). Drug response is the pharmacodynamics profile of the drug, or the collection of effects, intended and unintended, that the drug has on the body. Drug response includes both intended effectiveness and adverse effects, such as toxicity and allergic reactions[24]. Applying knowledge of the interaction between genotypes and medications to inform medication and dosage choice can optimize treatment and prevent adverse medication events[28], yet that knowledge is not regularly applied[29,30].

Consequences of not knowing a patient's genotype and resulting phenotype can be severe, even fatal, as in the death of a breastfed newborn whose mother was an ultra-rapid metabolizer of codeine, which caused her breast milk to contain toxic levels of codeine's active metabolite, morphine[31]. As a result, breastfeeding mothers are typically not prescribed codeine. Another drug, clopidogrel, has reduced effectiveness for some patients. The FDA now requires the boxed warning section of the clopidogrel product label to warn that poor metabolizers of clopidogrel may not be effectively treated by the drug, and may have a higher risk of heart attacks, strokes, and death than normal metabolizers[32], implying that genetic testing may be appropriate prior to prescription. In one more example, Epstein et al. found that integrating warfarin genotyping into the clinical workflow reduced the risk of hospitalization in the six months following therapy initiation by 31%. (adjusted hazard ratio

[HR]: 0.69, 95% CI: 0.58 to 0.82)[33]. These examples are only a fraction of the drugs that have pharmacogenomics implications.

Table 2: Pharmacokinetic Phenotypes

Phenotype	Phenotype description	Genotype description
Ultra-rapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than two normal function alleles
Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers	Combinations of normal function and increased function alleles
Normal Metabolizer	Fully functional enzyme activity	Combination of normal function, decreased function, and/or no function alleles
Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combination of normal function, decreased function, and/or no function alleles
Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles

At this time, the metabolism subset of pharmacokinetic phenotypes are the best characterized pharmacogenomics phenotypes (Table 2)[34]. A normal metabolizer, also referred to as an extensive metabolizer, is the phenotype that exhibits a normal metabolism rate, and is the phenotype to which the other phenotypes are compared. A poor metabolizer exhibits a slower metabolism rate than the normal population. This phenotype usually exhibits at least one nonfunctional allele of the drug metabolizing enzyme. An intermediate metabolizer also exhibits a slower metabolism rate than the normal population, but not necessarily as slow

as a poor metabolizer. An intermediate metabolizer is likely to carry at least one partially-functioning allele of the drug metabolizing enzyme. A rapid metabolizer has increased metabolism activity compared to normal metabolizers, but less than ultra-rapid metabolizers. An ultra-rapid metabolizer is the phenotype that exhibits a faster than normal metabolism rate. The ultra-rapid metabolizer phenotype is likely to carry at least one allele with enhanced enzyme activity, or multiple copies of normal function alleles. As the number of copies of the allele increases, the rate of metabolism also increases[34].

These phenotypes appear simple to interpret, but the interpretation is complicated by the interaction between the variant and the medication. For example, per the Food and Drug Administration (FDA) and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, a poor metabolizer (CYP2C19*2/*2) of clopidogrel should not be given clopidogrel, but given an alternate therapy such as prasugrel[35]. The same poor metabolizer should be given a 50% reduced starting dose of amitriptyline[36]. Further complicating matters is a recent study that found that CYP2C19 poor metabolizers can be given clopidogrel, but they need up to 4 times the normal dose for it to be effective[37]. These differences among recommendations of how to manage patients with important pharmacogenomic variants are introduce a significant challenge of interpretation for the clinician.

1.1.2 History of pharmacogenomics* in clinical practice

Gene-medication interactions have been observed since 1969, when the first pharmacogenonomic biomarker was identified. Patients deficient in glucose-6-phosphate

*Pharmacogenetics and pharmacogenomics are terms used interchangeably to refer to the same concept, but pharmacogenomics is the broader term that encompasses both genetics and genomics. For the purposes of this thesis, I will use pharmacogenomics, but citations may refer to pharmacogenetics.

dehydrogenase developed hemolysis if they were given primaquine[38]. Other drugs have been known to be metabolized at different rates in different patients, but the genetic factors influencing the metabolism were not well understood. For instance, researchers knew that variability existed in rates of metabolism of drugs such as tolbutamide[39], debrisoquine[40], and desipramine[41], to name a few. Clinicians and researchers have been aware of these phenotypes, but they had no way of testing for them prior to prescribing the patient the drug. The advent of assays for the gene variants has made genetic-based treatment decisions available to the individual patient.

In 2003, De Leon, et al. introduced the Amplichip CYP450 Test, which used microarray technology to perform CYP2D6 and CYP2C19 genotyping[42]. This was the first combination pharmacogenomic test available, and was FDA approved in January 2005. de Leon genotyped 4532 psychiatric patients. His laboratory successfully performed 94% of assays for CYP2D6 and 98% of assays for CYP2C19. They found practical issues with DNA collection and testing due to insufficient saliva and blood collection that contributed to the 6% and 2% respective failure rates. AmpliChip was groundbreaking as the first step toward clinical application of pharmacogenomics because it directly identifies 27 allelic variants of CYP2D6 and 3 allelic variants for CYP2C19 in only one test. Previous, more expensive, tests required 30 individual tests for each allele, requiring a much larger sample volume.

In 2004, Donald Gardner proposed that genomic information regarding the CYP450 enzyme could be used to predict drug interactions and avoid adverse drug events. CYP450 refers to a group of enzymes that are well-established as being part of the metabolic and

bioactivation pathway of many drugs. Multiple known polymorphisms of these genes result in variation in drug metabolism and response. Gardner demonstrated, prior to the availability of commercial, clinical genetic tests for pharmacogenomic variants, that it is possible to apply both patient-specific genomic information and drug interactions information to provide clinical decision support to improve medication management and reduce the risk of adverse drug events[43].

Developing clinical guidelines for use of these genetic variants in practice was the next step toward clinical application of pharmacogenomics. de Leon et al. drafted clinical guidelines for psychiatrists to direct their use of pharmacogenomic testing for CYP2D6 and CYP2C19, as well as how to treat patients who are identified as poor metabolizers[44]. They suggest that patients with a history of adverse drug events that point to being poor metabolizers, such as a serious case of neuroleptic malignant syndrome or priapism, be considered for genotyping. Other patients, such as those claiming that multiple drugs are ineffective or intolerable, or those who do not respond to drugs that are not metabolized by CYP2D6 or CYP2C19, were not candidates for genotyping.

Metabolism-related pharmacogenes are not the only clinically-relevant phenotypes. Oncology is another area where biomarker information has allowed physicians to tailor treatments to their patients. For instance, the presence of epidermal growth factor receptor (EGFR) on tumor cells indicates that patients would benefit from treatment by certain cancer drugs, such as afatinib and erlotinib[45]. These genes help guide treatment decisions, much like non-oncology genes guide decisions. However, oncology pharmacogenes differ from non-

oncology genes because the gene expression is tumor tissue specific, rather than a germ-line gene that a person carries all their life in every cell. The tumor gene expression can change over time, unlike germ-line genes. Cancer cells can express different combinations of pharmacogenes in different levels, which complicates decision making.

In 2000, the National Institute of Health funded the Pharmacogenomics Research Network (PGRN) (www.pgrn.org)[46] to advance pharmacogenomics discoveries nationally and internationally through collaborative research of drug response genes. Six sites are implementing pharmacogenomics testing (University of Maryland, University of Florida, Vanderbilt University, St. Jude Children's Hospital, Ohio State University, and Mayo Clinic) and guideline development to overcome these barriers and enact pharmacogenomics knowledge in clinical care. In 2005, the Dutch Pharmacogenetics Working Group (DPWG) was established by the Royal Dutch Pharmacist's Association (KNMP) to develop guidelines and recommendations for pharmacogenomics-based treatment decisions[47] in Europe. In 2011, the Clinical Pharmacogenetic Implementation Consortium (CPIC) began developing clinical guidelines to support biomarker-based clinical decision making, in conjunction with the Pharmacogenomics Knowledgebase (www.pharmgkb.org) and PGRN. Other networks include the eMERGE network, which consists of 11 sites attempting to implement pharmacogenomics clinical decision support (CDS)[48]. The goal of these organizations is to research and implement clinical pharmacogenomics testing and decision making.

As of October, 2015, the U.S. Food and Drug Administration (FDA) has identified 47 biomarkers that affect 137 medications[24]. The FDA's "Table of Pharmacogenomic Biomarkers

in Drug Labels"[21] provides an overview of these details, including pointers to sections of medication product labels that describe pharmacogenomics implications. In 2011, the FDA published an Industry Guidance describing when genomic information should be considered during drug development and regulatory review. The guidance informs pharmaceutical companies on how to include pharmacogenomic data and design studies during drug development, to better inform subsequent use of the drug in populations with affected variants. The guidance also specifies to pharmaceutical companies what pharmacogenomic information should be mentioned in product labeling, including polymorphic enzyme descriptions, population frequencies, positive and negative predictive values associated with biomarkers, effect of the variant on pharmacokinetic profiles, the evidence supporting the genetic basis of response variability, and dose changes based on genotype. The guidance represents an important communication in the use of pharmacogenomic data in drug discovery, drug deployment, and clinical application of pharmacogenomic knowledge[24].

The last step to move pharmacogenomics into clinical care is establishing the effectiveness of genetic testing to tailor drug decisions to individual patients, which requires significant investment in genetic research for precision medicine. In 2015, President Barack Obama introduced the Precision Medicine Initiative, with the intent of using genetic information to cure diseases and identify the best treatments for individual patients. As a result of that initiative, the director of the National Institutes of Health, Dr. Francis Collins, implemented the Precision Medicine Initiative Cohort Program. This program will enroll a million patients nationwide as a research cohort to accelerate the understanding of health and

disease, including how to tailor medications to specific patients[49]. Clearly, broad support exists scientifically, clinically, and now politically for using genetic information to provide tailored care to patients. Pharmacogenomics is a critical first step in achieving precision medicine.

1.1.3 Stakeholders' Views of Pharmacogenomics in Practice

The lack of pharmacogenomics genotype testing in most health care systems prevents the realization of personalized medicine[22,50]. Poor adoption is not solely based on cost. The price of genotyping continues to fall, and with the advent of whole genome sequencing, a patient can be sequenced once and the information will be relevant for the rest of his or her life, making the acquisition of this information affordable[51]. As a result, genotyping will become common practice[19,23,52,53]. Physicians, nurses, and pharmacists will encounter genotype results in their practice, and will need to understand how to interpret and implement the information they receive.

Lack of appropriate education and information might contribute to poor adoption of pharmacogenomics. Studies have shown that physicians feel poorly informed about pharmacogenomics testing and that they have a difficult time interpreting test results[14,30]. In a large survey of physicians, Stanek et al. found that 12.9% of respondents ordered or recommended a pharmacogenomic genetic test in the previous 6 months[14]. Of those who had not ordered genetic tests, 67.1% said that they did not order them because they did not feel adequately informed about the test or the results.

Pharmacists expect that both physicians and pharmacists will have to play a role in pharmacogenomics test interpretation[54]. In semi-structured interviews of pharmacists, Dias et al found that almost all (18/21) felt that lack of training in pharmacogenomics was a barrier to pharmacogenomics use. As clinicians with extensive training in pharmacology, drug selection, drug dose and drug-drug interactions, pharmacists are poised to be leaders in integration of pharmacogenomics in clinical practice[55,56]. They want to recommend pharmacogenomic testing and employ the results in their clinical advice[57]. Pharmacists feel that they and their profession as a whole would benefit from pharmacogenomics instruction[58,59]. In a study assessing physician attitudes toward pharmacogenomic decision support during medication prescribing, Overby et al. found that internal medicine physicians are generally positive about genomic medicine in prescribing, but they lack sufficient knowledge and personal comfort with interpreting and using genetic information[60].

The PGRN Translational Pharmacogenetics Program identified seven barriers to adoption of pharmacogenomics testing in clinical practice: 1) lack of ability to perform genotype testing quickly in a Clinical Laboratory Improvement Amendments - compliant laboratory (CLIA); 2) lack of genotype test result standardization in electronic medical records (EMRs); 3) lack of pharmacogenomics randomized clinical trials validating treatment algorithms; 4) lack of clinicians' ability to interpret and use pharmacogenomics information; 5) lack of clear pharmacogenomics testing recommendations; 6) lack of pharmacogenomics clinical decision support infrastructure; and 7) cost and reimbursement concerns[61].

At Vanderbilt, one of the PGRN sites, the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program has genotyped approximately 3000 patients who were scheduled for cardiac catheterization to determine their CYP2C19 variant status prior to administration of clopidogrel[5] and provided that information with decision support to clinicians via the EMR. PREDICT demonstrates the feasibility of implementing pharmacogenomics testing as a strategy for personalized medicine. PREDICT was formed in 2009, and CYP2C19 testing began in 2011. The project involved coordination of cardiologists, patients, EMR technical staff, geneticists, informaticists, user interface experts, pharmacists, pharmacologists, clinical pathologists, program managers, the Medical Center ethics committee, and the organization of a CLIA-certified molecular diagnostics laboratory. It cost $5 million over 2 years to develop and implement.

The University of Maryland has implemented the Personalized Anti-Platelet Pharmacogenetics Program (PAP3) as part of the PGRN program [62]. They offer CYP2C19 genetic testing to cardiac catheterization patients. As of December 2013, they have approached 203 patients, 166 of whom consented to genetic testing. Of those, 39.1% were intermediate or poor metabolizers, and 17 patients were prescribed alternative therapy. No further results on this work have been published at the time of this writing.

Other efforts have centered on pharmacogenomics alerting in electronic medical records. St. Jude's Children's Research Hospital, another PGRN site, has developed an active clinical decision support (CDS) tool for pharmacogenomic test results. They developed 35 pharmacogenomics rules for two biomarkers and eight medications, and found that the alerts

appropriately guided prescribing in 95% of patients[63]. A group at the University of Utah studied how to present genotype information to clinicians in the electronic medical record (EMR) as a form of decision support. Using CYP2C9 genotype information, they found that both SNP and allele representations of genetic information are effective, but SNP results contain more information that could be accessed in the future for reinterpretation[64].

These efforts remain admittedly United States centered. The Dutch Pharmacogenetics Working Group and the European Pharmacogenetics Implementation Consortium are addressing pharmacogenomics implementation efforts in Europe. At this time, we are not aware of comparable efforts in Asia.

Clinical decision support for pharmacogenomics is an important aspect of achieving pharmacogenomics in clinical care, but it requires the support of the health system and EMR development team to enact it. These programs demonstrate the extensive health system coordination that is necessary to fully implement this knowledge into clinical care.

1.1.4 Medication prescription information needs

Information resource designers must understand clinicians' pharmacogenomics-related information needs during the prescribing process to develop resources that communicate pharmacogenomics knowledge effectively[65]. At this time, to the best of our knowledge, the information needs of clinicians, specifically pharmacists, when engaging with genetic

information during drug decision-making, have not been studied. Technical requirements for moving genomic information into clinical care have been identified by Masys, et al[66]:

1) Maintain separation of primary molecular observations from the clinical interpretations of those data.
2) Support lossless data compression from primary molecular observations to clinically manageable subsets.
3) Maintain linkage of molecular observations to the laboratory methods used to generate them.
4) Support compact representation of clinically actionable subsets for optimal performance.
5) Simultaneously support human-viewable formats and machine-readable formats in order to facilitate implementation of decision support rules.
6) Anticipate fundamental changes in understanding human molecular variation.
7) Support both individual clinical care and discovery science.

However, those requirements focus on data structure rather than on the specific types of information necessary.

Multiple studies have examined the generic information needs of clinicians[67–71]. A systematic review of the information seeking behaviors of physicians found that physicians use a wide range of information resources, including reference texts, primary sources, and Internet search engines, but overwhelmingly rely on tertiary, scholarly knowledgebase resources[71]. Others have studied pharmacists' information needs: Wong et al. surveyed pharmacists in Singapore about where they find drug information[72]. Investigators found that pharmacists overwhelmingly use reference texts, which they rated as very or somewhat comprehensive. Fewer respondents said that they used websites or search engines, which were rated as less comprehensive than reference texts. A survey of Swiss community pharmacists supported Wong's finding that drug reference texts are the preferred information resource: Zehnder

found that pharmacists experience information deficits most frequently in pediatrics, alternative medicine, pregnancy and lactation indications, and therapy guidelines[73]. Researchers in Greece performed a survey of hospital pharmacists, and found that hospital pharmacists in Greece seek pharmaceutical information, specifically drug indications, storage, dosage, and prices. The authors suggest that efficient information resources intended to support hospital pharmacists could contribute to more efficient and safer healthcare[74].

However, specific information about a drug and sources of information are not the only factors that influence how drug prescribers and pharmacists use medications. Other factors exist that affect the decision making process. To understand what factors contribute to medication prescribing decisions, Schumock et al. surveyed physicians, clinical pharmacists, and formulary committee members (Table 3)[75]. Participants rated drug-related, direct, and indirect factors that influence drug prescription decisions on a 6 point Likert scale. All participants rated safety, effectiveness, formulary status, and restrictions on prescribing as highly influential. Physicians rated drug samples availability and personal experience higher than other participants did, while clinical pharmacists and formulary committee members rated clinical pharmacist recommendations, prescribing guidelines, and cost higher than physicians did[75].

Studies on information needs and drug decision making are helpful and informative about generic drug information needs of pharmacists and prescribers, but do not provide significant help in developing information resources for pharmacists that support pharmacogenomics. Pharmacogenomics considerations can impact, where appropriate, six

influential factors identified by Schumock that govern which drugs and dosages are chosen (Table 3). These include: drug safety and effectiveness, monitoring requirements, FDA indications, local guidelines and clinical pharmacist recommendations. Schumock et al. identified many more factors that influence prescribing decisions, such as cost and experience, but only six are related specifically to pharmacogenomics in that they would change if a medication has pharmacogenomics implications (Table 3). For instance, a medication could be less safe or effective for a patient who has a specific genotype, and guidelines for administration would change in that case. In contrast, a medication's cost would remain the same regardless of the patient's genotype.

Table 3: Factors that influence prescribing decisions (Schumock et al. 2004). Factors in gray have been identified by the author as possibly being affected by pharmacogenomics**.**

Category	Factor
Drug-Related	Effectiveness
	Safety
	Personal experience
	Formulary status
	Ease of dosing
	Monitoring requirements
	Ease of administration
	FDA-approved indications
	Cost
	Availability of patient education materials
Direct	Restrictions of Prescribing
	Prescribing guidelines
	Recommendations by clinical pharmacists
	Providing cost comparisons
	Feedback about prescribing practices provided by hospital
	Hospital newsletter article(s) about the drug(s)
	CE speakers provided by hospital
	Peer review of prescribing patterns
Indirect	Free drugs for indigent patients
	Written technical information provided by pharmaceutical company
	Sample drugs
	Face-to-face detailing
	CE programs sponsored by pharmaceutical company
	Advertisements distributed by sales representatives
	Advertisements in medical/professional journals
	Displays at professional meetings
	Grant or research support provided by pharmaceutical company
	Honorarium provided by pharmaceutical company
	Luncheons of food provided by pharmaceutical company
	Visual reminders provided by pharmaceutical company (e.g., pens)
	Direct-to-consumer advertising on television

However, we cannot know for certain that these information needs and factors are accurate or appropriate when applied to pharmacogenomics without asking that question directly of pharmacists. Collectively, these studies demonstrate that pharmacists and physicians have pharmaceutical information needs, and information influences their prescribing and recommendation activities. Information resources geared specifically toward pharmacists can help the medication-related information needs not just of pharmacists, but of the other clinicians that they support, and can influence the prescribing decisions made by clinicians. The information needs will guide the information model of clinicians' pharmacogenomics information needs, which will inform the development of an information resource to meet those needs.

1.1.5 Current Methods of Presenting Medication Information

Clinicians have access to medication information resources, but those resources often lack the ability to effectively communicate pharmacogenomics medication information to clinicians for decision support. For instance, Structured Product Labels (SPLs) are the FDA-approved medication information resource for clinicians and pharmacists[24], so clinicians gravitate to product labels for information due to that status. The FDA has also determined the structure of the product labels, with predictable sections that provide important information, aiding clinicians in navigating the information[76]. However, clinicians prefer tertiary sources that digest information in a more accessible way [71].

Despite the FDA-approved status of the product label and the FDA's attempts to make the information structured and accessible, problems remain in terms of accessibility and usability of the information by clinicians[77], particularly in pharmacogenomics information. The FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels"[21] links to specific product label sections, but it does not provide direct access to specific implications for clear and actionable advice. Variations in product labels complicate matters further: pharmacogenomics information may be found in different product label sections for different drugs. For example, pharmacogenomic information in the abacavir label is located in the boxed warning, contraindications, warnings and precautions, and patient counseling sections; comparable details for aripiprazole are found in the clinical pharmacology, and dosage and administration sections. Other drugs have extensive differences in the location of pharmacogenomics information, as illustrated in Table 4.

Table 4: Differences among drugs in location of pharmacogenomics information in SPLs (based on FDA Table of Pharmacogenomic Biomarkers in Drug Labels[21]**)**

	Abacavir	Aripiprazole	Atomoxetine	Atorvostatin	Azathioprine	Boceprevir
Boxed Warning	X					
Contraindications	X					
Warnings and Precautions	X		X	X	X	
Patient Counseling Information	X					
Clinical Pharmacology		X	X	X	X	X
Dosage and Administration		X	X	X	X	
Drug Interactions			X		X	
Indications and Usage				X		
Clinical Studies				X		
Adverse Reactions					X	

Furthermore, the current interface for accessing this information from the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling impedes the ability of users to easily access the

information in the label. The user has to navigate a minimum 5 webpages, knowing what the correct links are, to access the label itself, and then navigate the label to find the information. Figure 1 illustrates the navigation necessary to access the label from the main page of the FDA Table of Pharmacogenomics Biomarkers in Product Labeling.

Figure 1: FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

1.

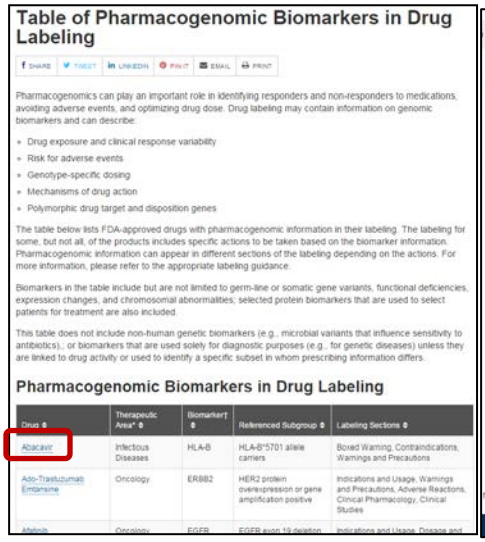


Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions. For more information, please refer to the appropriate labeling guidance.

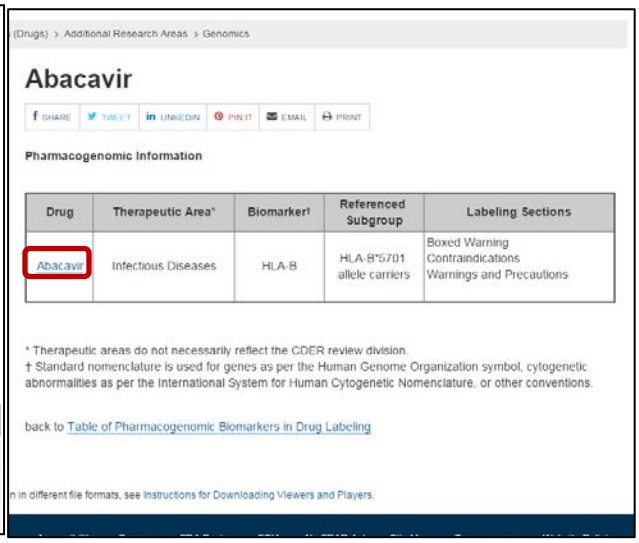
Biomarkers in the table include but are not limited to germ-line or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities; selected protein biomarkers that are used to select patients for treatment are also included.

This table does not include non-human genetic biomarkers (e.g., microbial variants that influence sensitivity to antibiotics), or biomarkers that are used solely for diagnostic purposes (e.g., for genetic diseases) unless they are linked to drug activity or used to identify a specific subset in whom prescribing information differs.

Pharmacogenomic Biomarkers in Drug Labeling

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion	Indications and Usage, Dosage and

2.



(Drugs) › Additional Research Areas › Genomics

Abacavir

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Pharmacogenomic Information

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning Contraindications Warnings and Precautions

* Therapeutic areas do not necessarily reflect the CDER review division.
† Standard nomenclature is used for genes as per the Human Genome Organization symbol, cytogenetic abnormalities as per the International System for Human Cytogenetic Nomenclature, or other conventions.

back to Table of Pharmacogenomic Biomarkers in Drug Labeling

in different file formats, see Instructions for Downloading Viewers and Players.

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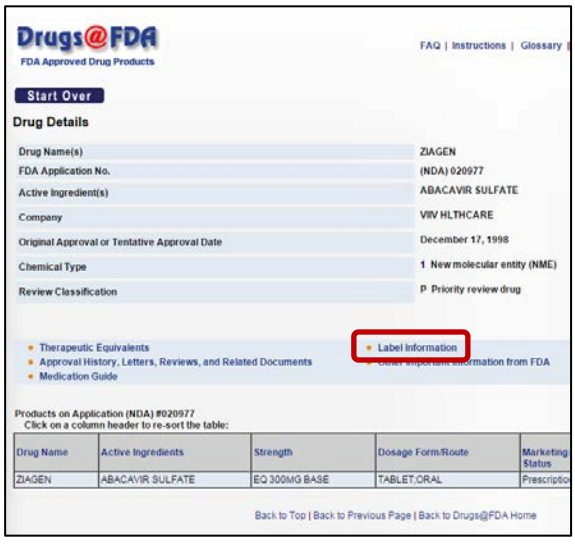

Drugs@FDA

FDA Approved Drug Products

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Start Over

Drug Details

Drug Name(s)	ZIAGEN
FDA Application No.	(NDA) 020977
Active Ingredient(s)	ABACAVIR SULFATE
Company	VIIV HLTHCARE
Original Approval or Tentative Approval Date	December 17, 1998
Chemical Type	1 New molecular entity (NME)
Review Classification	P Priority review drug

- Therapeutic Equivalents
- Approval History, Letters, Reviews, and Related Documents
- Medication Guide
- Label Information
- Other important information from FDA

Products on Application (NDA) #020977
Click on a column header to re-sort the table:

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status
ZIAGEN	ABACAVIR SULFATE	EQ 300MG BASE	TABLET;ORAL	Prescriptio

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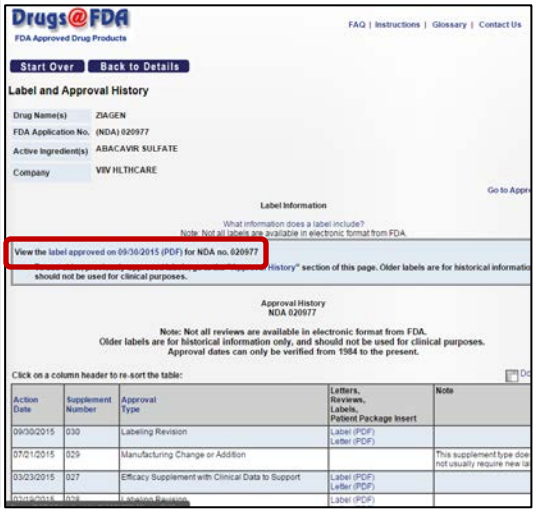
4.



Drugs@FDA

FDA Approved Drug Products

FAQ | Instructions | Glossary | Contact Us

Start Over | Back to Details

Label and Approval History

Drug Name(s)	ZIAGEN
FDA Application No.	(NDA) 020977
Active Ingredient(s)	ABACAVIR SULFATE
Company	VIIV HLTHCARE

Label Information

What information does a label include?
Note: Not all labels are available in electronic format from FDA.

View the label approved on 09/30/2015 (PDF) for NDA no. 020977

should not be used for clinical purposes.

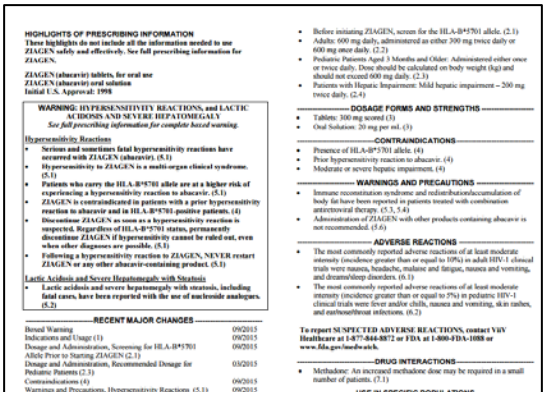
Approval History
NDA 020977

Note: Not all reviews are available in electronic format from FDA.
Older labels are for historical information only, and should not be used for clinical purposes.
Approval dates can only be verified from 1984 to the present.

Click on a column header to re-sort the table:

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
09/30/2015	030	Labeling Revision	Label (PDF) Letter (PDF)	
07/21/2015	029	Manufacturing Change or Addition		This supplement type doe not usually require new la
03/23/2015	027	Efficacy Supplement with Clinical Data to Support	Label (PDF) Letter (PDF)	
02/19/2015	028	Labeling Revision	Label (PDF)	

5.



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIAGEN safely and effectively. See full prescribing information for ZIAGEN.

ZIAGEN (abacavir) tablets, for oral use
ZIAGEN (abacavir) oral solution
Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY
See full prescribing information for complete boxed warning.

Hypersensitivity Reactions
- Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). (5.1)
- Hypersensitivity to ZIAGEN is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)
- ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)
- Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)

Lactic Acidosis and Severe Hepatomegaly with Steatosis
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)

RECENT MAJOR CHANGES

Boxed Warning	09/2015
Indications and Usage (1)	09/2015
Dosage and Administration, Screening for HLA-B*5701 Allele Prior to Starting ZIAGEN (2.1)	09/2015
Dosage and Administration, Recommended Dosage for Pediatric Patients (2.3)	03/2015
Contraindications (4)	09/2015
Warnings and Precautions, Hypersensitivity Reactions (5.1)	09/2015

- Before initiating ZIAGEN, screen for the HLA-B*5701 allele. (2.1)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.2)
- Pediatric Patients Aged 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg daily. (2.3)
- Patients with Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily. (2.4)

DOSAGE FORMS AND STRENGTHS
- Tablets: 300 mg scored (3)
- Oral Solution: 20 mg per mL (3)

CONTRAINDICATIONS
- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir. (4)
- Moderate or severe hepatic impairment. (4)

WARNINGS AND PRECAUTIONS
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)
- Administration of ZIAGEN with other products containing abacavir is not recommended. (5.6)

ADVERSE REACTIONS
- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. (6.1)
- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and earache/throat infections. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Methadone: An increased methadone dose may be required in a small number of patients. (7.1)

The dispersal of the information within the product label and the variability of its location among drugs impede the acquisition and use of the information. The information is structured in that it is placed into FDA-mandated sections, but pharmacogenomics information is not conveyed in a predictable, consistent format, or in an easily-identified location. Using just the product label, a user cannot easily extract all of the pharmacogenomics-related information. Structured representation of this information within the SPL sections using a semantic model and structured and computable representation to identify information from the product label as referring to a specific pharmacogenomics-related concept will make it searchable, and thus more accessible and usable. A semantic model is a set of explicitly defined terms and relationships that represents the concepts or information it is describing. Clinicians feel ill-prepared about engaging with pharmacogenomics[58], possibly due to lack of awareness of pharmacogenomics resources or due to the fact that those resources do not adequately meet their information needs. The Pharmacogenomics Knowledgebase (www.pharmGKB.org)[78–83] is primarily used by researchers. It includes information about gene variants that influence drug response the scientific literature supporting the associations, dosing guidelines, variant information, and depictions of drug pathways, among other things. PharmGKB is not designed to assist in real-time dosage and prescription decisions. The pharmacogenomics information available in SPLs is abstracted and available on PharmGKB (Figure 2), but clinicians with whom we have spoken about it do not find it easily accessible or useful, nor do they necessarily view it as having regulatory authority in the same way as information clearly from the FDA does.

Figure 2: PharmGKB.org Drug Labels Information

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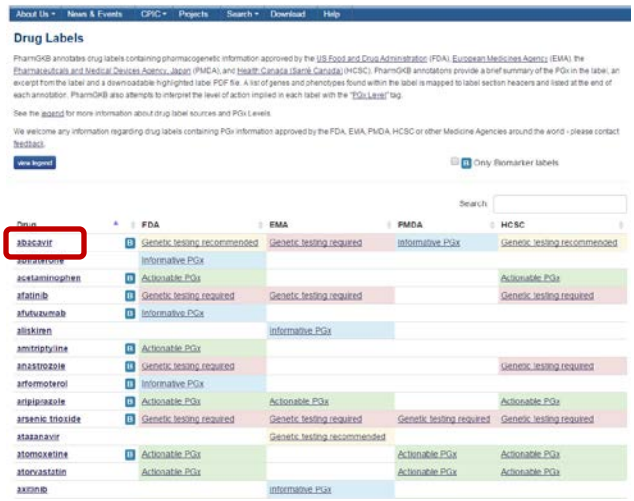

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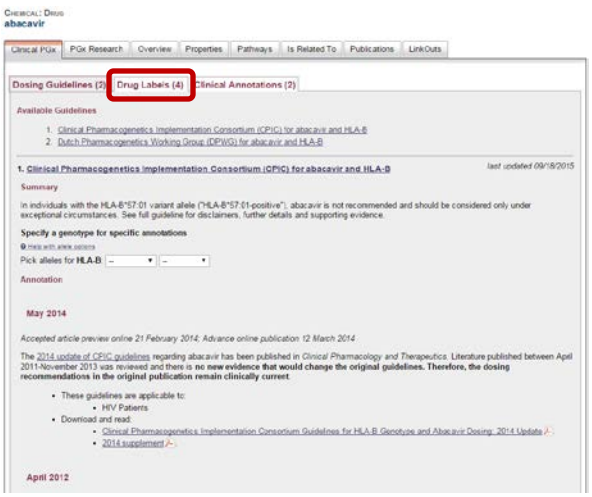

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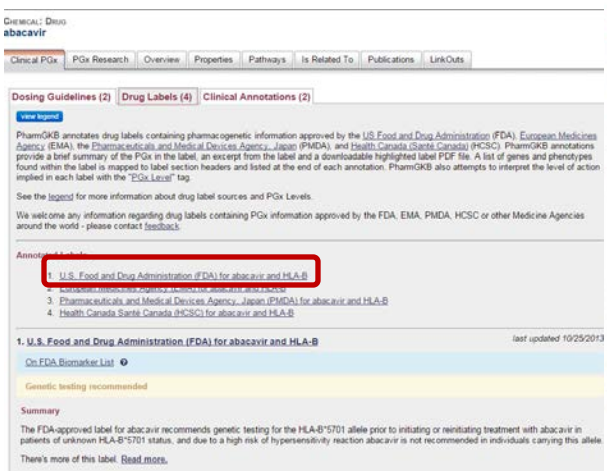

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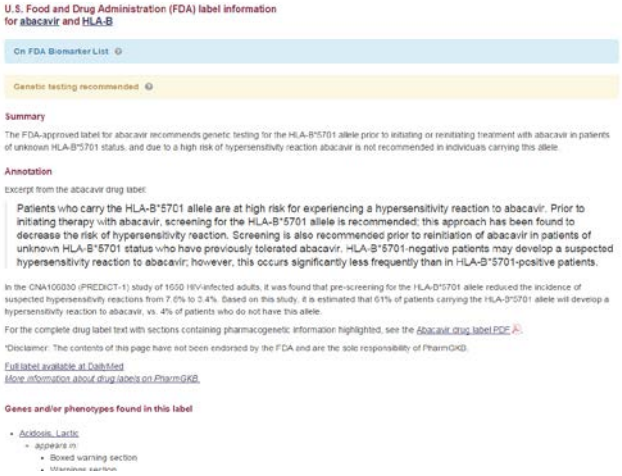


Pharmacogenomics education programs have been developed to bridge these gaps. The Pharmacogenomics Education Program (PharmGenEd) from the University of San Diego developed continuing education modules tailored to pharmacogenomics instruction[84] for pharmacists and other healthcare professionals. It is not intended to fulfill specific information

needs at the point of care, but rather to educate professionals about pharmacogenomics in general. The Genetics/Genomics Competency Center (www.g-2-c-2.com) developed by the National Human Genome Research Institute provides educational resources to genetic counselors, nurses, and physician assistants on genetic and genomic topics in health care. Development of a section specifically for pharmacists was released in 2014[85,86].

Clinicians need both general education on the topic[87], and quick answers at the point of care[58]. PharmGenEd and G2C2 fill only one of these requirements: general education, not quick answers. Further training is certainly an important component of pharmacogenomics training, but an information resource that can be referenced at the point of care has the potential to complement formal pharmacogenomics training[50,88], but data shows that it does not work well. Attention from the informatics community in the form of user-centered tools built on structured information models has the potential to improve the way clinicians interact with this information, an important step in integrating pharmacogenomics knowledge into clinical care. To be effective, pharmacogenomics information labeling needs to be well aligned with user needs. If clinicians struggle to locate this information in the product label, they may struggle to make informed decisions about their patients' care. Mismatches between the structure of product labels and clinician goals, the lack of clear indication where information can be found, and difficulties in navigating and interpreting the information may lead to difficulties in finding the right information.

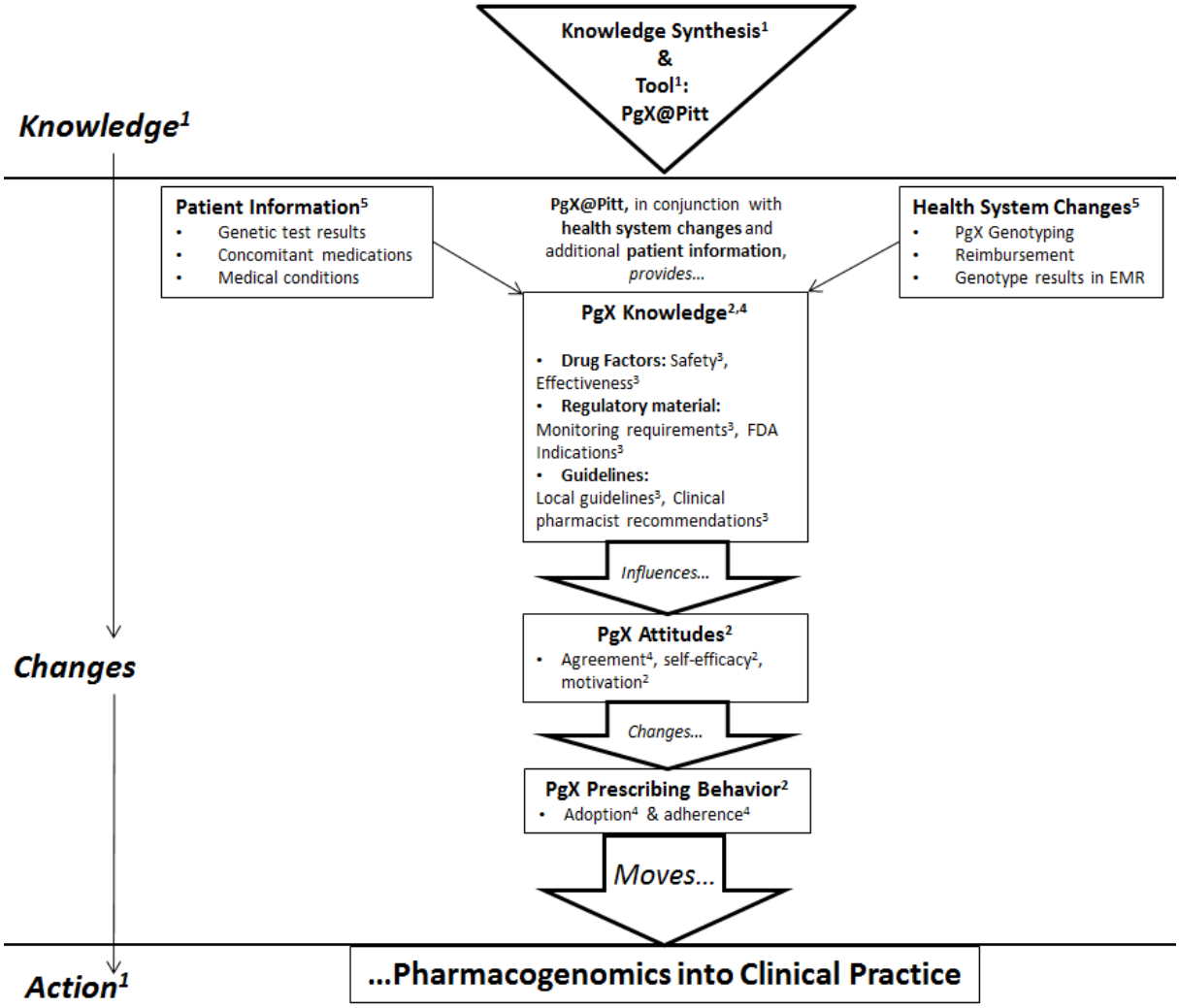
1.1.6 Knowledge translation

Difficulties in translation -- the process of synthesizing, disseminating, exchanging and applying knowledge to improve healthcare[89] – represent a significant barrier to the use of pharmacogenomics in clinical care. Medicine in general experiences challenges in knowledge translation: in the United States, only 55% of the care received by adults was recommended by guidelines[90]. The problem is multi-faceted: the sheer volume of research papers to read can overwhelm clinicians; decision-makers lack the skills to perform effective literature searching or appraise it critically; systematic reviews do not necessarily provide actionable recommendations; financial disincentives exist; and clinicians depend on experience over evidence[89,91,92]. In 2006, Graham et al. proposed a conceptual framework for knowledge translation, called the knowledge-to-action cycle[93]. This framework describes how knowledge is created, used, and adopted. Pharmacogenomics currently remains in the knowledge creation portion of the cycle, because the use of pharmacogenomic genotyping to inform medication prescribing is not widespread at this time. Knowledge inquiry occurs as bench researchers identify more pharmacogenomic variants. This knowledge is synthesized into reviews, guidelines, and recommendations.

The Knowledge to Action Cycle illustrates how pharmacogenomics relates to influences on physician prescribing decisions, and how an effective knowledge tool can move pharmacogenomics information from the knowledge creation portion of the cycle to the action portion[93]. First, health system changes must occur, such as genotyping, testing results and relevant patient data available in the EMR, and reimbursement[61]. Once that is in place, local

guidelines and information resources can encourage the use of pharmacogenomics in clinical practice (Figure 3).

Figure 3: Preliminary model of how a pharmacogenomics information resource has the potential to integrate pharmacogenomics knowledge into clinical practice. ([1]Graham et al. 2006, [2]Cabana et al. 1999, [3]Schumock et al. 2004, [4]Pathman et al. 1996, [5]Shuldiner et al.



Informaticians, health systems, and clinicians must develop resources that effectively synthesize and communicate actionable recommendations to clinicians to move pharmacogenomics knowledge into the action cycle and apply it to care. Pathman et al.

developed a framework describing physician adoption and use of guidelines: physicians need to be aware of guidelines, agree with them, adopt them, and adhere to them consistently in order for guidelines to be effectively used[94]. Cabana et al. performed a systematic review to augment Pathman's framework with a behavior change sequence and factors that influence each step[95]. Physicians require knowledge first, which includes familiarity and awareness of the information. In the case of pharmacogenomics, the knowledge includes the pharmacogenomics-related factors identified by Schumock as influential on prescribing: safety, effectiveness, monitoring requirements, FDA indications, local guidelines, and clinical pharmacist recommendations[75]. Then, they must adopt attitudes (agreement, self-efficacy, and motivation) that spur behavior changes: adoption and adherence. More simply, knowledge changes action. This model fits well into the first two constructs of the Unified Theory of Acceptance and Use of Technology, which posits four constructs of how technology is incorporated into users' workflow: 1) performance expectancy; 2) effort expectancy; 3) social influence; and 4) facilitating conditions[96]. When users' expectations of usability and functionality are met (constructs 1 and 2), they are more likely to use the technology and possibly change their behavior as a result. A pharmacogenomics resource has the potential to provide the knowledge to change attitudes and behavior, moving pharmacogenomics knowledge into clinical practice.

We propose to design, develop implement, and evaluate a knowledge resource - PGx@Pitt - which moves pharmacogenomics knowledge into action. A resource that distills this information in a usable way, with a semantic model to make the information searchable and

linked, to clinicians at the point of care might influence prescribing behavior in a positive way, and bring pharmacogenomics knowledge into clinical decision making.

1.1.7 Usability and User-centered Design in Pharmacogenomics

Usability measures how well a resource performs the function for which it was designed[97]. Improved usability is one potential solution to the problem of poorly structured and presented pharmacogenomics information. Nielsen identified five facets of usability: learnability, efficiency, memorability, errors, and satisfaction[97]. A new user of a resource should learn how to use it quickly, be able to be highly productive using the resource quickly, remember how to use the resource easily, not experience many errors, and be subjectively pleased with the experience. Optimizing usability factors during design will make it more usable and able to fill the need the developers sought to address.

Experience has shown the crucial importance of showing the right information in the right way, particularly in clinical information resources[65]. A computerized information resource in healthcare that fails at presenting information well can increase the risk of mistakes and adverse events. Studies of drug alerting systems illustrate the importance of presenting information appropriately[98–102]: it must be presented in a way that catches clinicians' attention, clearly depicts the vital information, and suggests a reasonable course of action. This is particularly the case regarding new, unfamiliar, and rapidly changing pharmacogenomics information.

Furthermore, merely displaying the information in the optimal user interface is insufficient. Resource developers must use user-centered design principles that keep the user's needs, abilities, expectations, and workflows in mind. The information that fulfills the user's information need is key: in order to meet information needs, one must understand the role of information in the user's work[103]. This requires the application of qualitative research, with its mixed methods of observations, interviews, free-flowing discussions, and workflow modeling, to understand the information needs that exist and how to design more effective information resources[103]. Clinicians' work processes and thought models when they work with medications with pharmacogenomics implications must be understood to design highly usable pharmacogenomics information resources. Then, as it is being designed and implemented, the resource must be evaluated thoroughly to assure that it does not violate any of the usability requirements, and that it is providing the pharmacogenomics knowledge that clinicians seek. Our goal is to understand clinician information needs, design a resource that meets them effectively, and evaluate the resource to ensure that it does, to produce a user-centered, clinical pharmacogenomics information resource, which clinicians do not currently have. That resource is PGx@Pitt.

1.2 RESEARCH QUESTIONS

1. Is it feasible to build a prototype pharmacogenomics information resource based on annotated pharmacogenomics statements from product labels?

2. What are the information needs and resource requirements of pharmacists regarding pharmacogenomics information?
3. How does our pharmacogenomics information resource compare to available alternatives in terms of perceived usability and functionality (task completion time and task correctness)?

1.3 DISSERTATION OVERVIEW

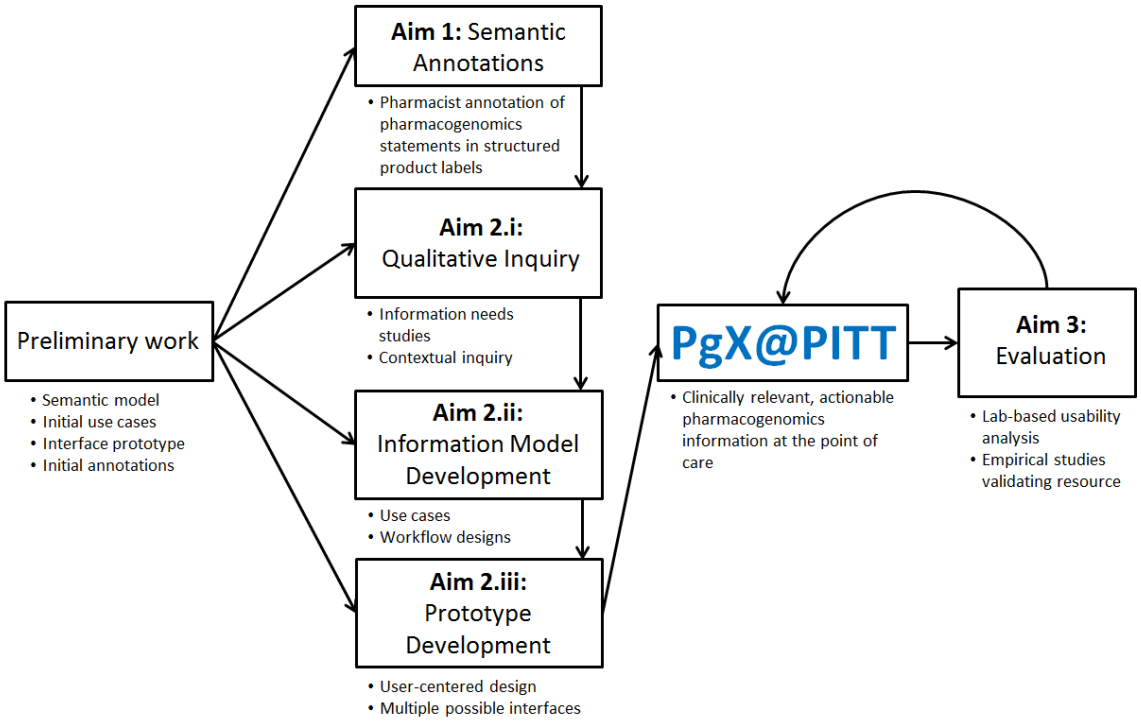


Figure 4: Dissertation Overview

Figure 4 provides an overview of the dissertation, consisting of 3 aims:

- **Aim 1: To build a semantic model and preliminary prototype.**
    - Develop a semantic model that describes the types of information available about pharmacogenomics and how it relates to other information.

- Write use cases to describe how the pharmacogenomics information resource will support information seeking behavior.
- Annotate the pharmacogenomics statements in product labels and make them linked and searchable using the semantic model to build a searchable, computable graph of pharmacogenomics statements in product labels.
- Develop a prototype pharmacogenomics information resource (PGx@Pitt v. 1.0)

- **Aim 2: To re-design a pharmacogenomics information resource through qualitative inquiry.**
  - Identify pharmacists' relevant pharmacogenomics information needs and resource requirements using qualitative inquiries and observations.
  - Refine use cases into user persona and use case scenarios based on the qualitative inquiries and observations.
  - Re-design the pharmacogenomic information resource interface to develop PGx@Pitt v. 2.0 based on pharmacists' information needs and resource requirements.
- **Aim 3: To evaluate the performance of pharmacogenomics information resource.**
  - Evaluate PGx@Pitt v. 2.0 using lab-based usability evaluations with pharmacists to determine if user-centered re-design improved the pharmacogenomics information resource usability compared to alternatives (PGx@Pitt version 1.0, PharmGKB.org, and the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling).

2.0 AIM 1: SEMANTIC MODEL AND PRELIMINARY PROTOTYPE DEVELOPMENT

2.1 METHODS

2.1.1 Use Case Development

To inform the design of the semantic model, we worked with two pharmacists (a clinical pharmacist with pharmacogenomics expertise and a drug information specialist) to develop five use cases representing pharmacogenomics information needs.

2.1.2 Semantic Model Development

Efficient retrieval of the pharmacogenomics information available in product labels requires that information to be structured. Our research group used the use cases described above to guide the development of the first semantic model of clinical pharmacogenomics statements. We chose to structure the information with a semantic model because it supports knowledge integration with other resources and enables querying [104–110]. We developed a semantic model that would contain enough detail to meet the needs of those use cases. That work produced an RDF representation of annotated pharmacogenomics statements.

2.1.3 Semantic annotation of pharmacogenomics statements from product labels

We finished annotations of pharmacogenomics statements in product labels using the semantic model developed in 2.1.2. The pharmacists used a Domeo plug-in[111] instead of Protégé Knowtator[112] to complete this set of annotations. Domeo is a web-based annotation tool which provided a more robust annotation environment for the purposes of this project. We chose to annotate labels for drugs for which recommendations have been rated "strong" by CPIC.

2.1.4 Interface Prototype Development

As a proof of concept, we developed a preliminary prototype interface using a subset of the annotations developed by the pharmacists. The prototype attempts to fulfill the information needs identified in the use cases.

2.2 RESULTS

2.2.1 Use cases

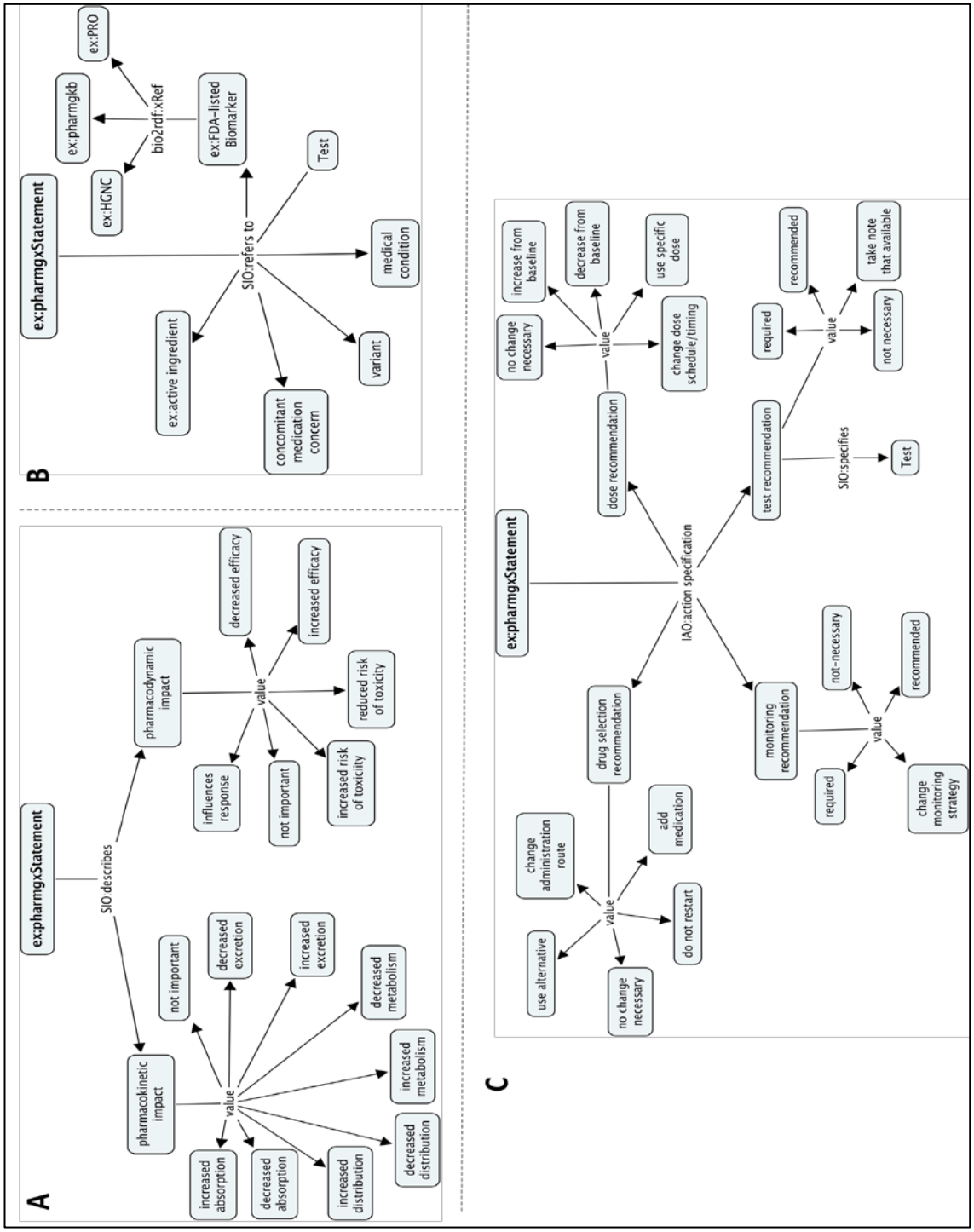
The use cases (Appendix A) cover a range of circumstances, such as the pharmacogenomic genes that may impact a drug, the implication of gene test results, interpretation of gene

variants, treatment recommendations, testing recommendations, and the other drugs that are affected by a genotype. These use cases also account for other factors that influence the interpretation of pharmacogenomics impact, such as pharmacokinetic or pharmacodynamic impact, ethnicity, other medical statuses such as lactation, and risk from concomitant medications. We wanted to identify the types of information clinicians might seek to answer their questions.

2.2.2 Semantic Model

The semantic model contains three parts to describe a pharmacogenomics statement: the subject, or what is described; the object, or what is referred to; and the recommendation, or what action is specified by the statement (Figure 5). However, not all of the statements have all three information elements. For instance, not all pharmacogenomics statements contain a recommendation.

Figure 5: Three parts of the semantic model with preliminary ontology mappings. A) What is described, B) what is referred to, and C) what action is specified. SIO: Semantic science Integrated Ontology. IAO: Information Artifact Ontology (Boyce et al. 2013)



2.2.3 Semantic annotation of pharmacogenomics statements from product labels

Five pharmacists associated with UPMC and the University of Pittsburgh used the semantic model to annotate 162 pharmacogenomics-related statements in 10 SPLs (abacavir, aripiprazole, azathioprine, carbamazepine, citalopram, clopidogrel, codeine, letrozole, tamoxifen, warfarin), which is a fraction of the total number of SPLs that require annotation. They used Protégé Knowtator[112] to create the annotations. We demonstrated the feasibility of turning product labels into actionable, semantically clear, linked data[105]. This knowledge representation approach moves towards clearly expressed semantics of the pharmacogenomics statements, which is necessary to quickly and effectively present the relevant pharmacogenomics information to clinicians in an information resource.

2.2.4 Interface Prototype

The main page of the prototype (Figure 6) is intended reflect the presentation of the same information available in the FDA's Table of Pharmacogenomic Biomarkers in Drug Labels (Figure 4). We chose to represent the information in the same format as the FDA table because we wanted the information and structure of the information to be familiar to pharmacists who have previously used it. Familiarity and trustworthiness of the source of information are important factors in acceptance of information by clinicians[95], so we preserved that structure in our prototype interface.

Figure 6: Preliminary PGx@Pitt Interface Main Page

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Pharmacogenomics @ PITT

Personalizing medication therapy decisions through an understanding of genetics

Pharmacogenomics in FDA Drug Labels

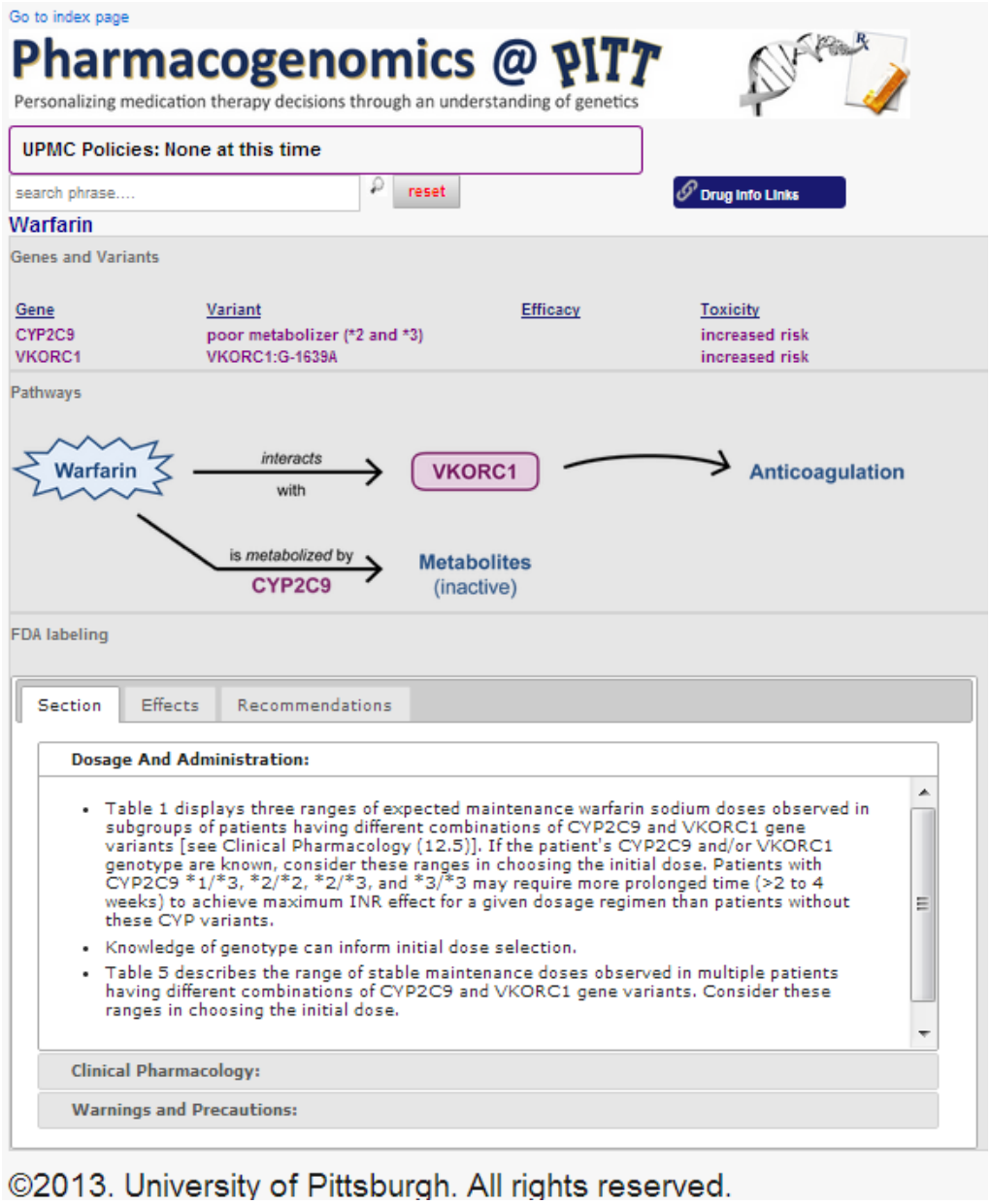
The FDA provides a "Table of Pharmacogenomic Biomarkers in Drug Labels" that lists all drugs with pharmacogenomic content in approved product labeling. We have annotated this content so that you can more quickly learn about the biomarker's effects, available tests, and any clinical recommendations. **Click anywhere on the row with the drug and biomarker of interest** to begin browsing the annotated product label statements. Click on the links in the Drug column to see more detailed information in a new window/tab. **Use "search phrase"** to filter the drugs listed to those with a particular type of product label statements..

List all drugs where pharmacogenomics... reset

search phrase

Drug	Therapeutic Area	Biomarker	
Abacavir (Ziagen©)	Antiviral	HLA-B	Click to **Expand**
Clopidogrel (Plavix©)	Antiplatelet agent	CYP2C19	Click to **Expand**
Warfarin (Coumaden)© (1)	Anticoagulation	CYP2C9	Click to **Expand**
Warfarin (Coumaden)© (2)	Anticoagulation	VKORC1	Click to **Expand**

Figure 7: Preliminary PGx@Pitt Prototype Drug Page



When the user selects the drug name, the complete drug information page is displayed (Figure 7). This is an improvement on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels because it directs the user to the information, rather than listing only the source of the

information. The top table provides information about the gene variants, the phenotype, and whether the impact is on the drug's efficacy or toxicity. This answers the basic questions about what variants impact drug response. Below that is a simplified pathway diagram illustrating how the drug interacts with and is metabolized by the gene(s) to produce the drug's effect. This explains graphically how these genes interact with the drug, and why a variant has the impact it does on drug metabolism. At the bottom of the page are tabs containing pharmacogenomics information from the annotated SPLs, which answer his questions about what the gene test results mean, and FDA recommendations regarding how to change his patient's treatment.

Warfarin's product label contains pharmacogenomics information in the Dosage and Administration, Clinical Pharmacology, and Warnings and Precautions sections. A different drug will have pharmacogenomics information in different sections. The effects tab contains information about the pharmacogenomics pharmacokinetic and/or pharmacodynamic effects. The Recommendations tab contains treatment or testing recommendations related to pharmacogenomics. All the information in these sections was taken from the structured RDF annotations described above. We presented it in a tabular format to make it more easily accessible: the concise organization of the knowledge is easy to scan and obtain quick, actionable information. Users can read about the drug's pharmacogenomics-related pharmacokinetic or pharmacodynamic effects and recommendations without having to sift through text to find them.

This preliminary proof of concept demonstrated that we can retrieve and present clinically relevant pharmacogenomics information from SPLs. The interface will change as a

result of input from clinicians about their information needs and workflow constraints, and involving concepts from other presentations of medication information.

2.3 DISCUSSION

These drugs represent over half of drugs rated by CPIC as having a strong recommendation for therapeutic action. Though the resource is incomplete in terms of information, we completed a significant number of annotations for drugs with major pharmacogenomic implications. This allows us to evaluate the interface and usefulness of the resource on many clinically relevant, high impact questions as we work to finish the semantic annotations of all 130+ drugs identified by the FDA as having pharmacogenomics implications.

2.4 LIMITATIONS

We were unable to complete all 130+ annotations due to the significant investment of resources and pharmacists' time required. This was not feasible during the timeframe of this dissertation work. Future work will be focused on completing all the drugs identified by the FDA as having pharmacogenomics implications, as well as maintaining the resource as new drugs are

added to the FDA's list. We also worked with a small group of local pharmacists to complete the annotation, and do not claim that the consensus annotations represent the consensus of all pharmacists regarding pharmacogenomics.

3.0 AIM 2: QUALITATIVE INQUIRIES INFORMED REDESIGN

3.1 AIM 2.I: QUALITATIVE INQUIRIES TO USER NEEDS AND RESOURCE REQUIREMENTS

3.1.1 Materials and Methods

To better understand pharmacists' information needs and resource requirements, I conducted qualitative inquiries, consisting of semi-structured interviews and observations of pharmacists in their work environment. I used a semi-structured approach to elicit a wide range of pharmacist perceptions about information seeking both for general prescribing and specifically with respect to pharmacogenomics. I also presented an early prototype (PGx@Pitt 1.0) to the users for feedback. We developed an interview guide (Appendix B) as a team based on information needs research strategies[113,114]. Each interview lasted approximately 45 minutes and was audio recorded, with permission from participants. The study was approved by the University of Pittsburgh Institutional Review Board (IRB).

I recruited 14 pharmacists through professional connections of the team using a convenience sampling strategy[114] designed to represent the diversity of needs and

perspectives associated with different care contexts including tertiary care centers, community practice, and private nursing home consulting pharmacy. I recruited until we reached saturation in the interviews and determined that no new concepts were being mentioned by participants. Interviews took place from December 2013-August 2014, and were conducted in the participant's place of employment.

3.1.2 Data analysis

Audio recordings of interviews were transcribed verbatim before being analyzed using descriptive coding[114,115]. We developed a codebook (Appendix C) with a preliminary structure answering four basic questions, in general and specific to pharmacogenomics:

1. What information needs do pharmacists experience while managing drug decisions?
2. What resources do they use to find drug information and why do they use them?
3. What do they like and dislike about them?
4. What tasks do they complete in a typical day related to drug decisions?

We coded using a structural approach: we developed conceptual phrases a priori that represent ideas from the research questions, then applied them to the interview transcripts, adding codes throughout the process within the structure of codes (described above) as necessary to more finely represent the participants' responses[115]. This analysis was intended to identify themes and sub-themes regarding information seeking behavior and perceptions of information resources in general and regarding pharmacogenomics. After coding was

completed, we grouped them into similar categories and assigned theme terms that connected them as a group of repeated, similar ideas[115]. Codes were assigned to sections of text and organized using QSR NVivo™.

Two analysts coded seven of the transcripts independently to identify information need themes related to pharmacogenomics and to revise the emerging codebook accordingly. They discussed the differences to resolve disagreements and achieve consensus on codes that were used for the remainder of the transcripts. The number of subjects who mentioned each code was counted for descriptive purposes.

3.1.3 Results

Fourteen pharmacists participated. Table 5 describes their demographic information. Participants varied in length and type of experience (students, residents, and clinical pharmacists), and distribution of work contexts, including hospital, ambulatory care, nursing homes, and retail pharmacy.

Table 5: Demographics

	N=14
Sex (N)	
Female	10
Male	4
Ethnicity (N)	
Caucasian	13
Asian	1
Job Title (N)	
Clinical pharmacist - hospital	5
Clinical pharmacist - nursing home consultant	3
Clinical pharmacist - ambulatory care	2
Pharmacy student (3rd year)	2
Pharmacy resident - hospital	1
Retail pharmacist	1
Years as Pharmacist	
<5	5
5-15	5
>16	4
Years at Current Employer	
<5	6
5-15	7
>16	1
Pharmacogenomics Experience	
Had patients with pharmacogenomics testing in last year	0
Recommended pharmacogenomics testing	0

3.1.3.1 Pharmacogenomics in Practice

All of the pharmacists had encountered pharmacogenomics through seminars, continuing education, or reading. None of the participants reported current use of pharmacogenomics information in practice. None had previously recommended genomic testing or personally managed a patient who had undergone pharmacogenomics testing. However, all anticipated that pharmacogenomics will have a growing impact on their practice in the near future by

assisting them in making informed recommendations that improve quality of care and health outcomes.

3.1.3.2 Pharmacogenomics Information Needs

Analysis of the interview transcripts led to the identification of 36 information needs that are directly or indirectly related to pharmacogenomics. Table 6 contains general information needs that can apply to pharmacogenomics. Table 7 contains information needs specific to pharmacogenomics. Other identified information needs not directly related to pharmacogenomics include general prescribing information such as cost, intravenous stability, and additive information, among others. The full list of information needs is available as supplementary material (Appendix C). The information needs were grouped in to four categories: background information, patient-specific information, medication information, and guidance information.

Participants indicated that they find information in a variety of places, including books, journals, primary literature databases such as PubMed, resources provided by or mandated by the FDA, such as product labels and DailyMed, professional societies, drug companies, electronic health records, internal information resources at their place of employment, patients, search engines such as Google, the Centers for Disease Control and Prevention, and Medwatch. They also use tertiary resources, including the following frequently mentioned: Clinical Pharmacology, Dynamed, Facts and Comparisons, GlobalRPH, Hippocrates, Lexicomp, Micromedex, RXpertise, and UpToDate. The complete list is available in Appendix C.

Table 6: General Information Needs Related to Pharmacogenomics

Information Need	N=14	Example Quote
Background Information		
Evidence	6	"I like…actually being able to pull… the study [where], they actually had data that said that these people did better or didn't require dosages [changes]."– Pharmacist 9
Patient Information		
Concomitant medications	9	[Regarding other information needed]: "Other medications, type of stent, timing (of previous [myocardial infarction]), other medications they might be on, [proton pump inhibitor]PPI controversy, other medical conditions, any other anti-coagulation thrombotic type of conditions the patient might have. That I could find in the e-record. I'm not sure there would be much else outside of that." – Pharmacist 2 "What other medications he may be receiving, currently…if it was one of those situations where I had to adjust the dose, I would still like to see what else they were on. Because sometimes, depending on some different factors, there could be other anticoagulants involved. You know, even if its low dose aspirin, there could be something potential there that would increase a bleeding risk or a side effect, based on what he was already receiving." – Pharmacist 10
Medical condition	7	
Allergies	3	
Medication previously taken	1	
Patient preferences	1	
Length of time taking drug	1	
Population-specific information	1	
Medication Information		
Drug Safety	13	"If it's a completely new drug, mechanism of action, pharmacokinetics and pharmacodynamics, and depending on the specific question, potentially metabolism, elimination, and major side effects." – Pharmacist 9 "I would like to know what is the efficacy rate of patients getting clopidogrel with that variant and what are the bleeding rates of patients getting clopidogrel with that variant. I would want, what I always want, is safety and efficacy. Do the risks outweigh the benefits? That's everything I do so that's the information I would want." – Pharmacist 3 "Our system supplies medications in peoples' claims history, so that they may be filling [drugs] that have the interactions… there's other ones that I'm not as familiar with and I like to go and actually plug them into a database and see what the interaction is to learn for myself. So I don't like to arbitrarily say, 'Oh, there's an interaction here, like you need to take care of that' – I like to actually know for myself, like the mechanism of the interaction."- Pharmacist 5
Drug Efficacy	12	
Drug-drug interactions	7	
Other drugs in same class	4	
Comparative Effectiveness	3	
Drug toxicity	3	
Pharmacokinetics	2	
Drug equivalency	1	
Mechanism of Action	1	
Pharmacodynamics	1	
Drug metabolism	1	
Drug elimination	1	
Side effects	1	
Guidance Information		
Recommendations or guidelines	14	"I want to learn more about what is actually going on so that I could understand it and give a clinical recommendation rather than just, "ok, this is what it does and that's what I should do," you know? I like reading into it, maybe that would be helpful for some people that really need like a quick answer but I thought it was better to look for what's actually happening and … this is what's occurring and this is what you should do." - Pharmacist 8
Monitoring requirements	13	
Drug indications	13	
Dosing	8	
Alternative drug choices	6	

Table 7: Pharmacogenomics-specific Information Needs

Information Need	N=14	Example Quote
Background Information		
Pharmacogenomics Background Information	10	"I was definitely looking for just a description of the basic, 'what does this [gene] do' before we even talk about the drug" –Pharmacist 8
Pharmacogenomics Evidence	6	
Test Information	8	
Test Parameters	2	
Patient Information		
Phenotype Information	14	"What I would want to know is … what does this mean for this person? You know, they're a poor metabolizer, OK, can I give the drug? Can I not give the drug? If I give the drug, what do I have to do as far as dosing? What do I have to look for, as far as side effects? So, whatever you could do to simplify…you know…poor metabolizer, do this, rapid metabolizer, do this, that would be helpful." –Pharmacist 10
Variant Information	13	
Severity of Pharmacogenomics Risk	4	
Population Frequency (of biomarker)	3	
Medication Information		
Other drug(s) affected by the biomarker	5	"I would want to know if there's any other drugs that might be affected by this [biomarker]?" –Pharmacist 3
Guidance Information		
Pharmacogenomics Guidelines	6	"I would like to see guidelines around it, outcomes research, something that I could confidently say, if we had a drug on formulary we're thinking about, here's the patient I would restrict to, here's the group that needs to be involved to prescribe it." – Pharmacist 2

3.1.3.3 Pharmacogenomics Resource Requirements

Pharmacists identified what they perceived to be strengths and weaknesses of information resources and information. We identified three major themes that these traits fit into: the structure of the resource, pharmacists' perception of the resource, and characteristics of the information provided in the resource. These traits are defined and summarized in Table 8.

Table 8: Pharmacists' Resource Requirements

Requirement	N=14	Example Quote
Structure of the Resource		
Has references	6	"I liked that it had that reference so that I could click and learn more about it from the original report to the FDA, when they found that. So I liked that. I like to know where things come from. – Pharmacist 13
Visualizations	6	
Links to other resources	3	
Peer-reviewed	1	
Online	1	
Full-text	1	
Perception of the Resource		
Organized	12	"I like the different sections, and where you can…on the application, hit "Jump to", and you can quickly go to dosage forms it's in, or monitoring parameters, and you just jump around very quickly." – Pharmacist 14 "[It has] pretty thorough information from a reputable source, and it breaks down the various types of information that are available. And depending on the medication, it gives the clinical significance, what has been done, and also the recommendation." – Pharmacist 9 "We get Micromedex™ for free, so that's why a lot of people use that one, and I think it's obviously much more reliable." – Pharmacist 5 "I couldn't practice very well without [drug information resources?]. There's a lot of data that is internal but a lot of this as far as medical education has gone more to focusing on the amount of data that you cannot possibly internalize and the deviations in how quickly it changes, it's impossible to keep up with every little thing so it's always good, even if you are sure of something, to check it out." – Pharmacist 1
Familiar	8	
Available	6	
Credible	5	
Good reputation	3	
Regularly Updated	2	
Free	2	
Helpful	2	
Reliable	2	
Necessary	2	
Good mobile version	1	
Preferred by physicians	1	
Perception of the Information		
Easy to use	14	"I like it because it's easy. I usually go to certain ones that I'm familiar enough with, using them online, or in a book, or on my phone, so that I know where to retrieve the information quickly when I need it." – Pharmacist 10 "Up-To-Date™, you can actually use to treat a patient. Like I have one patient who is going through alcohol withdrawal and you can kind of really look it up and figure out that they need…I think Up-To-Date™ is a lot more useful clinically." – Pharmacist 14 "I think it's quick. I think it's easy. And I think it's concise. All things that you want, when looking for information of this type. " – Pharmacist 10
Quick	13	
Concise	12	
Thorough	10	
Clinically relevant	5	
Accurate	4	
Objective	1	

The pharmacists had strong feelings about the resources they prefer to use. They all discussed using multiple resources depending on the situation, including tertiary resources (e.g. Lexicomp™, Up-To-Date™, and Micromedex™), primary literature, the FDA, and even drug companies. Eleven out of 14 pharmacists mentioned using the FDA product labels. While they all trust the information provided by the labels, it was not usually their first choice.

Interestingly, many stated that they dislike seeking information in the product label because "the hard part about the label is you end up having to go to multiple sections to find information." (Pharmacist 2). She prefers to start in a tertiary source, see what they say, then check the label itself to confirm, and then to be sure, she goes to the literature: "I like to confirm everything a couple places and sometimes the labels are a little behind the actual evidence. So I would probably take this information, go to the literature to see if I could confirm that." Pharmacist 9 has a similar workflow: she finds answers and then confirms them with the product label, because "not that there's bias, or potentially wrong information, but getting it from the source is better than…more accurate, generally, is what I would say."

3.2 AIM 2.II: USER PERSONA AND USE CASE SCENARIOS

3.2.1 Materials and Methods

We used the results of the qualitative inquiries to develop a use case persona of a composite pharmacist and use case scenarios. The persona was written by the authors as a composite of the characteristics discussed and observed during the qualitative inquiries. The user scenarios describe the likely use cases, information needs, and workflows of pharmacists who will engage with pharmacogenomics information.

3.2.2 Results

The following persona (Table 9) is a composite of the pharmacists who participated in the interviews, with results of the interviews informing descriptions of values and goals.

Table 9: User Persona

Description of a Composite Pharmacist Based on Interviews	
Demographics	Margaret, Clinical Pharmacist, female, 40 years old , 15 years of experience at large academic health system
Work style	As Margaret's work is fast-paced, she is often multi-tasking. To meet these demands, Margaret places a high value on using easily accessible, trustworthy information to make fast decisions.
Job Tasks	Margaret's job requires her to round on patients, answer questions from physicians, and make recommendations about medication treatment plans. She interacts with clinicians of all types, including physicians, nurses, and other pharmacists.
Experience with information resources	Margaret has worked with many different information systems, including electronic medical records, tertiary drug information resources, and literature searching tools. She uses all of them regularly. Her favorite tertiary resources are Lexicomp™ and Dynamed™, but she also uses Micromedex™ and Up-To-Date™. She checks everything against the FDA product label.
Preferences in information resources	Trustworthy information from a familiar resource is important to Margaret. She is particularly inclined to trust familiar resources that answer her questions quickly and succinctly, with the ability to get more details if she needs them. She wants to know the source of the information, and prefers primary sources and FDA information.
Values and goals at work	Margaret takes her job very seriously. As she is particularly interested in evidence-based medicine, she strives to stay apprised of the latest developments in the literature. Her colleagues consider her very well informed, and trust her judgment and advice. Margaret values having and using cutting edge medical knowledge; educating herself and her colleagues on new developments in both medical science and clinical practice. She has a strong interest in continuous improvement of medical care and information resources.
Experience with Pharmacogenomics	She is aware of pharmacogenomics and the effects genotypes can have on different drugs. She would like to incorporate pharmacogenomics information and data into his practice, because she wants to both optimize patient care and safety, and protect her license. Genotyping is not currently being performed in her health system but she expects it to become more common in the future, and thinks it will improve clinical care and outcomes.

The following use case scenarios (Tables 10 and 11) describe situations where a pharmacist encounters a question about pharmacogenomics and needs to make a decision about how to find information, use information, and make a decision based on the information.

Table 10: Use Case 1: General Pharmacogenomics Question During Hospital Rounds

Tasks	Margaret is on rounds, using her mobile device to find and share medication information with the clinicians. She also has access to the EMR system.
Information Needs	One of the residents wants to switch a patient's medication to clopidogrel, and asks Margaret what the group should know about it. She wants information about the drug, specifically the presence of important genotypes that could predict the patient's response before she fills the prescription, whether the patient has been tested for any of those genotypes, and what the results are, if the test has been performed, what the results of the test might mean, and if/how the treatment should be changed based on the results.
Information Seeking	She has tried using other resources to answer these questions, such as the hospital's intranet resources, Micromedex™, Lexicomp™, and Up-to-Date™, but they don't answer her questions. She has heard about other resources, such as PharmGKB and GeneTests, but when she looked at them previously, she did not understand the information presented to her enough to use it.

Table 11: Use Case 2: Clinical Decision Based on Patient Genotype

Tasks	Margaret is verifying medication orders. She sees in the EMR that the patient has a genotype that can result in an undesirable response in patients taking abacavir.
Information Needs	She wants information about how severe the response is, how likely it is that the patient will experience an adverse medication event as a result, what the adverse medication event is likely to be, whether she should recommend the physician switch to a different treatment, and what the change ought to be (different drug, or different dose).
Information Seeking	The information Margaret is looking for is not available in the EMR. She has to leave this system to find any information about pharmacogenomics, and she has a hard time understanding the information she finds in other resources. She finds a recommendation in the product label, which she considers difficult to use, though she trusts the information.

3.3 AIM 2.III: PGX@PITT REDESIGN

Using the information needs, resource requirements, and information models identified and developed in Aims 2.i and 2.ii as guides, we iteratively re-designed the prototype interface to better meet pharmacists' needs and support their information seeking behavior when managing medications with pharmacogenomics implications.

3.3.1 Materials and Methods

We used web development tool web2py[116] to develop and extend the existing prototype tool. Web2py is an open source web framework that uses Python to develop secure, database-driven web applications. It has a model-view-controller web framework. It can interact with SPARQL to query a triple store to access the RDF representation of the annotated pharmacogenomics statements.

Using the information needs, resource requirements, and information models identified and developed in previous work, we re-designed the prototype interface to better meet pharmacists' needs and support their information seeking behavior when managing medications with pharmacogenomics implications. Specifically, we reorganized the information available in the resource to minimize the time spent searching for answers to the most pertinent questions pharmacists have. We also redesigned graphical pathways illustrating the relationship between the drug, genotype(s), phenotype(s), and FDA recommendations. We presented the iterative interface changes to five pharmacists and pharmacy students 3 times throughout the design process for feedback.

3.3.2 Results

3.3.2.1 Design Changes

Figure 8: PGx@Pitt v. 1.0, Main Page

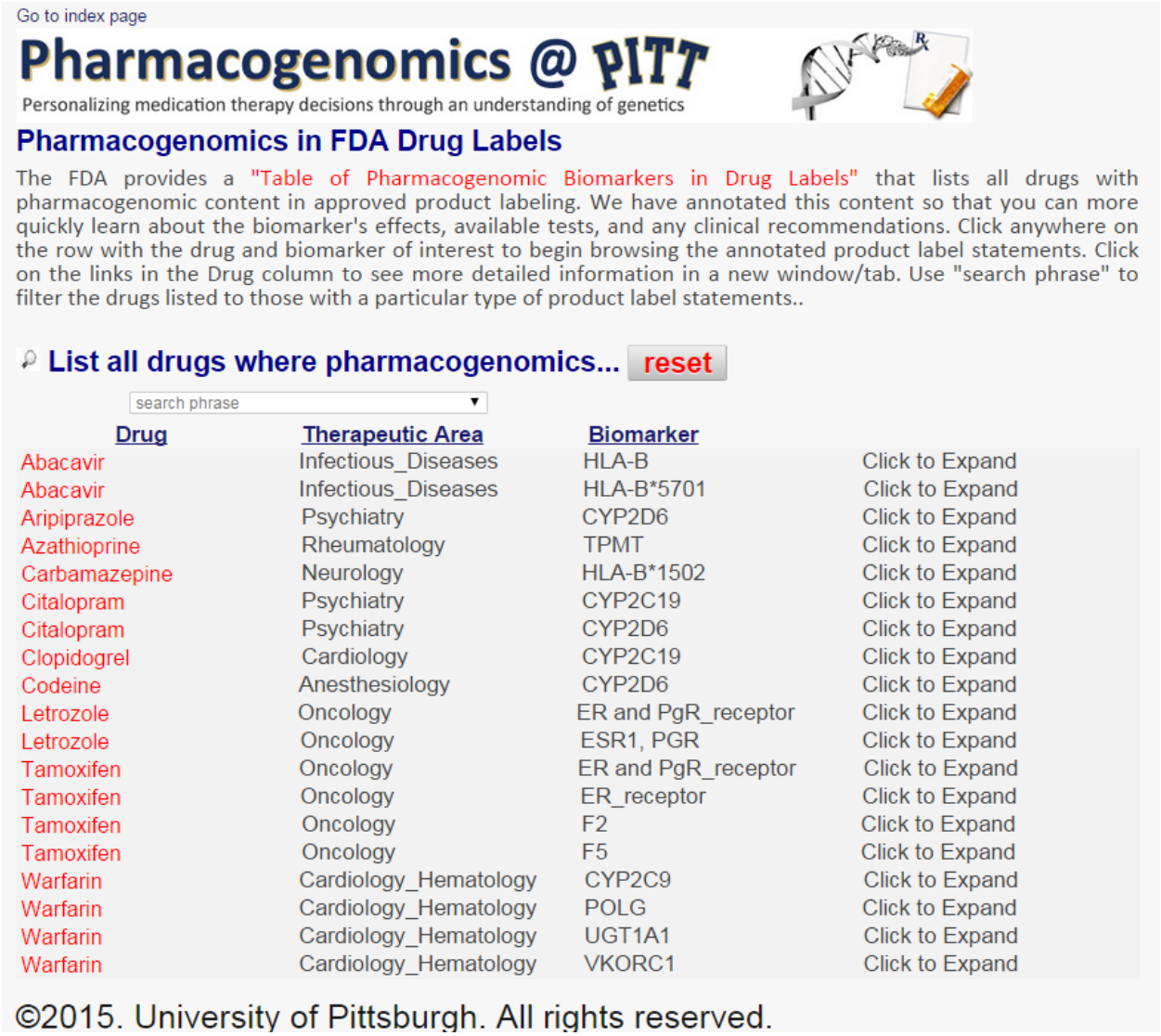


Figure 9: Drug page of PGx@Pitt v. 1.0

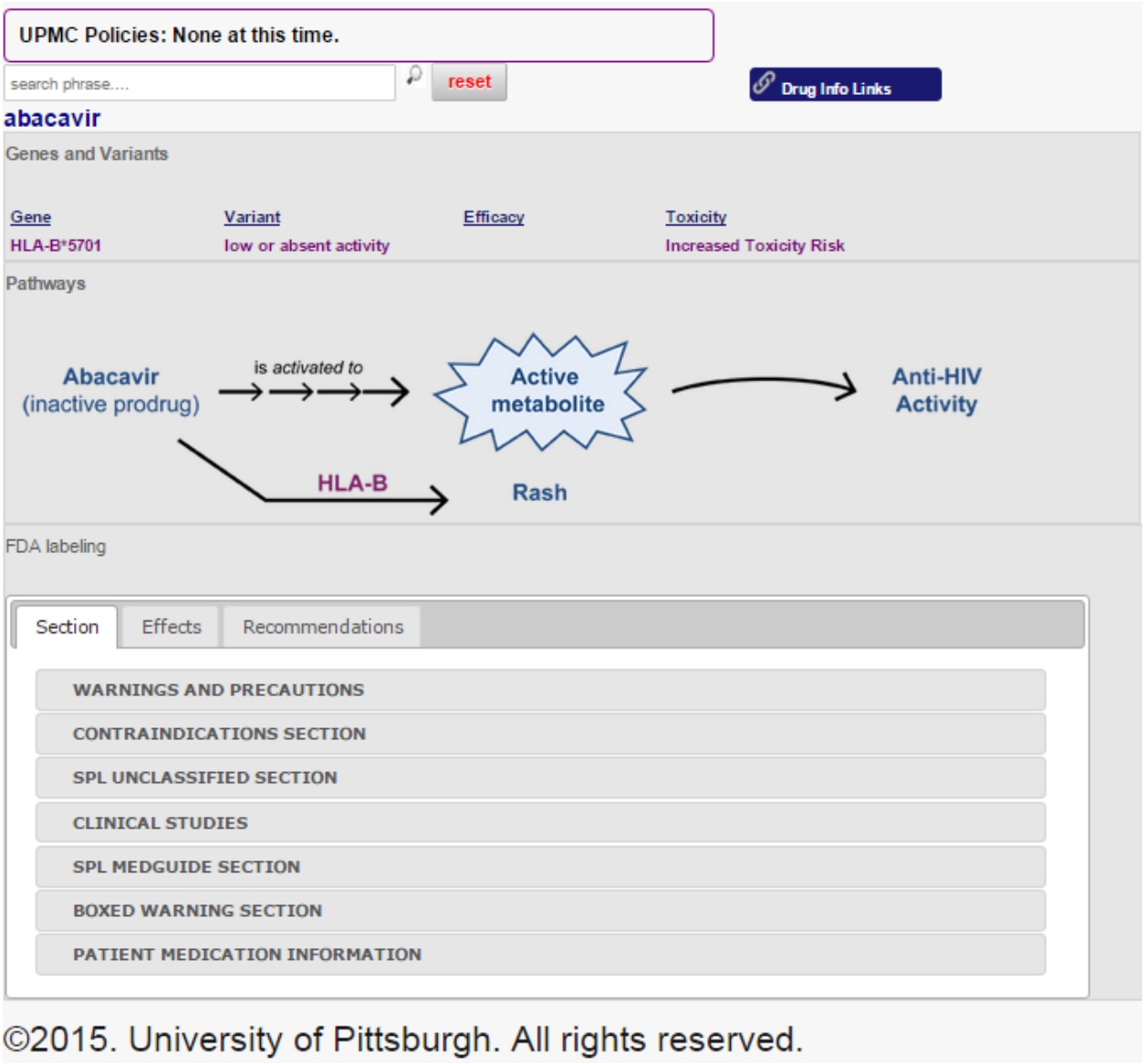


Figure 10: Expanded FDA Label Annotations Section of PGx@Pitt v. 1.0

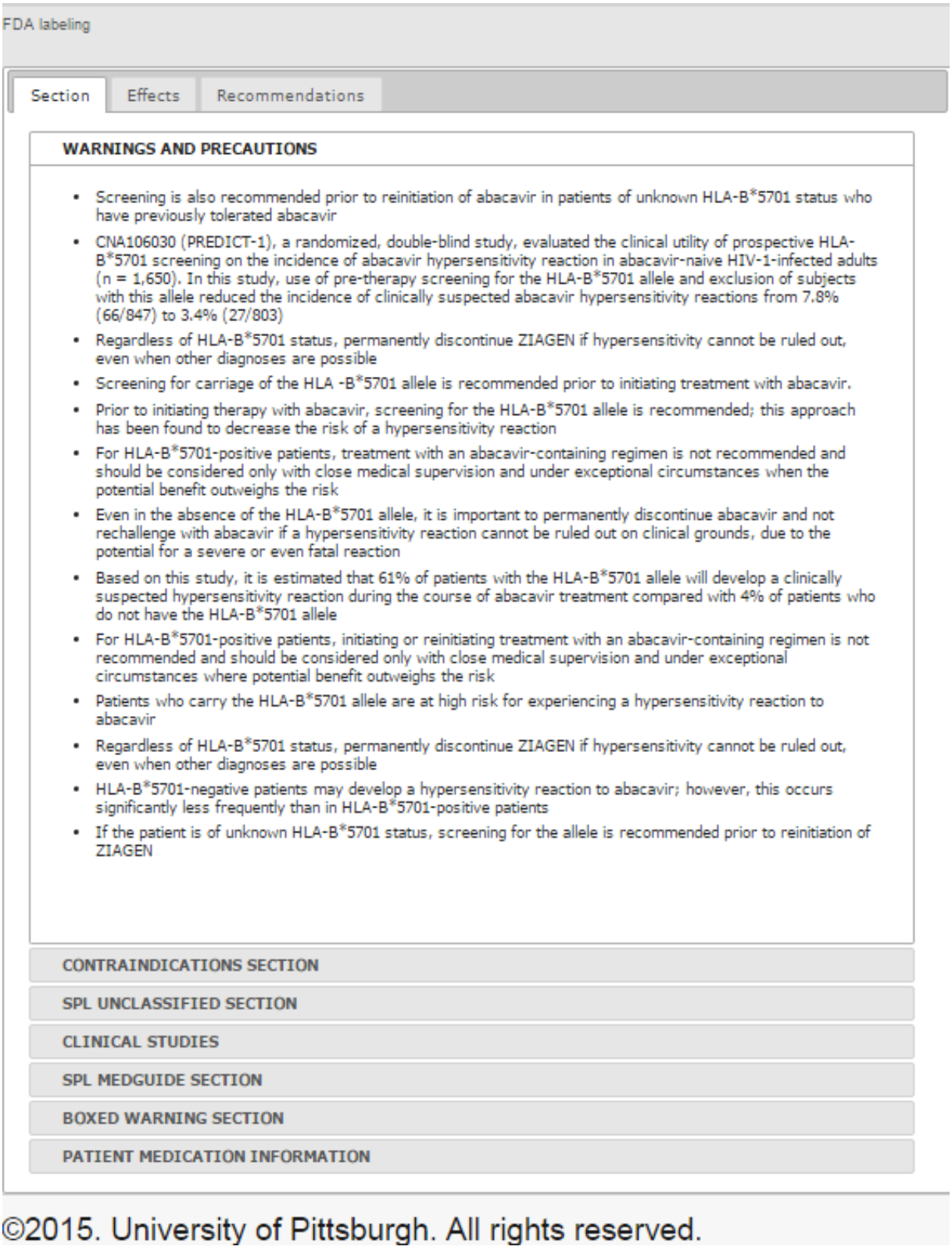
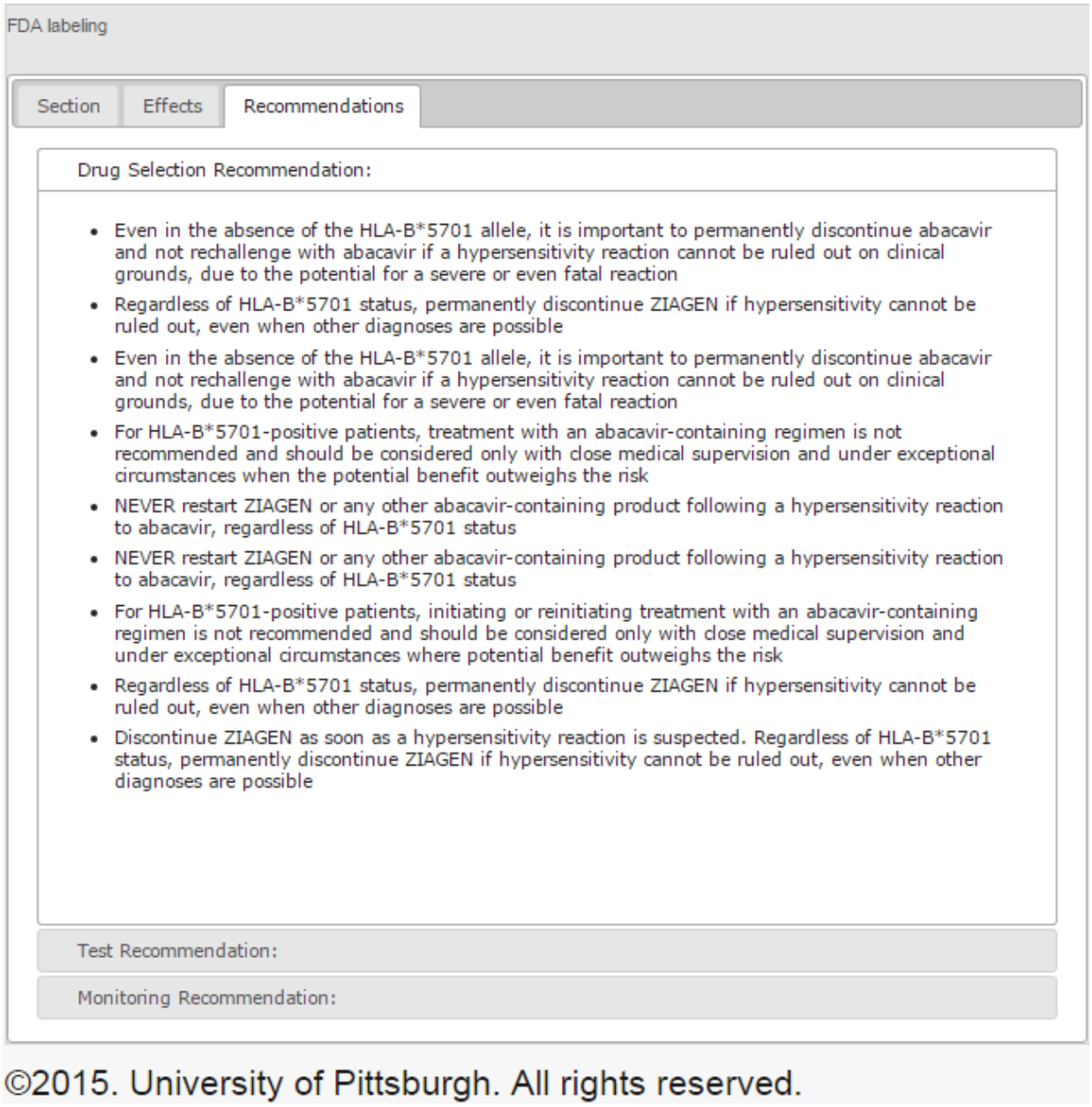


Figure 11: Expanded Recommendations Section of PGx@Pitt v. 1.0



The first version of the prototype was designed to provide information on the following: the change in efficacy or toxicity as a result of a particular gene variant (Genes and Variants, Figure 9); a simple pathway illustrating the relationship between the gene variant and the drug (Pathways, Figure 9); and the annotated statements from the product label in an accordion-style interface (Figures 10 and 11), organized by product label section, pharmacokinetic and pharmacodynamic effects, and recommendations (such as dose or testing recommendations). These prototype design decisions were made based on the recommendation of a two pharmacists, to provide a simple interface for potential users to use and provide feedback.

Table 12: Usability Observations and Design Changes

	Layout		Information Display			Information	
Observation	Users did not notice accordion sections.	Users appeared to not notice "Drug Info Links" table and links.	Efficacy and toxicity not well understood, phenotype explanations were confusing	"Star" notation unclear	Participants wanted a clear recommendation	Participants wanted to know information source	Participants requested background info to be able to understand pharmacogenomics
Change	Change tab design of SPL sections	Change "For more info" box	Combine toxicity and efficacy information with pathway diagram in new table diagram			Provide source of information more clearly	Provide background information
Specific changes	Reorganize tabs: Boxed warning, PD/PK, and recommendations in "Summary", rest in 2nd tab	Move to right of screen, permanently open	Replace efficacy and toxicity information with phenotype information	Have "variant" column in new diagram	Provide recommendation, if appropriate, with a visual aid	Make links box easier to find, with clear link to source product label at DailyMed	Add links to other resources "primer" pages

The pharmacists were generally receptive to the information provided by the first version of the pharmacogenomics resource during the qualitative inquiries. However, they experienced some difficulty related to usability and understanding the information presented to them. We organized these problems into three categories (Table 12): Layout, Information Display, and Information. The layout was problematic because the accordion design of section containing the information from the product label seemed almost invisible. They also did not

notice the Drug Info Links table. As a result, many of the pharmacists were unable to access in the product label information, and they requested links to other sources despite those links being available. While they liked the illustration of the interaction between the drug and the gene, they were often confused by the table containing information about efficacy and toxicity, or how that influenced the phenotype. They were also confused by the notation of the gene variants ("star" notation), and they wanted a clear recommendation. Finally, they were concerned about the source of the information. It was not clear to them that all the statements originated from the FDA-approved product labels. They also wanted more background information in general about pharmacogenomics, and specifically about the drugs and genes to understand the information presented to them.

3.3.2.2 Re-designed Interface: PGx@Pitt v. 2.0

We made very few changes to the main page, except we streamlined the table (Figure 12). We re-designed the pathway portion of the drug page by combining the table at the top of the page (Figure 9) with the graphical pathway. This ultimately became a table with visual aspects (Figure 13), leading the user from the interaction between the drug and the variant, to information about the phenotype, and finally to the FDA recommendation. We reorganized the tabs so the most relevant information is presented first: Boxed Warning, and recommendations related to the drug selection, dosage, and genetic testing, if relevant. Then all the other information was provided on the second tab, organized by product label section (Figure 14). Our goal was to focus their attention to the product label information with the most relevant information first, then allow them to explore the rest of the label information on the second tab while making it

clear that it all came from the product label. We also made the links to other resources more visible, including a link to the exact product label used for the annotation.

Figure 12: PGx@Pitt v. 2.0, Main Page

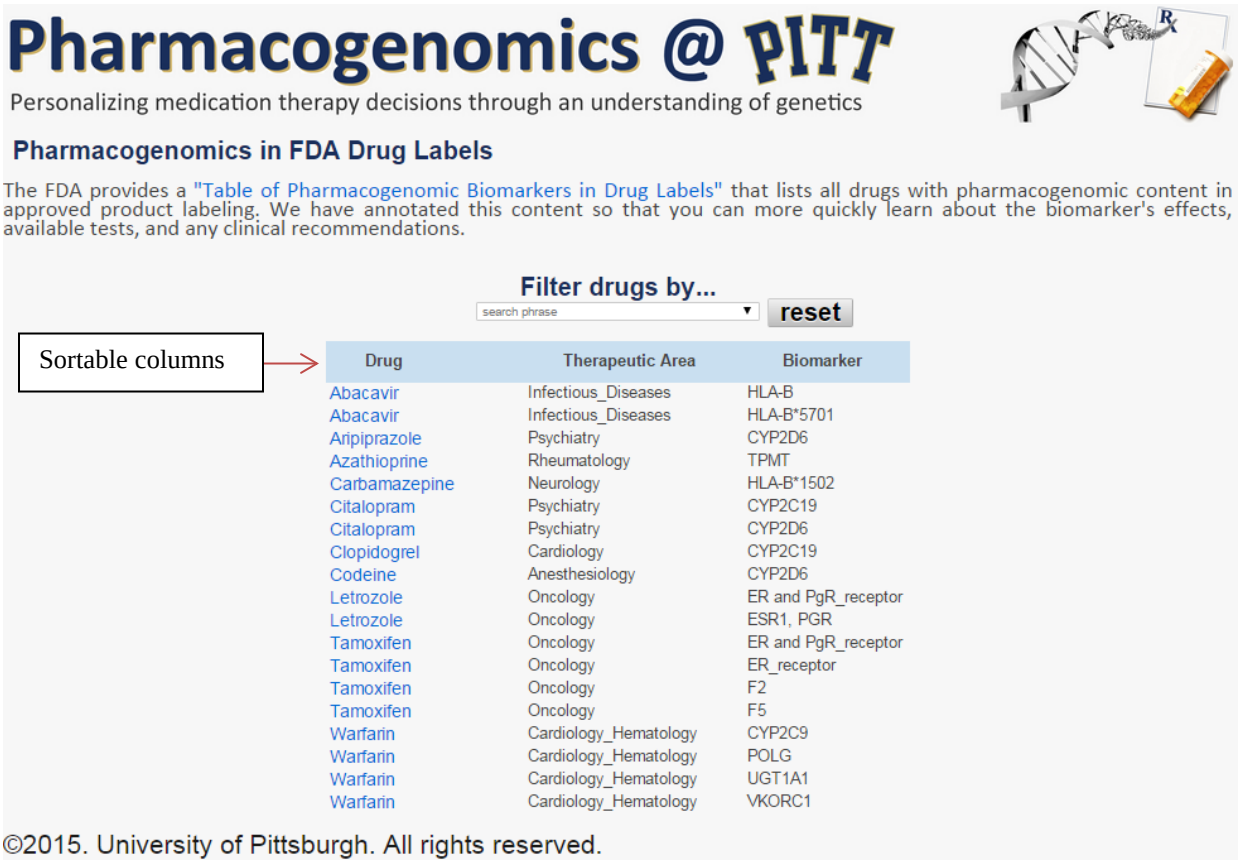


Figure 13: PGx@Pitt v. 2.0, Drug Page

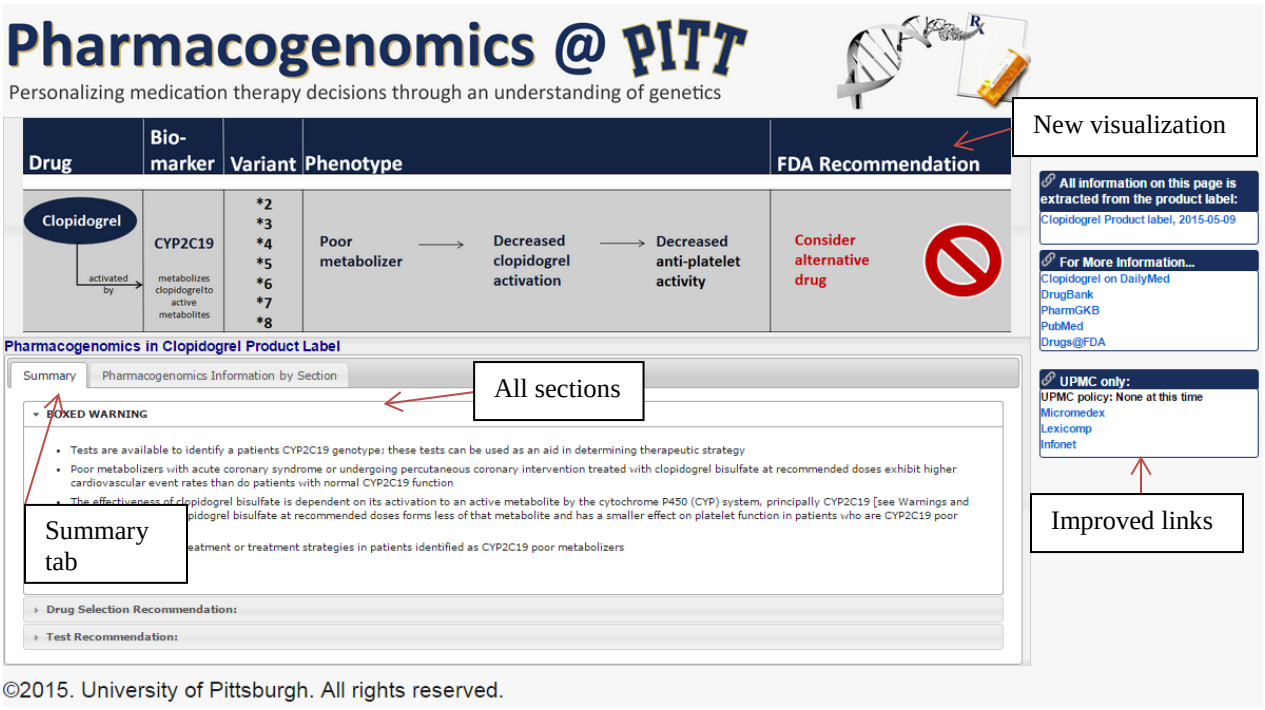
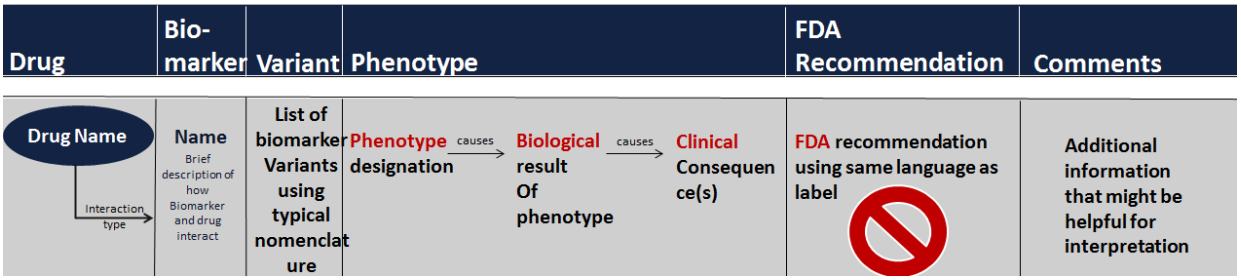


Figure 14: PGx@Pitt v. 2.0, Product Label Annotations section

3.4 DISCUSSION

To our knowledge, this is the first study to explicitly identify pharmacogenomics-related information needs of pharmacists, and to discuss these needs in the context of preferences and requirements regarding pharmacy information resources. We sought to understand the pharmacogenomics-specific and general information needs of pharmacists, and how they would incorporate pharmacogenomics information into their practice. We used qualitative inquiries to elicit information needs and information resource requirements of pharmacists when engaged with pharmacogenomics information. The novel findings of this study include a list of general and pharmacogenomics-specific information needs, and a related list of requirements for information sources. We also re-designed the interface of our pharmacogenomics information resource based on the results of the qualitative inquiries. In particular, we developed a novel way of presenting the complex information that comprises pharmacogenomics information: drug, gene, variant, phenotype, and recommendation information. The generic presentation is shown in Figure 15.

Figure 15: Generic Model Presentation of Pharmacogenomics Information



Participating pharmacists' information needs, both generally and specifically for pharmacogenomics, fall into four categories: background, medication, patient-specific, and guidance-related information. These needs are similar to those of physicians, particularly with respect to the interpretation of test results, recommendations for alternatives, prevalence in various ethnic groups, and genotypic testing information[7,8]. We found specific information needs directly and indirectly related to pharmacogenomics that were not identified in similar studies of physicians pharmacogenomics knowledge gaps[7] and the usability of pharmacogenomics decision support aids[8]. These include monitoring information, severity of risk, and other drugs affected by a biomarker. Table 13 shows the themes identified in this work compared to themes identified in other work.

Table 13: Pharmacogenomics Information

Theme	Current study	Johansen Taber, et al.[7]	Devine, et al.[8]
Background Information	X	X	
Patient Information	X	X	X
Medication Information	X	X	
Guidance Information	X	X	X
Structure of Resource	X	X	
Perceptions of Resource	X		X
Perceptions of Information	X		X

Pharmacists in this study prefer resources that are peer-reviewed, online, full-text, referenced, with visualizations and links to other sources (Structure of the Resource). They perceive high quality resources to be familiar, trustworthy, up-to-date, and well organized (Perceptions of the Resource). Finally, they perceive high quality information to be quick, concise but thorough, relevant, accurate, and easy to use (Perceptions of the Information). In particular, they are very concerned with the provenance of the information: they want references, access to full-text studies, and prefer information that comes from FDA-mandated product labels. If they are unsure of the provenance, they prefer to rely solely on what the product label states.

3.5 LIMITATIONS

Alternative approaches (focus groups, surveys, embedded observation) exist that could have been used to address these questions and may have found different results. None of the participants had had prior knowledge of the information resource. Coder bias in analysis and interpretation can be a limitation of studies of this type. To address this bias, the transcripts were reviewed and coded with 50% overlap by two researchers. Discrepancies in agreement were discussed by the coders and brought to consensus. In addition, we validated the results with member checks with pharmacists. It is possible that the unfamiliarity of participants with pharmacogenomics is a limitation, but it is an accurate reflection of the current state of the practice. While the study provides a detailed description of pharmacists' information seeking behavior and information needs, the results may not be generalizable to all pharmacists or all clinicians in other settings. The participant clinician types were slightly skewed towards nursing home consultant pharmacists. That group has had the least exposure to pharmacogenomics. While their feedback was very helpful, we decided to write the user persona to reflect a hospital-based pharmacist rather than a community or nursing home based pharmacist, because we anticipate that hospital pharmacists will encounter pharmacogenomics before other environments. The study is limited by the small sample size, but we found a priori that the study was sufficiently powered with only 12 participants based on the time measurement in seconds. We sought 16 so we could have even distribution of the 8 questions across all 4 resources.

4.0 AIM 3: EVALUATION

4.1 MOTIVATION

Researchers have established the feasibility of incorporating genomic information into EMRs[117], and we know that interpreting this information clinically at the point of care is difficult[7,22,54,118]. Little work has been performed focusing on the display and interpretation of genomic pharmacogenomic information in the context of medication prescription.

4.2 AIM 3: CONDUCT USABILITY STUDIES TO EVALUATE THE TOOL AND INFORM POTENTIAL IMPROVEMENTS.

I conducted laboratory-based usability studies, specifically, empirical comparisons of simulated decisions[119]. Pharmacists and pharmacy students were asked to find pharmacogenomics information available in FDA-approved product labels to answer specific questions using the redesigned version of PGx@Pitt (version 2.0), the previous version of

PGx@Pitt (version 1.0), the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, and the FDA labeling information in PharmGKB.

Measurements included: time to answer the question; correctness of the answer; and the user's subjective satisfaction with the information found and the resources used. Task correctness was measured as whether or not the subjects found the information they were asked to find, as determined by the researchers. Subjective satisfaction was measured using the System Usability Scale[120].

We hypothesized that PGx@Pitt version 2.0 would perform better than the other three resources on average time to answer questions, rate of finding a correct answer, and the user's subjective satisfaction with the information and resources. Further, we hypothesized that PGx@Pitt version 2.0 would outperform the other three resources particularly well on the multi-drug tasks.

4.2.1 Materials and Methods

Pharmacists and pharmacy students were asked to find pharmacogenomics information available in FDA-approved product labels to answer specific questions using the first version of the pharmacogenomics information resource (PGx@Pitt 1.0), the redesigned version (PGx@Pitt 2.0), the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm), and the FDA labeling information in PharmGKB (https://www.pharmgkb.org/view/drug-labels.do). We recruited pharmacists through professional connections of the authors using a

convenience sampling strategy[23] designed to represent the diversity of needs and perspectives associated with different care contexts including tertiary care centers, community practice, and private nursing home consulting pharmacy. Evaluations took place during July and August 2015, and were conducted in the participant's place of employment.

I developed 8 pharmacogenomics information tasks that could be answered on all 4 information resources: PGx@Pitt version 1.0, PGx@Pitt version 2.0, the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, and the FDA label pharmacogenomics information in the PharmGKB. The tasks are listed in Table 14. Four of the tasks are single drug questions, and four are multi-drug questions. The tasks were developed with the help of a professor of pharmacy with pharmacogenomics expertise. They are all able to be answered correctly using each resource. They cover a range of pharmacogenomics concepts that have been identified as important pharmacogenomics competencies for pharmacists by the American Society of Health System Pharmacists (ASHP) and the Pharmacogenomics Education Program at UC San Diego (PharmGenEd)[84].

The task order and the order of the resources were varied among participants to avoid order effects using a pseudo randomization technique. The order of tasks was randomly assigned to the first participant, and the order of tasks were assigned to each subsequent participant based on that first participant, to ensure that each task was performed on each resource an equal number of times. The order of resources was assigned randomly to each participant.

The resources were available locally, to guarantee that access would not be dependent on internet connectivity. We used HTTrack Website Copier[121] to download the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (downloaded June 2, 2015) and the FDA Drug Labeling portion of PharmGKB.org (downloaded June 5, 2015).

The pharmacists were instructed to only use the assigned resource for each task, and not to seek the information on any other sites. I recorded the pharmacists' activity on the screen and their voices simultaneously using SnagIt, a Chrome web browser extension, for screen capture[122]. The participants were instructed to highlight the text of the answer to each task on the screen when they found it. Each task had a maximum completion time of 10 minutes. Tasks that were not completed in this time were marked as incorrect. The task completion times for incorrect and incomplete tasks were measured as the time it took them to find the incorrect answer, give up, or reach 10 minutes. After all 8 tasks were finished, the participants completed the System Usability Score questionnaire[120], a validated assessment of perceived usability of systems and interfaces, for each resource. Measurements included: the time to complete each task from start to finish, as indicated by highlighting; the correctness of each answer as determined by the investigators; and the System Usability Score for each resource.

Table 14: Pharmacogenomics Evaluation Tasks

Task	*Correct Answer*
Single Drug Tasks	
1. A new patient with a prescription for warfarin is genotyped for all major pharmacogenes. Results indicate that he is CYP2C9 *2/*3, VKORC1 G-1639A AA. Using this resource, what starting dose is indicated for this patient, based on solely the genotype?	0.5-2mg, depending on other factors like weight, age, etc.
2. A physician has a patient with rheumatoid arthritis. She has had genotyping performed for all major pharmacogenes, and results indicate she is heterozygous *3A (1 copy of *3A, 1 copy of *1) for TPMT. The doctor wants to know if she can prescribe azathioprine to this patient.	Consider lower dose
3. Why should a patient with a CYP2C19 genotype other than *1 limit his exposure to citalopram to 20 mg/day?	Poor metabolizers are at risk for Qt prolongation.
4. A postpartum, breastfeeding mother tried to pick up her medications after being released from the hospital. The community pharmacist refused to fill the prescription for codeine because of a possible genetic issue. Why is the community pharmacist refusing to fill a codeine prescription for this patient?	Codeine should not be given to breastfeeding mothers due to the risk of neonate morphine overdose if the mother is an unknown ultra-rapid metabolizer
Multi-Drug Tasks	
5. A new patient is genotyped for all major pharmacogenes. Results indicate he is a CYP2D6 poor metabolizer. The patient is taking lisinopril, citalopram, metformin, warfarin, and zolpidem. Which of those drugs, if any, are affected by CYP2D6 genes?	None
6. If a patient is positive for HLA-B*5701, which of these drugs can she take: carbamazepine or abacavir? Both? Neither?	She can take carbamazepine, but not abacavir.
7. A cardiologist wants to know if genetic testing is available by the FDA prior to initiating cardiology drugs he frequently prescribes, such as clopidogrel, warfarin, atorvastatin, or prasugrel.	Clopidogrel and warfarin.
8. A patient who is predicted to be a CYP2D6 extensive (*1/*1) metabolizer based on genotype alone is taking fluoxetine. If her physician is considering adding aripiprazole, what is the recommendation regarding dosing?	50% dose reduction.

4.2.2 Data Analysis

Data was analyzed using MiniTab[123] and R[124]. Analysis included: descriptive statistics of demographic data of participants; regression to examine task completion time versus task number for order effect; the Kruskal-Wallis and Dunn test for post hoc pairwise correction to analyze the significance of task completion time comparing the four resources across all eight

tasks; a one-way ANOVA and Games-Howell test to analyze the significance of System Usability Scale scores of all four resources; and a Chi-square test of the correctness of answers for each resource, with a post-hoc pairwise comparison Bonferroni correction. *p*-values were considered significant at 0.05. We considered 3 types of incorrect answers: the user gave an answer that was wrong; the user failed to find an answer before 10 minutes; and the user gave up before finding an answer, but before the 10 minute mark. All of these are considered incorrect as they are a failure to find the correct answer.

4.3 RESULTS

16 pharmacists representing a variety of clinical practice environments with an experience range from 2 months to over 20 years participated in the usability evaluation. Most of the pharmacists were clinical pharmacists (9), and of those, a majority (5) was nursing home consultant pharmacists. Their demographic information is summarized in Table 15.

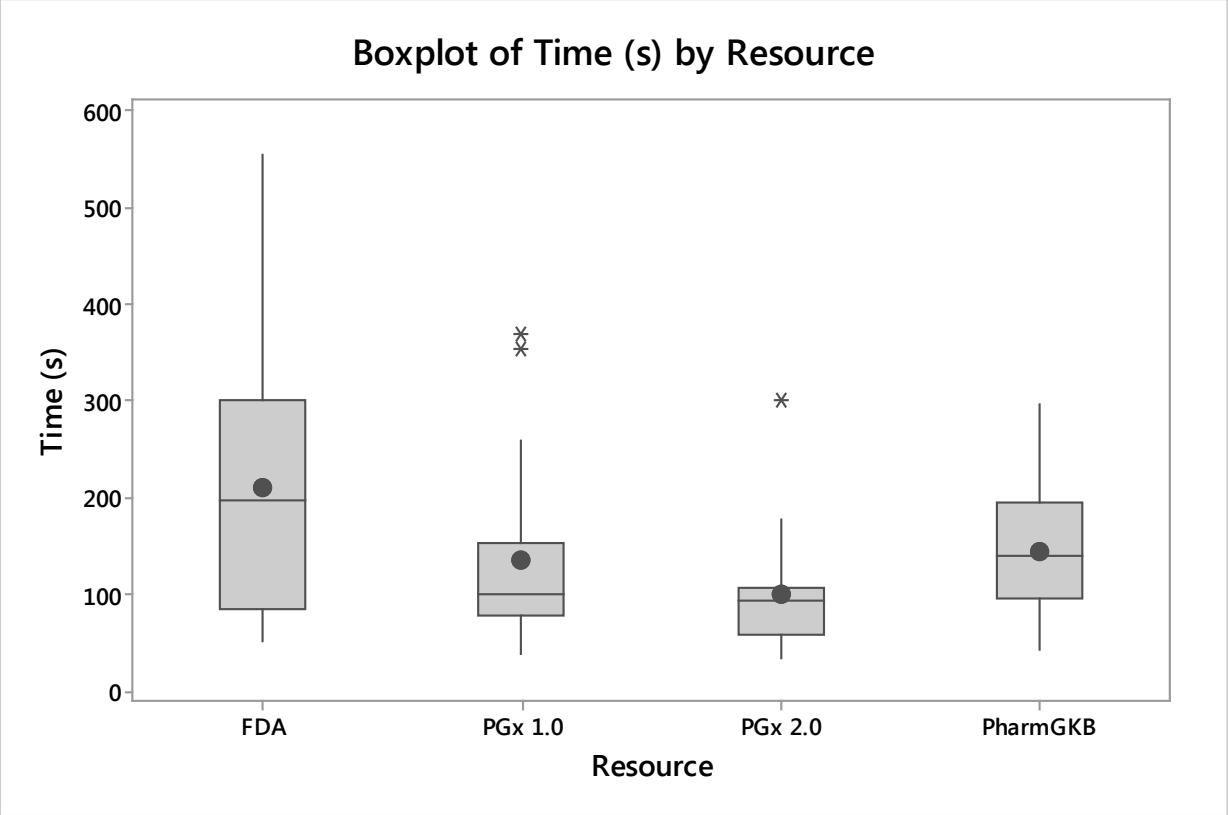
Table 15: Demographics

	N=16
Sex (N)	
Female	12
Male	4
Ethnicity (N)	
Caucasian	13
Asian	1
Hispanic	1
Other	1
Job Title (N)	
Pharmacy Student	1
Pharmacy Resident	2
Professor of Pharmacy	2
Clinical Pharmacist, nursing home consultant	5
Clinical Pharmacist, unit based	3
Clinical Pharmacist, director of patient care	1
Pharmacy director	1
Pharmacist, PhD Candidate	1
Time as Pharmacist (Years)	
Mean	7.54
Median	3
SD	8.9

4.3.1 Task Completion Time

The various resources had significant differences in task completion times (Figure 16) (Kruskal-Wallis, $p = 0.001$). Task completion time and order are not correlated ($p = 0.08$, $r^2 = 0.02$). Task completion times all followed a lognormal distribution, requiring the use of Kruskal-Wallis instead of ANOVA. Search tasks were completed more quickly using PGx 2.0 resource compared to both the FDA table (Dunn, $p = 0.003$) and PharmGKB (Dunn, $p = 0.0087$), as well as using PGx 1.0 compared to the FDA table (Dunn, $p = 0.0473$). All other pairs were not statistically significantly different.

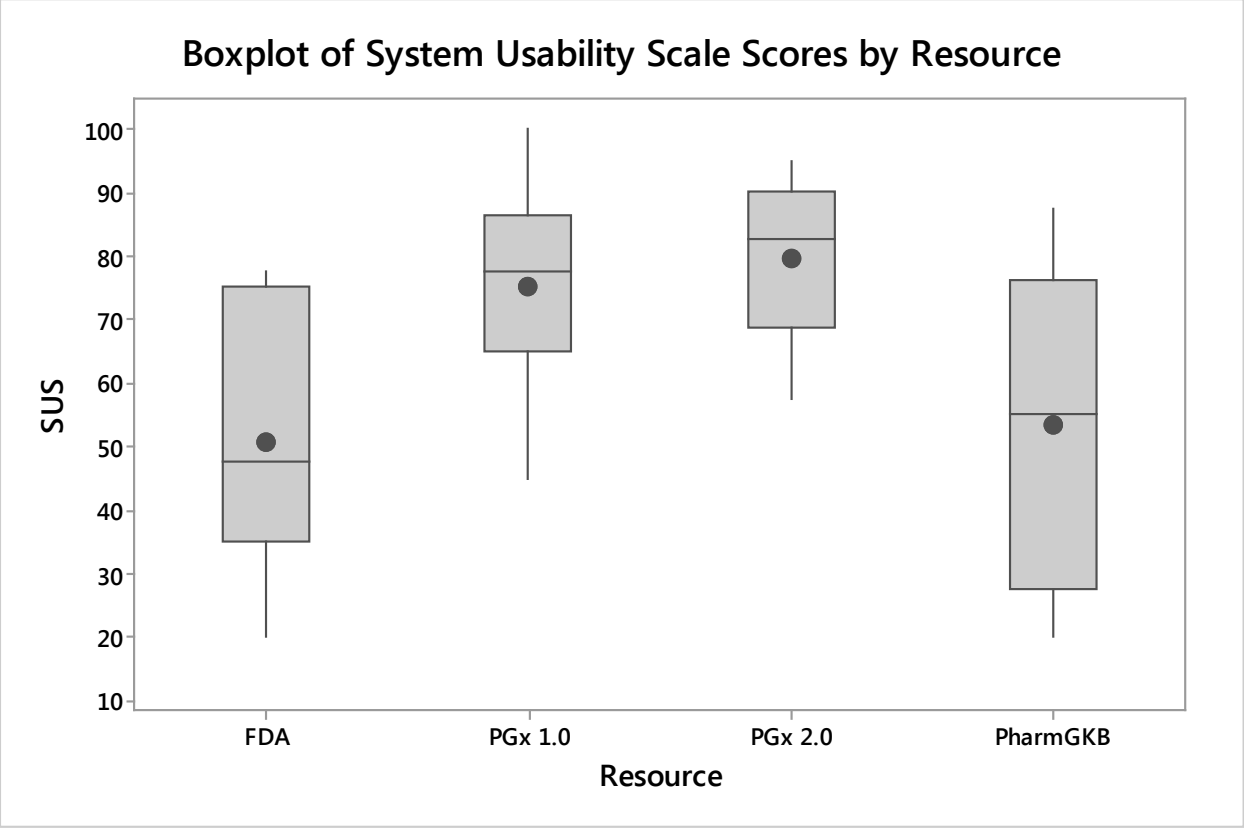
Figure 16: Boxplot of Time (s) by Resource. The boxes and whiskers represent the median interquartile ranges. The asterisks represent outliers. The solid circles represent the mean task completion times.



4.3.2 System Usability Scale Scores

Significant differences in SUS scores exist between the various resources (Figure 17) (ANOVA, $p < 0.0005$). The SUS score data are normally-distributed, allowing for use of ANOVA. The resources do not show equal variance so Games-Howell was used for post-hoc analysis. SUS scores were higher for PGx 2.0 than either the FDA table (Games-Howell, $p = 0.001$) or PharmGKB (Games-Howell, $p = 0.013$), as well as higher for PGx 1.0 than the FDA table (Games-Howell, $p = 0.01$). All other pairs were not statistically significantly different.

Figure 17: Boxplot of System Usability Scales by Resource. The boxes and whiskers represent the median and interquartile ranges. The asterisks represent outliers. The solid circles represent the mean SUS scores.



4.3.3 Task Correctness

Of the different resources, on only one (PGx 2.0) did users find the correct answer 100% of the time (Table 16). A Chi-square test with a Bonferroni correction showed a difference among the resources in rate of task correctness ($\chi 2(3,N=128)=13.393$, $p = 0.004$). Pairwise Chi-square tests with a Bonferroni correction showed that PGx 2.0 performed statistically significantly better than all other resources ($p = 0.006$). Of the incorrect answers (total = 22), in 2 cases, the participants ran out of time (maximum = 10 minutes); in 6 cases, the participants gave up; and

in the remaining 14, they found an answer they believed to be correct, but it was not the correct answer.

Table 16: Task Correctness Data

Resource	Correct	Incorrect	Total
PGx 1.0	27	5	32
PGx 2.0	32	0	32
PharmGKB	26	6	32
FDA	21	11	32

4.4 DISCUSSION

On task completion time and System Usability Scale scores, PGx@Pitt version 2.0 performed better than both PharmGKB annotated drug labels and the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling. PGx@Pitt 2.0 performed better than the FDA Table on task correctness. PGx@Pitt 2.0 was the only resource on which users answered every question correctly. Also, PGx@Pitt version 1.0, designed prior to the qualitative inquiries with pharmacists, was only better than the FDA table, not PharmGKB, on task completion time and SUS scores. PGx 2.0 was not better than PGx 1.0 on any measures. Considering that the underlying data and data structure are identical, this is not surprising. However, the changes made based on the problems identified in the qualitative inquiries improved the web interface, boosting its usability higher compared to PharmGKB, as measured by task completion time and SUS scores. While it might appear that PGx 2.0 is not an improvement on PGx 1.0 if it is not

significantly better than 1.0 in any measures, the fact that PGx 2.0 performs significantly better than PharmGKB but PGx 1.0 does not is a notable achievement, as PharmGKB is the gold standard of pharmacogenomics information resources at this time. Furthermore, users were able to find the correct answers 100% of the time using PGx 2.0, but not with 1.0. This demonstrates that the improvements to PGx@Pitt made it measurably better than both the FDA and PharmGKB.

Participants in both the qualitative inquiries and the evaluations indicated that while the information provided by PGx@Pitt was important, a stand-alone web interface would not be adequate for effectively using pharmacogenomics information clinically. Ideally, they would prefer a resource that is integrated into the electronic medical record and connects actual patient genotype data with FDA-approved drug label information. They also felt that the information provided by the FDA did not always give them a satisfactory recommendation on how to proceed with a specific patient. Recommending that a dose be lowered is not as helpful as recommending a specific dose; recommending that an alternative drug be given is not as helpful as recommending specific alternatives. The FDA hesitates to provide actual clinical recommendations, instead preferring to let clinicians draw their own conclusions from the information provided. The Clinical Pharmacogenetics Implementation Consortium (CPIC) develops clinical guidelines for pharmacogenomics variants that can help address that gap[46]. PharmGKB, it must be noted, offers CPIC guidelines where relevant. However, pharmacists do not necessarily recognize those guidelines as having regulatory authority the way FDA label information does, and may hesitate to use them.

Clinicians of all types struggle with pharmacogenomics information[14,58,30,59,60], and find it confusing. To make a decision, a clinician, either a physician or a pharmacist, has to incorporate information about a gene, how it interacts with a drug, what the phenotype of a given gene variant is, and the phenotype of that variant when the patient is given an affected drug[58]. Interpreting this information presents multiple challenges, including unfamiliar and potentially confusing notation for describing gene variants and phenotypes. Studies have shown that clinicians feel poorly informed about pharmacogenomics testing, and that they have a difficult time interpreting test results[14,30] and the complex interactions between drugs and genes[58].

One possible solution to managing this overwhelming information is to identify the clinically relevant information and make it useful. This is what we have attempted in building PGx@Pitt: a simple, single page that does not aim to be comprehensive, but instead gives label information clearly and concisely, with a visualization to help explain the relationship between the gene variant(s), drug(s), and phenotype(s). We designed it with the help of pharmacists, who told us what information they value and how they want to use it. The results from our evaluation indicate that presenting pharmacogenomic information in this way makes it easier for clinicians to access it, understand it, and use it quickly when making drug decisions. We do not claim to have developed the best method of presenting this information to pharmacists in an effective way. More research into phenotypes, pharmacogenomics, and clinician decision making workflows is necessary to further improve clinical phenotype presentation.

Eleven sites in the Electronic Medical Records and Genomics (eMERGE) Network are implementing pharmacogenomics clinical decision support (CDS). A recent article found that while these sites have experienced delays and barriers in implementation of pharmacogenomics CDS, they are generally surmountable[48]. Another related study found that significant heterogeneity exists among sites in how genetic information is entered and stored[125]. Each institution enters and stores it differently, and each institution may enter it multiple different ways and display in multiple different areas of the EHR system. This variability poses a considerable barrier to interoperability to successfully share and display genetic information. The eMERGE group is working to develop an Infobutton that will author genomic medicine information to share with genetic testing results with clinicians within the eMERGE Network[126]. The eMERGE network is working toward this goal in parallel to our efforts, and we have come to the same conclusions about the need to incorporate genetic information into electronic health records. Trust-worthy, well-presented, clear pharmacogenomic information presented in a clinically useful way and combined with patient data and local or CPIC practice guidelines have the potential to move pharmacogenomics into clinical practice.

4.4.1 Limitations

Limitations include a small sample size, range of possible designs, and number of tasks. The results of this work cannot be generalized to other resources or domains, nor can we claim that any one of the interface changes definitely improved usability or performance. We cannot claim that the improved usability leads to improved pharmacogenomics-related outcomes. Clinical

implementation of genetic testing and genotype-guided clinical decision support is necessary to determine improved clinical outcomes.

4.5 CONCLUSIONS AND FUTURE WORK

As genotyping becomes less expensive and more common in clinical practice, clinicians of all types will need trustworthy, easily accessible information about pharmacogenomics to make informed decisions. Genetic variation is only one class of factors to consider when making a drug decision, but in the era of personalized medicine, knowing genotypes is a necessary step to tailor treatments to a patient. Our semantic model of pharmacogenomics information in product labels makes the information computable and searchable; the user-centered design methods make the information usable. The resulting resource is demonstrably more usable than alternative resources when locating clinically relevant pharmacogenomics information. The design and development of our pharmacogenomics resource is a necessary step toward integrating genetic information into drug decisions and personalizing medicine. The next step is finishing the annotations of the rest of the SPLs with pharmacogenomics information, and maintaining the information as it changes over time.

The participating pharmacists told us repeatedly that a stand-alone web portal for pharmacogenomics information will be insufficient when attempting to integrate genetic information in decision making. The eMERGE network sites attempting to integrate

pharmacogenomic information into EHRs support this idea[125]. This information will need to be paired with genetic, medication, diagnosis, and co-morbidity information about a patient and provide tailored recommendations at the point of care to be clinically useful. That requires connecting the semantic model, product label statements, and interpretations to current electronic health records and computerized physician order entry systems. All of this depends on patients having genotype testing performed, which is not currently the standard practice. However, when that happens, our resource is ready to be integrated into current information systems to support clinical decision making.

5.0 FINAL CONCLUSIONS AND FUTURE WORK

In this dissertation work, we have used qualitative methods to design, build, and evaluate a pharmacogenomics information resource that supports the use of genetic data in drug decision making by pharmacists better than alternatives. We demonstrated that the redesigned interface is more usable in terms of task completion time, correctness, and perceived usability than comparable alternatives. We were able to achieve the three aims we set out to achieve in section 1.3:

- **Aim 1: Semantic model and preliminary prototype development.**
    - We developed a semantic model that describes the types of information available about pharmacogenomics and how it relates to other information.
    - We wrote use cases to describe how the pharmacogenomics information resource supports information seeking behavior.
    - We annotated the pharmacogenomics statements in 10 SPLs.
    - We developed a prototype pharmacogenomics information resource (PGx@Pitt v. 1.0)
- **Aim 2: Qualitative inquiries informed redesign.**

- We identified 36 pharmacists' relevant pharmacogenomics information needs in 4 themes and resource requirements in 3 themes using qualitative inquiries and observations.
- We refined use cases into a user persona and use case scenarios based on the qualitative inquiries and observations.
- We re-designed the pharmacogenomic information resource interface to develop PGx@Pitt v. 2.0 based on pharmacists' information needs and resource requirements.

- **Aim 3: Evaluation.**
  - We evaluated PGx@Pitt v. 2.0 using lab-based usability evaluations with pharmacists and found it out-performed PharmGKB.org and the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling in 3 measures: task completion time, perceived usability, and task correctness.

5.1 PHARMACOGENOMICS SEMANTIC MODEL AND ANNOTATED STATEMENTS PROVIDE THE UNDERLYING DATA FOUNDATION FOR PGX@PITT

We built a prototype pharmacogenomics information resource, with a semantic model of pharmacogenomics information in product labels and annotated statements as the underlying data source. The completed annotations represent over half of drugs with major pharmacogenomics implications, per the FDA and CPIC. Though the resource is incomplete in terms of information, we completed a significant number of annotations for drugs with major pharmacogenomic implications. This allowed us to evaluate the interface and usefulness of the resource on many clinically relevant, high impact questions as we work to finish the semantic annotations of all 130+ drugs identified by the FDA as having pharmacogenomics implications.

5.2 QUALITATIVE INQUIRIES INFORM PHARMACOGENOMICS INTERFACE DESIGN

We conducted qualitative inquiries to identify information needs and resource requirements of pharmacists as they engage with pharmacogenomics information. We identified 36 information needs in 4 themes: background information, patient information, medication information, and guidance information. We identified 3 themes in pharmacists' resource requirements: the structure of the resource, perceptions of the resource, and perceptions of the information. We then developed user personas and use case scenarios to illustrate pharmacists'

pharmacogenomic information seeking behavior based on the information needs and resource requirements. We then re-designed the interface of the prototype information resource based on the results of the qualitative inquiries. As part of the redesign, we developed a novel way to present pharmacogenomics information to pharmacists.

5.3 EVALUATION DEMONSTRATES PGX@PITT IS HIGHLY USABLE INFORMATION RESOURCE FOR PHARMACOGENOMICS DECISION MAKING

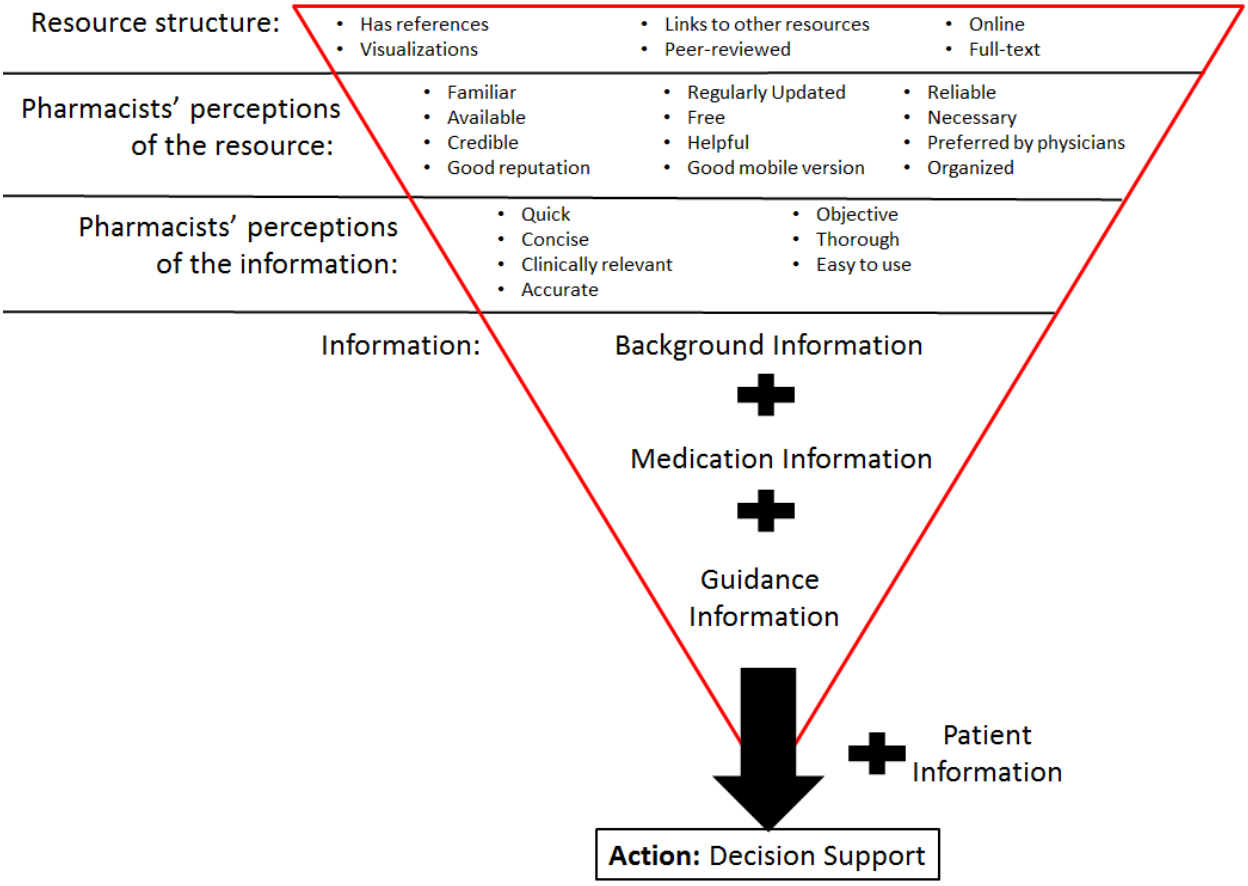
We evaluated the usability of the pharmacogenomics information resource and demonstrated that demonstrated that user-centered, qualitative methods applied to biomedical informatics applications can improve the usability of the application. Specifically, we learned that the use of qualitative inquiries and iterative, user-centered design of a pharmacogenomics information resource improved the resource to the point that it is significantly superior to alternatives in task completion time, task correctness, and perceived usability by pharmacists.

5.4 FUTURE WORK

Knowledge translation, also known as implementation science, is a vast area of research that attempts to integrate evidence-based practice into standard care in a given setting[89]. This thesis work offers a significant step forward in moving pharmacogenomics information from

the knowledge to action portion of Graham's Knowledge-to-Action Cycle[93,127]. We proposed to develop a resource that moved pharmacogenomics information into the action portion of that cycle. In Figure 18, we offer a more detailed view of the Knowledge Tools/Resources triangle in the Knowledge to Action cycle.

Figure 18: Pharmacogenomics Knowledge Tool/Resource Factors and Information



This thesis identifies the factors that influence pharmacists' use of a pharmacogenomics information resource: the resource structure, the pharmacists' perceptions of the resource, the pharmacists' perceptions of the information, and finally, the information itself. We also

identified four categories of pharmacogenomics information that influence decision making: background information, medication information, guidance information, and patient information. Until pharmacogenomics knowledge is connected directly to patient information, particularly genetic testing results, it cannot be used clinically.

Building pharmacogenomics resources that are connected to or part of electronic health records still requires a significant amount of work. A stand-alone, web-based resource as we have now would not be feasible, according to the comments made by the participating pharmacists in both the qualitative inquiries and evaluation. The information would need to be embedded in the EMR in some way, per their recommendations. Decisions would have to be made about whether to use on-demand, passive alerting, or more intrusive, active alerts that require justification for using a drug or a dose despite genetic information. The alerting field has well-documented challenges, most notably finding the balance between getting pertinent information to clinicians, and not overwhelming them with alerts and causing alert fatigue[128–130]. For instance, drug interaction alerts are common in practice. They often are not useful because they lack adequate specificity and sensitivity, thus aggravating the prescriber with inappropriate alerts. One way of reducing this is by tiering alerts by severity: only the most severe and important alerts with sufficient evidence are shown to the prescriber; the rest are passive[101]. A similar approach could be applied to pharmacogenomics: some biomarkers have more impact on the patient than others, and alerts could be tiered accordingly. Otherwise, pharmacogenomics alerts could become just another in a long cascade of aggravating pop-ups that clinicians click through and ignore. Effectively implementing the use of patient genetic data

requires understanding how best to present it to clinicians in the context of the EMR, not just the information itself, as we did in this thesis work.

Before pharmacogenomics can be adopted into standard practice, a number of substantial hurdles must be overcome: first, the comparable effectiveness and cost effectiveness of pharmacogenomics testing must be demonstrated. That is, we must demonstrate that pharmacogenomic testing can improve clinical outcomes compared to the standard of care, or not testing. We must also demonstrate that the cost of the testing is less in the aggregate than the cost of pharmacogenomics-related adverse events. Then, we must have sufficient Clinical Laboratory Improvements Amendment (CLIA) certified labs to process the genetic testing quickly and efficiently. Waiting weeks for genetic testing to inform a drug test is not effective. An even better process would be to perform pre-emptive pharmacogenomic testing: perform the test when the patient is well and not taking any drugs, so the information is available well in advance of the prescribing decision.

Further issues exist not just in understanding *how* to present pharmacogenomics information, but also *which* information about *which* drugs and genotypes are significant enough to alert clinicians. For instance, evidence remains mixed and unclear about whether warfarin improves warfarin dosing, specifically by shortening the time to reach appropriate INR, and by reducing adverse events and unplanned hospitalizations[4,15,16,33]. Warfarin is a powerful drug that requires precise dosing to reach its narrow therapeutic window. Many factors affect the dose for a given patient, including weight, age, concomitant medications, and comorbid conditions. Genetic factors do influence the dose, but they are only one among many,

and may not affect the clinical outcomes as strongly as other drugs. For instance, the HIV drug abacavir is contraindicated for patients who carry the gene variant HLA-B*5701, because they are at high risk of experiencing a severe, life-threatening hypersensitivity reaction[131]. Clopidogrel has strong recommendations for genetic testing based on clinical evidence that poor metabolizers do not experience a therapeutic benefit from clopidogrel, and thus should be prescribed an alternative[132]. This might be a case where biomarkers for certain drugs ought to have an interruptive alert, but another biomarker for another drug should not. Identifying the drug-gene combinations that must be urgently alerted will require more research.

Just as we do not know which biomarkers have the greatest impact on outcomes at this time, we also do not know what changes to our interface had the greatest impact on the usability. We did not change the information provided, but we did change how it was presented. More information is available in the new table of the drug pages, and the presentation of the pharmacogenomics statements from the product label has changed. The users appeared to interact with all parts of the interface, but for different purposes. They appeared to use the table that illustrates the relationship between the variant, the drug, and the phenotype for a general introduction to the drug in question, but then read through the FDA label annotations below to find the specific answers to the task questions. A more detailed usability analysis testing specific changes would be necessary to elicit which piece of the interface influenced the improved usability.

One of the strengths of our resource compared to alternatives is a direct result of the use of the RDF graph and semantic model as the underlying data model. It allows users to query

the graph and answer questions that PharmGKB and the FDA Table cannot easily answer, such as “What drugs require genetic testing?” Our prototype demonstrates this by allowing users to query the resource in this way with pre-written SQL queries. In PGx@Pitt 2.0, users can sort the drugs by column, by drug name, therapeutic area, and biomarker. This allows users to easily answer questions such as, “What drugs are affected by CYP2C19?” to determine if other drugs the patient might be on are affected. However, at this time, the resource is drug-centric, rather than biomarker-centric. We offer detailed drug pages, but not biomarker pages. A future improvement to the resource is to add biomarker pages. The pages might include a visualization illustrating the biomarker itself and how it interacts with drugs, a list of all drugs that are affected by the biomarker, and links to those drug pages. This would allow users to answer more detailed questions about a given test result without having to go and look at each individual drug page, and better leverage the semantic model that supports these types of queries. Multi-drug information needs are significant, as many patients are on more than one drug, and will likely to be on more drugs over time as they age. Our prototype is already answering some of them well, but further development is necessary to answer them more completely.

Product labels contain other information that remains difficult for clinicians to access and use effectively. The mandated structure of product labels has improved the standard form of the information and made it easier to find pertinent information. However, inconsistency remains in the location of some types of information, such as drug-drug interaction data. The FDA mandates that known and predicted drug-drug interaction information be provided in the

product label [76], but does not require a standard form for sharing it. For instance, drug-drug interaction information typically appears in Clinical Pharmacology and Drug Interactions sections, but occasionally can appear in Warnings and Precautions. Older drugs may provide the information as unstructured text, while newer drugs may provide it as a table. A table is more concise and easily searchable by a user, but typically contains less information about the clinical studies that produced the data than the unstructured text does. We think it would be highly beneficial for the FDA to require pharmaceutical companies to provide more structured information for the SPLs (e.g., as annotation like those we created in this project) rather than providing in the current unstructured text.

Our success in annotating pharmacogenomics information in product labels using a semantic model to make it structured and computable demonstrates the feasibility of using similar methods to annotate drug-drug interaction information. Indeed, our group is already attempting this as part of Dr. Richard Boyce's R01 titled "Addressing gaps in clinically useful evidence on drug-drug interactions". In theory, these methods could be applied to the information contained in product labels as a whole, making them searchable, computable, and far more accessible to clinicians. Guidance, recommendations, clinical study data, and adverse events: all of these clinically relevant pieces of information from a source with regulatory authority can support clinical decision making more directly if only they were structured and computable.

Informatics research cannot achieve this alone: it requires a concerted effort from experts in many fields: domain experts, particularly pharmacists; clinical researchers to

determine the best, evidence-based care guidelines that can be tailored precisely to patients; knowledge translation and implementation science researchers to build and install new information resources; and of course, health care workers on the ground working out the bugs as they will inevitably arise. The technology, the information model, even the information itself is not enough to move pharmacogenomics into standard practice. For pharmacogenomics knowledge to be used effectively, it must be connected effectively to actual patients and their information, in a way that does not burden clinicians with a heavier alert load than they already have.

6.0 CONTRIBUTIONS

This thesis is innovative and novel in three ways. We built a novel, clinically relevant semantic model. We used qualitative methodologies to elicit 36 pharmacogenomics information needs in 4 themes and 3 areas of resource requirements of pharmacists, and then applied that knowledge to the redesign of the prototype interface. Finally, we evaluated the resource and demonstrated that the redesigned interface is more usable in terms of task completion time, correctness, and perceived usability than gold standard alternatives.

APPENDIX A

Preliminary Use Cases

Meet the Clinicians

Matt the Pharmacist: Matt is a pharmacist in UPMC Presbyterian Hospital's central pharmacy. He has been a pharmacist for 5 years, and is aware of pharmacogenomics and the effects genotypes can have on different drugs. He tries to incorporate pharmacogenomics information and data into his practice, because he wants to both optimize patient care and safety, and protect his license. He is familiar with clinical information sources like UPMC's electronic medical record system, Micromedex, and PubMed.

Lauren the Hospital Physician: Lauren is a 2nd year cardiology resident in UPMC Presbyterian Hospital. She learned about pharmacogenomics in medical school, and is aware of the drugs that she prescribes to her patients that have pharmacogenomics implications. She would like to incorporate pharmacogenomic genetic tests into her medication prescribing workflow, but is unsure of what genetic tests to order, how to order them, and what to do with the results. She also is not certain of all the drugs that might require a genetic test. She is familiar with clinical information sources like UPMC's electronic medical record system, Micromedex, and PubMed.

Janet the Hospital Nurse: Janet is a registered nurse in UPMC Presbyterian Hospital. She has worked as a nurse for 20 years. She occasionally sees genetic test results in her patients' charts, and would like to understand what the tests are for, and what the results mean. She also recently attended a seminar that discussed pharmacogenomics and wants to know if these tests could help her patients avoid problems like bleeding while on Warfarin.

Howard the Patient: Howard is a 64 year old African-American male who recently had a stent placed. He also has type II diabetes, and has experienced 2 minor heart attacks in the last 3 years.

The Situation

Matt, Lauren, and Janet are on morning rounds on the cardiac floor of UPMC Presbyterian Hospital. They are in Howard's room discussing adding clopidogrel to his medication regimen to avoid clots.

Use Case 1:

Matt is using his mobile device to find and share medication information. He also has access to the EMR system via a computer on wheels work station. Lauren asks Matt what they should know about clopidogrel, specifically how it relates to possible genotypes that Howard might have. She recently read an article discussing genetic testing and its importance in certain ethnic populations prior to prescribing the drug. She cannot remember the gene variant, or if it was prevalent in Asian- or African-American populations, or both. She wants easy access to information about clopidogrel and gene variants that affect it in ethnic populations, so she can decide whether or not to order the genetic test for her patient. She has looked for pharmacogenomics-related information on the UPMC intranet information resources, but has not been able to find answers to her questions. In general, she wants to know if any new information has been released about drugs and genetic variants that she should know.

To answer this, Matt wants information about the drug, specifically the presence of important genotypes that could predict the patient's response before he fills the prescription, how frequent they are in the African-American population, whether the patient has been tested for any of those genotypes, and what the results are, if the test has been performed, what the results of the test might mean, and if/how the treatment should be changed based on the results. He tries using other resources to answer these questions, such as UPMC's intranet resources, Micromedex, Lexicomp, and Up-to-Date, but they don't answer his questions in a comprehensive, clinically actionable way.

Lauren mentions other resources she recently heard about in a seminar on pharmacogenomics, PharmGKB and GeneTests. When they went to those websites, the information presented did not answer their questions clearly and they gave up. Lauren consulted her attending physician, who tells her to order a genetic test for CYP2C19 based on new recommendations from UPMC.

Situation Feature: Mobile Device

Pros: Provides mobile access to various information resources.

Cons: None of the information resources he can access with the mobile device answer his question in a way he can quickly parse, understand, and share with the other clinicians on rounds.

Situation Feature: Computer work station

Pros: Provides access to extensive patient information via the EMR, as well as access to other information resources. Organizes Matt's workflow in a familiar tool that he is used to using.

Cons: The information Matt is looking for is not available in the EMR or other information resources. He has to leave the UPMC intranet to find any information about

pharmacogenomics, and he has a hard time understanding the information he finds in other resources.

Use Case 2:

Lauren asks Janet (the nurse) to look for genetic test results for Howard for CYP2C19, and make sure she knows when they arrive. Janet has never heard of the test, and wants information about its indication, use, and explanation of the results. She looked in the EMR but did not find this information in the test order set.

Situation Feature: EMR order set

Pros: Provides standardized, electronic protocol for ordering things like genetic tests, that a nurse can submit the order without having much understanding of the test or its results.

Cons: Provides no useful contextual information about the genetic test to a non-expert, nor does it provide any links to other resources.

Use Case 3:

Later that week, Matt is verifying medication orders. He receives an alert informing him that Howard had tested positive for a genotype, CYPC2C19*2/*2 that can result in an undesirable response in patients taking clopidogrel. He wants information about how severe Howard's response could be, how likely it is that he will experience an adverse medication event as a result, what the adverse medication event is likely to be, whether he should recommend that Lauren switch to a different treatment, and what the change ought to be (different drug, or different dose).

Situation Feature: Computerized alert

Pros: Provides information in a familiar format.

Cons: The information Matt is looking for is not available in this format, nor is it available in the EMR or other information resources. He has to leave this system to find any information about pharmacogenomics, and he has a hard time understanding the information he finds in other resources.

Note: This situation is not currently a reality within UPMC as far as I know, since genetic tests are not being performed, nor are there alerts presenting the results.

Use Case 4:

Lauren also receives the CYP2C19 test result for Howard. Lauren wants to know quickly what the CYP2C19*2/*2 result means, and what the implications are for her patient, specifically clopidogrel, but also the other drugs Howard is currently taking. She knows this variant is concerning for clopidogrel, but does not know if it increases or decreases its effectiveness, and whether she should give the patient a higher or lower dose. She cannot map the variant to clinical implications.

Situation Feature: Pharmacogenomics genetic test result

Pros: Provides the factual information for the clinician to do with as he or she pleases.

Cons: Provides very little useful contextual information beyond that. Clinician is expected to either know the relevant information, or be able to acquire and understand it. Clinician may not be able to easily make an informed decision about what to do as a result of this genotype.

Use Case 5:

Lauren has discontinued Howard's simvastatin and wants to know if it is okay to prescribe another statin like pravastatin for him, considering the gene variant. She would also like information about all drugs that are affected by this gene variant, to double check the other drugs the patient is taking, and be able to reference in the future for other drugs she might need to prescribe. She spent some time on Google, and found the FDA's Table of Pharmacogenomic Biomarkers In Drug Labels (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). It told her the list of all drugs that might be impacted by the CYP2C19 genotype, but no information about this specific variant. She is not sure where to find information that detailed. When she looks at the sections the list mentions in the drug labels, she does not find any recommendation information.

Situation Feature: FDA's Table of Pharmacogenomic Biomarkers In Drug Labels

Pros: Reliable, trust-worthy list of all the biomarkers and associated medications that the FDA has deemed worthy of placing warnings in drug labels. Can be reordered by drug or biomarker.

Cons: Limited information provided. No information about specific variants, nor any links to other resources that might provide that information. No recommendation information

Situation Feature: Structured product labels

Pros: Detailed set of information about drugs, including information about pharmacogenomics biomarkers.

Cons: Difficult to read, understand, or find the relevant information a clinician might be seeking quickly. Pharmacogenomics biomarkers information does not provide recommendations.

APPENDIX B

Semi-structured interview questions:

1. General demographics: age, gender, ethnicity, number of years as a pharmacist, number of years at UPMC, job role
    a. Age
        i. 18-35
        ii. 36-50
        iii. 51-65
        iv. >65
    b. Gender
        i. Male
        ii. Female
    c. Ethnicity
        i. African-American
        ii. Asian-American
        iii. Caucasian
        iv. Hispanic

v. Other

d. Number of years as a pharmacist

i. <5

ii. 5-15

iii. 16-25

iv. >25

e. Number of years as a pharmacist at UPMC

i. <5

ii. 5-15

iii. 16-25

iv. >25

2. What is your job title?
3. What major tasks do you do in a normal day?
4. Approximately how many prescriptions do you fill in an average day?
5. What percentage of prescriptions do you manage that require you to find additional information?
6. Regarding question 3, what information do you need? How do you find it, usually? Show me.
7. Where do you go to find the following information:
    a. Drug effectiveness
    b. Drug Safety

c. Monitoring requirements

d. Drug indications

e. Guidelines about the drug

f. Recommendations from a clinical pharmacist

8. Can you give me an example of a time that you had a difficult time getting drug information? What happened? Show me.
9. Why do you use the resources that you do?
10. Approximately how many times on average per day do you participate in a drug prescription decision?
11. How many of these decisions require that you look up information about the medications in question?
12. Where do you look? Show me.
13. What do you like about the resources?
14. What do you dislike about the resources?
15. Have you had professional exposure to pharmacogenomics? Yes/no

Questions 16-18 only for people who answer "yes" to question 12.

16. How would you describe that exposure?
17. Do you anticipate that pharmacogenomics will have a growing impact on your profession soon? How so?
18. Do pharmacogenomics considerations play a role in your work?

19-28 only if answer to 18 is yes

19. How frequently do pharmacogenomics considerations play a role in your work?

20. When you are considering medications with pharmacogenomics implications, how frequently (i.e., what percentage of the time) do you need to find additional information to assist in your decision-making?
21. What types of information do you need?
22. How do you find it, usually? Show me
23. Can you give me an example of a time that you had difficult time getting pharmacogenomics information? What happened?
24. Where did you look for information?
25. Why were those resources inadequate?
26. How many patients that you manage have had pharmacogenomic test results in their charts (in the last year?)?
27. Have you ever recommended pharmacogenomics testing? Yes/no
28. If yes: For how many patients have you recommended pharmacogenomics testing (in the last year?)?

Interactive:

We are developing information tools that provide clinically-focused information about pharmacogenomics and related drugs to clinicians. To develop these tools, we would like to understand how you make prescription decisions about drugs in general, and about drugs that have pharmacogenomics implications. To do this, we would like you to think about a hypothetical patient, show us how you would find information to manage this patient currently, and then demo our information tool prototype to find that information. Afterward, we will ask you some follow-up questions.

29. Without POC:

a. Say you have a patient named Howard, a 64 year old African-American male who recently had a stent placed. He also has type II diabetes, and has experienced 2 minor heart attacks in the last 3 years. His physician is considering prescribing clopidogrel. What do you think is important to know before prescribing clopidogrel, that isn't already available in the EMR?
b. Where would you go to acquire that information? Show me.
c. Howard's physician orders a genetic test for Howard's CYPC2C19 status, and his variant is CYPC2C19*2/*2. What does this information tell you about prescribing clopidogrel?
d. What information do you think that you might want to learn about that variant with respect to that drug?
e. Where would you go to acquire that information? Show me.
f. What do you like about how the resource(s) presents drug information?
g. What do you dislike about how the resource(s) presents drug information?
h. What do you like about how the resource(s) presents genotype information?
i. What do you dislike about how the resource(s) presents genotype information?
j. Is there information you would like, but cannot find in the resource(s)?
k. Do/Does this/these resource(s) provide you with the information that you need to feel comfortable in prescribing this medication?
l. Do you have any other comments about this resource(s)?

30. On POC:

a. This is an information resource we're developing to provide pharmacogenomics information to clinicians. Consider Howard, the patient mentioned above. Using this resource, where would you go to acquire that same information? (clopidogrel information and genotype information)
b. What do you like about how this resource presents drug information?
c. What do you dislike about how this resource presents drug information?
d. What do you like about how this resource presents genotype information?
e. What do you dislike about how this resource presents genotype information?
f. Is there information you would like, but cannot find in this resource?
g. Do/Does this/these resource(s) provide you with the information that you need to feel comfortable in prescribing this medication?
h. Do you have any other comments about this resource?

31. Do you have any concerns or general comments?

APPENDIX C

Complete Codebook from Qualitative Inquiries

Name		Sources	References
Information need		14	457
Background Information		4	4
Insurance information		3	5
Location of information		1	2
medical condition		7	12
Allergies		3	3
Bleeding risk		1	1
Patient's weight		1	1
medication information		14	430
Additive information		1	1
Comparative effectiveness		3	6
Concomitant medications		9	11
Contraceptive information		1	1
Dispensing information		2	2
dosing		8	18
Drug availability		2	3
Drug compatibility		2	2
Drug efficacy		12	20
Drug equivalency		1	2
Drug identification		1	1
Drug indications		13	21
Drug Safety		13	51
Adverse effects		10	29
Drug-drug interactions		7	17
Frequency of interaction		1	1
Severity of interaction		3	3
Side effects		1	3
Drug toxicity		3	6
Evidence		2	2
Guidelines about the drug		13	13
IV information		5	7
IV compatibility		2	2

IV extravasation instructions		1	1
IV stability		1	2
Length of time taking medication		1	1
Mechanism of action		1	1
Medication previously taken		1	1
Monitoring requirements		13	16
Novel drug		1	1
Off-label use		3	3
Other drugs in same class		4	4
Patient population-specific information		1	1
Pharmacodynamics		1	1
Pharmacogenomics information		14	188
Other drug(s) affected by biomarker		5	5
Pharmacogenomics background information		10	14
Pharmacogenomics evidence		6	12
Pharmacogenomics guidelines		6	14
Phenotype information		14	39
Severity of pharmacogenomics risk		4	7
test information		8	14
Test parameters		2	3
variant information		13	51
Population frequency		3	5
Pharmacokinetics		2	3
Drug elimination		1	1
Drug Metabolism		1	1
Price		3	4
protocol information		0	0
QTc interval		2	2
recommendation		14	40
Alternative drug choices		6	10
Patient preferences		1	1
Information source		1	1
Benefit of tool or resource		14	244
Available		6	6
Available online		1	1
Clinically relevant		5	6
Contains visualizations		6	6
Credible		5	6
Disease-focused		1	1
Easy to use		14	93
Current		1	1
Familiar		8	9
Good mobile version		1	1
Organized		12	28
Quick		13	23
Free		2	4
Good reputation		3	3

Helpful		2	3
Information benefit		14	105
Accurate		4	5
Concise		12	26
Contains pharmacogenomics information		6	9
Objective		1	1
Peer-reviewed		1	1
Provide references or citations		6	11
Provides background information		4	5
Provides comparisons		1	1
Provides links to other resources		3	3
Provides off-label indications		1	1
Provides recommendations		9	19
Regularly updated		2	2
Thorough		10	20
Necessary		2	2
Preferred by physicians		1	1
Provides full text		1	1
Reliable.		2	3
Book		5	5
Managing Contraception		1	1
Clinical pharmacist		8	12
Digital Information Resource		14	400
CDC		1	1
FDA		8	36
FDA Table of Pharmacogenetic Biomarkers		1	1
Product label		6	28
DailyMed		1	4
Medwatch		1	1
PGXatPitt		14	51
PharmGKB		1	5
CPIC guidelines		1	5
Primary literature		13	63
Pubmed		11	43
Case reports		1	3
Clinical trials		7	16
Professional society		5	11
Beers Criteria		1	1
Clinical guidelines		2	3
Search engine		5	6
Google		4	5
Tertiary resources		14	224
Access medicine		1	1
AHFS Drug Information		1	10
Clinical Key		1	1
Clinical Pharmacology		3	8
CredibleMeds (AZCert)		1	1

Dynamed		2	8
Facts and Comparisons		3	5
GlobalRPH		2	4
Hippocrates		4	13
Johns Hopkins ABX Guide		1	1
Lab Values		0	0
Lexicomp		10	57
Micromedex		13	67
Pharmacists' Letter		1	5
Prescriber's Letter		1	1
RXpertise		2	3
Skyscape		1	4
STATRef		1	1
UpToDate		7	28
Drug company		5	7
Electronic medical record		1	1
Internal information resource		2	3
Journal		0	0
Patient		1	1
PDA		1	1
Problem with tool or resource		14	206
Biased		1	1
Difficult to use		14	64
Bad mobile version		3	3
Disorganized		6	9
Does not divide drugs by specialty		1	1
Information overload		10	22
Verbose		9	15
Information poorly displayed		7	10
Problems with workflow		4	4
Slow		5	6
Unfamiliar		2	2
Information problem		14	126
Confusing		6	9
Difficulty finding information		14	99
Difficult to search		2	2
Lacking information		13	76
Information not published		1	1
Lack of evidence		3	5
Lacks background information		6	8
Lacks dosage information		3	4
Lacks full text articles		1	1
Lacks indication about severity of implications		2	2
Lacks information about validity of clinical studies		2	2
Lacks IV compatibility		1	2
Lacks links to other resources		4	5
Lacks off-label indications		1	2

Lacks patient education		1	1
Lacks pharmacogenomics information		5	7
Lacks recommendations		7	13
Lacks source of information		5	9
Must leave database to get complete info		3	3
Problems with terminology or search terms		6	9
Inaccurate		4	4
Inconsistent		1	2
Out of date		5	5
Repetitive		1	1
Subjective opinion		3	5
Lacks source of information		2	4
Lacks visualization		1	1
Resource unavailable		1	1
Unnecessary		0	0
Pharmacogenomics experience		1	1
Clinician exposure to pharmacogenomics		12	22
Current state of pharmacogenomics		1	2
Pharmacogenomics currently unavailable		1	1
Unaware of where pharmacogenomics information is		1	1
Educational exposure to pharmacogenomics		4	7
Graduate		3	4
Undergraduate		0	0
Professional exposure to pharmacogenomics		10	12
CME		1	1
None		1	1
On the job		3	3
Reading literature		2	2
Research		1	1
Seminar		1	1
Effect on practice		8	10
Economic changes		2	4
Increase in information		9	22
Change in formulary decisions		1	2
Change in treatment decisions or recommendations		5	9
Outcome changes		6	6
Negative outcome changes		0	0
Positive outcome changes		1	1
Unknown outcome changes		1	1
Workflow changes		5	5
Pharmacy Task		14	73
Chart review		7	12
Lab value review		2	2
Community pharmacy practice		2	2
Patient care		2	2
Consulting		8	16
Patient follow-up		1	1

Provide therapy recommendations		5	7
Providing drug information		3	3
Drug monitoring		2	3
Formulary management		1	2
Medication reconciliation		1	3
Order entry		4	5
Order verification		4	5
Patient education		1	1
Pharmacy support		2	2
Prescription claims management		1	3
Prescription filling		2	3
Research		1	1
Rounding		4	8
Teaching students		2	4

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