

Design recommendations for Pharmacogenomics Clinical Decision Support Systems

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Abstract

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Abstract

The use of pharmacogenomics (PGx) in clinical practice is still facing several challenges in reaching full adoption. PGx is an emerging field that aims to deploy genetic information to target drug therapy. To incorporate this science into clinical practice, many support the use of Pharmacogenomics Clinical Decision Support Systems (PGx-CDS) for medication prescriptions. This interest emerged with the new guidelines developed to incorporate genetics to optimize drug dosage and reduce adverse events. In my thesis, I investigate the development of PGx-CDS to (1) identify challenges and barriers of the implementation of PGx-CDS in clinical settings, (2) develop a new design approach of CDS with functional characteristics that can improve the adoption of Pharmacogenomics guidelines and improve patient safety, and (3) create design guidelines and recommendations. Through this work, I aim to study the implementation of PGx-CDS and develop design features that can overcome the challenges of its adoption in clinical settings.

TABLE OF CONTENTS

I. Table of Contents

II. Introduction	8
A. Definitions, background and motivation:	9
1. Pharmacogenomics (PGx):	9
2. Clinical decision support systems:	9
B. Current state of PGX in clinical settings:	10
1. Electronic Medical Records And Genomics (eMERGE).....	10
2. The Pharmacogenomics Knowledgebase (PharmGKB) :.....	11
3. Clinical Sequencing Exploratory Research (CSER)	12
4. Clinical Pharmacogenetics Implementation Consortium (CPIC).....	12
III. Challenges and barriers in implementing pharmacogenomics in clinical settings	13
1. Research challenges and barriers:.....	13
A. The Pre-clinical-implementation challenges and barriers:	14
1. Research challenges and barriers:.....	14
2. Biobanks:	15
3. Cost effectiveness Studies.....	16
B. Clinical implementation challenges and barriers	16
1. Stakeholders engagement.....	16
2. Genome-enabled electronic medical record.....	16
3. Structure of genetic reports:	17
4. Integration of PGx testing in clinicians workflow	18
C. Post- Clinical implementation challenges and barriers	18
1. Ethical and social studies.....	18
2. Education and knowledge gap	19
IV. Design Process:	21
A. Summary of recommendations from the literature:	21
B. New approach to solve the alert fatigue problem	22
C. Prototype	23
V. Heuristic Evaluation:	27
A. Evaluation plan:	28
1. Evaluators	28
2. Evaluation Sessions:.....	29
B. Summary of recommendations and lessons learned:	30
1. Lists of Medication Design:	30
2. Genetic Information	32
3. Context-based Display:	33
4. Other General recommendations	33
VI. Limitations & Future Work	34
A. Limitations	34
1. Interoperability with Existing EHR:.....	34
B. Future work	34
1. Build an ontology for the context-based display	34
2. Improve the design of Genetics results	35
VII. Contribution:	35
A. 1. Methodological Contributions	35
B. Design contributions: Context-based display	36

VIII. Conclusion:	38
IX. References	39

LIST OF FIGURES

Figure 1: PGx from lab to the patient bedside: challenges and barriers.....	14
Figure 2 Masys et al. (2012) Genome-EHR technical desiderata.....	17
Figure 3 Display of context-based information	23
Figure 4: Prototype page 1 "List of medications"	23
Figure 5: Prototype page 2 "Personalize treatment"	24
Figure 6: Prototype page 3 "Relevant vitals and labs".....	25
Figure 7: Prototype page 4 "Drug-Drug Interactions"	26
Figure 8: Prototype page 5 "Genetic Information"	26
Figure 9: Usability inspection plan.....	29
Figure 10: Microsoft recommendations for "Choice Lists with Preferences" 1....	30
Figure 11 PGx-CDS medications' list	31
Figure 12 Microsoft recommendations for "Choice Lists with Preferences "2.....	31
Figure 13 "Genetic Information" box	32
Figure 14 Table of comparison	37
Figure 15 Relevant genetic information	37

LIST OF TABELS

Table 1: Summary from the literature of topics that should be known from the literature	21
Table 2 List of design features provided with the PGx test	27
Table 3: Neilson's Heuristics (1994)	28
Table 4 Evaluation results of the Genetic Information Box	32

II. Introduction

No one can deny the effects of drug discoveries during the last decades on improving the health of humankind. Drugs, such as antibiotics and vaccines, have helped increase life expectancy, reduce infant mortality, and improve the quality of life globally. To ensure the efficacy, efficiency, and security of drugs, the development of drugs has become a complex process that can take between 10 to 15 years. It relies on expertise from a wide range of disciplines, such as biochemistry, biology, pharmacology, mathematics, and molecular modelling. Yet, drug risks remain. Even with the complex process of developing new drugs, patients still have adverse events, which can be a cause of morbidity and mortality. These reactions are normally classed as idiosyncratic reactions that are not related directly to drug concentration but instead could be due to an unusual patient phenotype (1). The Human Genome Project (HGP) was a necessary first step in deciphering the interaction between drugs and the human genome. By identifying more than 30,000 genes, the HGP enabled the identification of genetic risk factors for idiosyncratic adverse drug reactions.(1). HGP revolutionized patient care by opening the door to personalized medicine, which aims to provide the patient with the right, effective and safe drug. The HGP helped in identifying the role of genetic variation in drug response yielding a new group of clinical tests known as pharmacogenomics (PGx) tests designed to improve drug efficacy and drug safety.

Applying this genetic information in clinical practice can make treatments safer and more efficient. By performing a DNA test, physicians could anticipate how patients will respond to the prescribed drug. Relationships between genotype/phenotype and drug response are being studied to help health care professionals make better decisions, accordingly.

However, the integration of PGx into clinical practice is still facing many challenges: limited genetic expertise of clinicians, constrained availability of genetics experts, the growing knowledgebase of genetics, and others. To address these issues, clinical decision support (CDS) is considered as a bridge needed to overcome these barriers. CDS is the way to achieve guided personalized medicine, and deploy PGx at the bedside of the patient.

For my thesis, I aim to (1) identify challenges and barriers of the implementation of PGx CDS (PGx-CDS) alerts in clinical settings, (2) develop a new design approach for computerized CDS with functional characteristics that can improve the adoption of PGx guidelines and thus improve patient safety, and (3) create design guidelines and recommendations for future PGx-CDS alerts.

A. Definitions, background and motivation:

1. Pharmacogenomics (PGx):

The term pharmacogenomics first appeared in a publication of Vogel in 1959 (2). PGx is the science that studies the effect of genetics on drug response. It aims to provide personalized therapy for individuals with safer and more consistent outcomes. Pharmacogenomics studies the variability of the human genome and its relationship with drug response. The term pharmacogenetics is often used interchangeably with pharmacogenomics, although pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics is more concerned with genome-wide interactions.(3)

2. Clinical decision support systems:

A clinical decision support system (CDS) is an emerging technology used in the health care system. This system is designed to assist health professionals with clinical decision-making. (Types of CDS)

Masys et al. (2012) state that clinicians' cognitive capacity is not sufficient to encompass all the traditional health information, in addition to structural genetics, functional genetics, proteomics and other effector molecules information. Therefore, there is a clear need to implement a computerized clinical decision support systems to help clinicians manage this information and deploy it for the patient's benefit.

Kawamoto et al. state that a national clinical decision support infrastructure is vital to realize the promise of a personalized medicine in which the patient's genetic information is deployed in his routine care.(4) Overby et al. also echo this point and state that CDS has the potential to the improve clinician's ability to use genetics data to make personalized drug therapy decisions (5).

In a different publication, Masys et al. emphasize the important aid that CDS can be, for physicians, in using PGx recommendations effectively. Masys states that CDS capabilities should support drug-gene interaction checking. In the article, he says:

“When a drug like warfarin is prescribed, in addition to checking patient-specific information such as age, weight, and other medications, the CDS rule could also automatically assess the patient’s genome for variants in related genes, such as VKORC1 and CYP2C9, and alert the ordering clinician to any potential complications”.

B. Current state of PGX in clinical settings:

Several experts and research groups are currently addressing the challenges facing the translation of PGx knowledge from laboratory research to the bedside of the patient. Different projects were launched to develop clinical recommendations, dosing guidelines, and study the integration of these recommendations into the routine of clinicians. Four of the major projects in this field are discussed briefly below in order to introduce the current state of PGx in clinical settings.

1. Electronic Medical Records And Genomics (eMERGE)

The eMERGE Network is a collaboration of US research institutions funded by the National Human Genome Research Institute (NHGRI) to foster, propagate, and apply approaches to combining genomic and Electronic Health Records (EHR) data for use in genetic research.

eMERGE works on collecting genetic data, then stores it in biorepositories that are then linked to the EHR. This work will help develop methods and best practices to deploy EHRs for genomic research. In addition, eMERGE is also helping to detect the role of genetic make-up in the susceptibility of a patient to certain conditions or his/her response to certain medications. The data is collected from patients from 9 clinical sites across the USA.(6)

eMERGE is currently (2015) on its second funding cycle, and comprises nine research groups and a coordinating center. Each group has its own biorepository where DNA specimens are linked to phenotypic data contained within EMRs. These sites are also geographically dispersed and involve a large number of study participants, which help in having considerable diversity.

eMERGE is advancing knowledge in multiple disciplines related to the implementation of genomics in clinical practice.(7)

2. The Pharmacogenomics Knowledgebase (PharmGKB) :

“PharmGKB is a knowledge base that captures the relationships between drugs, diseases/phenotypes and genes involved in pharmacokinetics (PK) and pharmacodynamics (PD)”(8).

PharmGKB is an online, publically available, database. It **assembles** PGx publications to extract gene-drug-disease relationships. From these publications, curators proceed to manual extractions of **Variants Annotations**: associations between specific genetic variants and drugs, as reported in a single publication, summarized in a uniform sentence. They mine for relevant associations between specific genetic variants, drugs and drug pathways. In addition to knowledge extraction and annotation, PharmGKB provides information that is relevant to the clinical implementation of PGx knowledge. Scientific curators provide clinical interpretation after reviewing variant annotations for a particular genetic variant - drug association pair. They summarize these findings in **Clinical Annotations**. They do also provide a measure of the strength of evidence for each summary based on the publications and resources used to support these findings. (9)

Taken from the PharmGKB website, the following list represents the roles that PharmGKB is playing in this field: “

- Annotate genetic variants and gene-drug-disease relationships via literature reviews
- Summarize important pharmacogenomic genes, associations between genetic variants and drugs, and drug pathways
- Curate FDA drug labels containing pharmacogenomic information
- Enable consortia examining important questions in PGx
- Curate and participate in writing pharmacogenomic-based drug dosing guidelines
- Contribute to clinical implementation projects for PGx through collaborations
- Publish pharmacogenomic-based drug dosing guidelines, very important pharmacogene summaries and drug-centered pathways
- Display all information on the website and provide comprehensive download”

3. **Clinical Sequencing Exploratory Research (CSER)**

CSER is a collaborative project that brings together health care professionals from different backgrounds and different sites. It involves clinicians, researchers, laboratories, bioinformaticians, economists, legal experts, ethicists, and patients

This initiative was launched by the National Human Genome Research Institute (NHGRI), and the National Cancer Institute (NCI). It aims to help improving the integration of genomic sequencing into clinical care. CSER aims to develop and share innovations and best practices. It is also working on capturing relevant ethical, legal, and psychosocial issues (10)(11)(12)

4. **Clinical Pharmacogenetics Implementation Consortium (CPIC)**

One of the challenges that needs to be addressed to ensure a successful implementation of PGx in clinical practice is the lack of guidelines that translate laboratory test results into actionable prescribing decisions. The Clinical Pharmacogenetics Implementation Consortium (CPIC) was established by The Pharmacogenomics Knowledgebase (PharmGKB) and the Pharmacogenomics Research Network (PGRN) to address this problem. CPIC creates practice guidelines available for clinicians to interpret genetics data and deploy it at the bedside of the patient.

CPIC focused on widely known PGx tests and their implementation in clinical settings. CPIC experts developed standardized guidelines and they provided a grading of evidence and measurement of strength to each prescribing recommendation.(13) (14). The CPIC guidelines are disseminated online through the PharmGKB website. (www.pharmgkb.org)

III. Challenges and barriers in implementing pharmacogenomics in clinical settings

In this section we identify the different barriers to the implementation of PGx-CDS in clinical settings as discussed in the literature. We classify these barriers into 3 groups: The development of the implementation process, its installation in a health care institution and the issues faced by the institution upon integration.

- **Pre-Clinical Implementation Challenges and Barriers:**
 1. Research challenges and barriers:
 2. Biobanks
 3. Cost effectiveness studies
- **Clinical implementation challenges and barriers**
 1. Stakeholder engagement
 2. Genome enabled electronic health records
 3. Structure of genetic reports
 4. Integration into clinician's practice
- **Post Implementation barriers:**
 1. Ethical and social issues
 2. Education and knowledge gap

Each of these challenges will be briefly defined and described below.

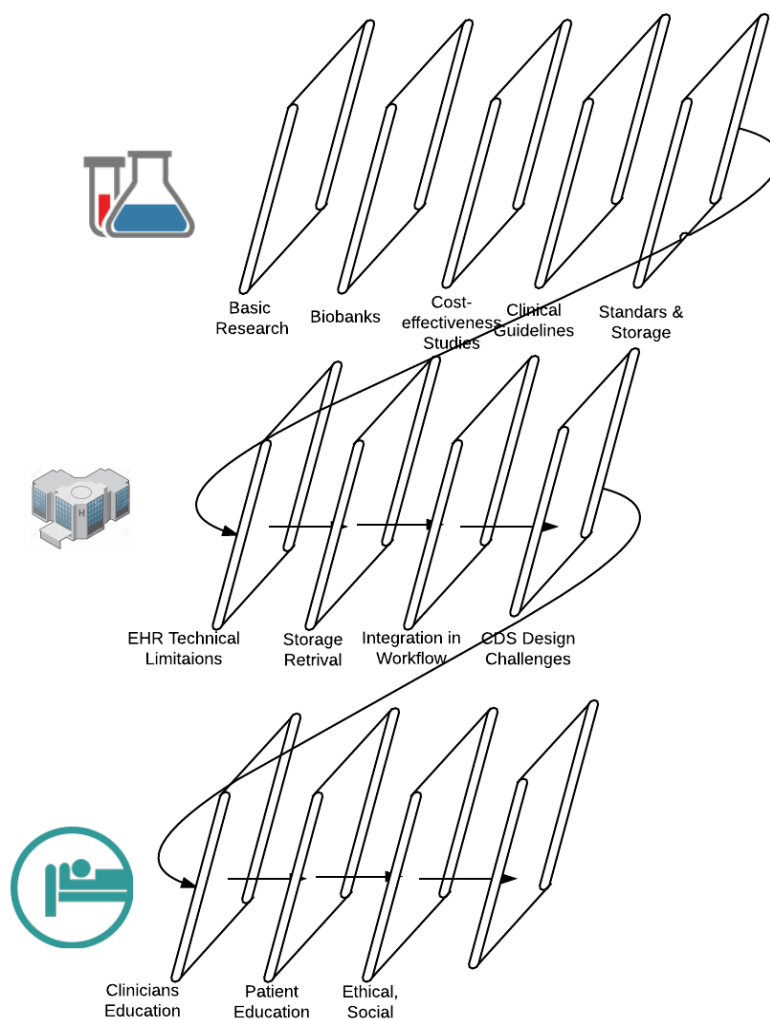


Figure 1: PGx from lab to the patient bedside: challenges and barriers

A. The Pre-clinical-implementation challenges and barriers:

1. Research challenges and barriers:

Since the Human Genome project, advances in genetics are occurring at a rapid pace. The cost of whole genome sequencing is predicted to fall from an initial cost of nearly \$3 billion in 2003, to \$1000 by 2015(15). Translational medicine is evolving to make these findings available for medical practice. PGx research is translational in nature. (16). It involves studying genotype–phenotype relationships underlying drug outcomes -and integrates this knowledge into medical practice to increase treatment efficacy and reduce adverse events. However one of the challenges is to identify which of the many existing PGx tests should be integrated in the clinical world. Consequently, an evaluation of validity and utility of tests is required.

Lose summarized three concepts that are essential in understanding how PGx tests can qualify for clinical integration. (17),(18)

These three concepts are:

- **Analytical validity:** which is defined as the likelihood that the reported results are correct.
- **Clinical validity:** the degree to which the test correctly assesses risk of health or disease
- **Clinical utility** is the degree to which the test guides medical management.

Some initiatives started evaluating a few of the PGx tests to assess their validity and utility. The National Heart, Lung, and Blood Institute began a prospective trial of approximately 1,200 patients to evaluate the use of clinical and genetic information to guide the initiation of warfarin therapy and to improve anticoagulation control for patients.(19)

2. **Biobanks:**

There has been a growing awareness of the importance of Biobanks -collections of biological specimens- for PGx research. Biobanks have existed for many years for medico-legal reasons. In the past decade, stored specimens were often linked to detailed medical records. Therefore the collection of biological specimens for research purposes has begun to enable personalized medicine. Yet, there are ethical issues that have to be addressed because these specimens are largely collected during routine clinical care. Consent of either the individual or the community is needed for their use. (20)

McCarty and Wilke summarize the Biobanks role in the development of PGx in these points :

- Biobanks are a resource for discovery and validation in PGx.
- Biobanks utility will increase with data harmonization across biobanks and EHRs.
- Biobanks will be valuable for drugs post-marketing surveillance
- Biobanks aid in the identification of genetic markers that predict rare adverse outcomes.

For the reasons presented above, retrospective discovery in biobanks and prospective application in electronic medical records has the capability to assist physicians at the point of prescribing. That being said, we should not forget that using specimens and medical information is ethically challenging. Lemke et al. (2010) , based on the eMERGE experience, raises the point that we need to engage stakeholders and community members to enhance the role of biobanks. The success of biobanks is tied to the willingness of individuals to share medical and genetic information. Therefore, stakeholder engagement is crucial to ensure advancement in precision medicine without breaching ethical and legal contracts(21)

3. Cost effectiveness Studies

A potential barrier to the widespread implementation of PGx testing is the lack of evidence on the cost-effectiveness of these tests. A critical review from 2010 states that the majority of the biomarkers evaluated in the study had clinical validity. But, only two of them were found to have both clinical validity and utility. These two biomarkers are HER-2 and HLA-B*5701.(22).

Several studies have stated an expectation that there is a greater chance that PGx test will prove cost-effective when costs for genotyping decrease.

B. Clinical implementation challenges and barriers

1. Stakeholders engagement

The engagement of stakeholders is a key factor for the successful implementation of PGx in clinical practice. Hartzler et al. states – based on the eMERGE experience– that the clinical integration of genomic information needs the involvement of clinicians, patients, staff, scientists, policy makers, citizens, industry, and domain experts from genetics, informatics, and bioethics, and related fields. During the implementation phase, people who will be affected by the change should be informed. Including them in the process can increase the acceptability. Support and training materials must be distributed widely, education evidently is an important tool in promoting stakeholder engagement.

2. Genome-enabled electronic medical record

Marsolo and Spooner state that “Not all electronic health records are created equal”.(23) EHR differ in their features, capabilities, and ease of use. In their article,

they identified critical features that an EHR should have to achieve a basic level of integration of genetics data in clinical practice. Their criteria are:

- The ability to store genetic information as discrete, computable data.
- The genetic tests data must be stored using standards to allow interoperability between different systems. This way data can follow the patient through different institutions.
- The phenotypic information must be stored using sufficiently expressive terminology.
- The genetic data must be well-suited for clinical decision support processes in the EHR
- The EHR must be able to retrieve and display external information needed to interpret the genotypic and phenotypic data.

Masys et al. (2012) proposed a framework for integrating genomic data in EHR. This Desiderata was also discussed by Welch et al. and they did provide an additional work the extend the original proposal of Masys et al. (24), (25)

Desiderata Number	Desiderata Description
1	Maintain a 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 the linkage of molecular observations to the laboratory methods used to generate them
4	Support a compact representation of clinically actionable subsets for optimal performance
5	Simultaneously support human-viewable formats and machine-readable formats in order to facilitate the implementation of decision support rules
6	Anticipate fundamental changes in the understanding of human molecular variation
7	Support both individual clinical care and discovery science

Figure 2 Masys et al. (2012) Genome-EHR technical desiderata

3. **Structure of genetic reports:**

Tarczy-Hornoch et al. conducted a survey with CSER consortium members about their respective EHRs. The article states that even though all EHRs are from the same commercial vendor, and CSER projects use the same sequencing technology, there exist inconsistencies between approaches for the return of results. The survey was able to detect significant variation between the different CSER sites.(11), (26)They had different databases, variant predictors, allele frequencies, variant curation strategies, laboratory information systems, and interfaces between the laboratory information systems and the EHR.

In addition to the inconsistency across CSER sites, lack of structured data presents another impediment to the effective use of genomic data. Unstructured data cannot be “read” by a computer and cannot be used to run clinical decision support engines. (This issue can be addressed by using NLP processing which is still far from being a completely reliable process and continues to evolve).

Genomic medicine relies on the generation and analysis of data. Therefore, clinical settings should optimize the structure and the storage of data.

Ury also addresses these issues related to data. Ury defines three data types: granular (structured), textual (unstructured), and image. He also discusses an additional challenge with genomic data. This data has a very long life span and is relevant for the entire life-time of the patient and ideally should be transferrable across medical institutions and sites. During this time, genomic data should be well stored and ready to be used in case of need. (27)

4. Integration of PGx testing in clinicians workflow

The 1200 Patients Project addresses incorporating PGx testing into routine medical care. This process can be challenging due to several factors like availability of genetic testing, delays, results interpretation, and the lack of understanding of PGx results.

The 1200 Patients Project is studying these challenges. The project is genotyping patients and providing results to their treating clinicians. Then, researchers will track whether the genetic information were used in the routine health care or not.

This project is helping to develop a model of care that can leverage the role of genetic testing in the daily work of clinicians.

C. Post- Clinical implementation challenges and barriers

1. Ethical and social studies

Hazin et al. assert that the inclusion of genomic data in the electronic health record raises significant ethical, legal, and social issues. In their article (Hazin et al., 2013) they highlight these challenges and propose potential solutions. They discussed the importance of equitable access to genome-enabled electronic health records.

According to the article, this will help in reducing the health disparities across

demographic groups by ensuring that health care interventions will no longer be confined to practices based on race or ethnicity. Interventions will be tailored to each individual through using their genetic information.

In addition to that, the authors emphasize the importance of privacy. The sharing of genomic information requires stringent security measures. These measures should ensure the security of information when shared within a single health-care institution, across institutions, and with the patients themselves. They also raise issues like the incidental genomic findings, storing and reinterpreting genomic data, and non-documentation and ethical duty to warn family members at potential genetic risk. Hazin et al. claim that patients and providers may prefer a non-documentation approach to the genetic test results. They support this claim with the fact that neither the Health Insurance Portability and Accountability Act nor the Genetic Information Nondiscrimination Act have eliminated the risk of genetic discrimination—nor the fear of it.

In addition to that, Marsolo and Spooner identified other social issues that remain vital for a successful implementation of genetics data in clinical practice. These issues include The transition of care: since the genetic test remain relevant for a longer time than other healthcare tests, there is a need to maintain and transport this data throughout the lifetime of the patient. This same data are also valuable for the descendants of the patient. Unfortunately, determining with whom this information can be shared remains unclear. Should the information remain with the patient or the provider?

Genetic testing Technology is still evolving. The clinical significance and utility of older tests will most likely be affected. The old interpretation may be less useful and questions exist around the sharing of new interpretations. Should the patient be contacted again? Who will contact him/her? And, who will be responsible for his education on the interpretation?

2. **Education and knowledge gap**

Johansen Taber & Dickinson (2014) conducted a survey with primary care physicians, cardiologists, and psychiatrists to evaluate their familiarity with PGx knowledge. In this study, they discovered that understanding of PGx persists to be low and that knowledge gaps remain prevalent among the health care professional

population. They also provided a list of content topics that should be included in an ideal PGx resource:

- Recommendations for prescribing
- Effect of genetic variation on mechanism of drug action
- Demographics of populations likely to carry variations
- References such as scientific literature
- A list of laboratories offering testing
- A description of PGx information in drug labeling
- Price of tests and whether they are covered by insurance

Overby and Tarczy-Hornoch raised concerns regarding patient and family education. There is an evolving need to assist patients with interpretations of genetic test results. The implementation of genetic information in clinical care settings should be accompanied by the recruitment of geneticists and genetic counselors. In this article, they also mention a number of online educational resources that were created in different institutions. Those resources provide genetic education for families and clinicians. The Pharmacogenomics of Anticancer Agents Research 4Kids (PG4Kids) project was mentioned as an example. This project was created at St Jude Children's Research Hospital. Overby and Tarczy-Hornoch recommend that the outcomes of such intervention should be well studied to evaluate the effect of online resources in patient education.(28)

➔ **Nota benne:** Each one of these challenges should be taken into consideration in the design process. The design should be compliant with the needs identified in the literature. Since we are we are proposing a 'low-fi' prototype, we chose to address only two challenges:

- Physician Education
- Integration of PGx testing into clinicians' workflow

IV. Design Process:

In the design process, we took on consideration the challenges identified above. In addition to that, we reviewed the literature for more recommendations for the design of CDS tools in general. Then, we looked for more specific articles discussing the design of PGx-CDS. We were able to capture several recommendations about features that should be included. Last and not least, we developed a new approach to replace alerts in CDS.

A. Summary of recommendations from the literature:

Based on the literature discussing CDS in general or CDS for pharmacogenomics, we were able to extract this list of recommendations. We were able to identify features that should be included in the design.

Below, we list the most relevant features that we were able to capture from the literature.

Table 1: Summary of the literature's recommendations

<ul style="list-style-type: none"> • Provide the strength of the recommendation about the PGx test • A description of PGx information in drug labeling • Price of tests and whether if they are covered by insurance • A list of laboratories offering testing • Explain the effect of genetic variation on mechanism of drug action • Provide references such as scientific literature • Provide prescribing recommendations 	Johansen Taber & Dickinson (2014)
<ul style="list-style-type: none"> • Provide drug dose recommendations rather than just information about adverse interactions 	Masys et al.
<ul style="list-style-type: none"> • Use partial drug name search function for ordering medications. • Avoid Free text- Pre-built order sentences can save time • Too many dosage change options created complexity when changing dose frequency. • Clinicians like knowledge resources- • Icons for knowledge resources should be intuitive- • Too many knowledge resources can be overwhelming. • Clinicians want a way to assess the credibility of knowledge resources • Communicating genetic information to clinicians is challenging- It is recommended to provide dosing guidelines and recommendations. • Use Smart PGx-CDS guidelines • Provide only clinically relevant information 	(29) Devine et al.
<ul style="list-style-type: none"> • Avoid excessive alerting that leads to high override rates 	(30) Horsky et al.

<ul style="list-style-type: none"> • Colors: Use Blue links, black text, grey labels – common web design conventions. • Display a set of graded recommendation 	(31) Microsoft 2008
<ul style="list-style-type: none"> • Changing Direction is easier than stopping • Anticipate clinician needs and bring information to clinicians at the time they need it. • Recognize that physicians will strongly resist stopping 	Bates et al. (2003)

The recommendations listed in the table were taken into consideration in the prototyping phase. In addition to that, we tried to find a new approach to solve the alert fatigue problem. Our approach is explained in the next section.

B. New approach to solve the alert fatigue problem

Displaying alerts can help clinicians make the right decision and avoid making medical errors. However, reading all the alerts remains challenging for health care professionals. According to several articles from the literature, clinicians tend to ignore alerts and override them. Ash et al. held an expert panel conference with 19 experts to reveal unintended sequences of CDS. They state that clinicians tend to override “drug-drug interactions” alerts. (32)

To solve this problem, we propose a new approach. Instead of stopping clinicians after making a decision, we believe that is better to provide them with more relevant information throughout the process of decision making.

In the 10 commandments for CDS article of Bates et al., the fifth and sixth commandment were:

- ❖ “5. Recognize that physicians will strongly resist stopping”.
- ❖ “6. Changing direction is easier than stopping.” Bates et al. provided (33).

Following these “commandments” we propose to display context-based information. Relevant information will be displayed in a box on the right side. The content of the Information box will be relevant for the task that the physician is making.

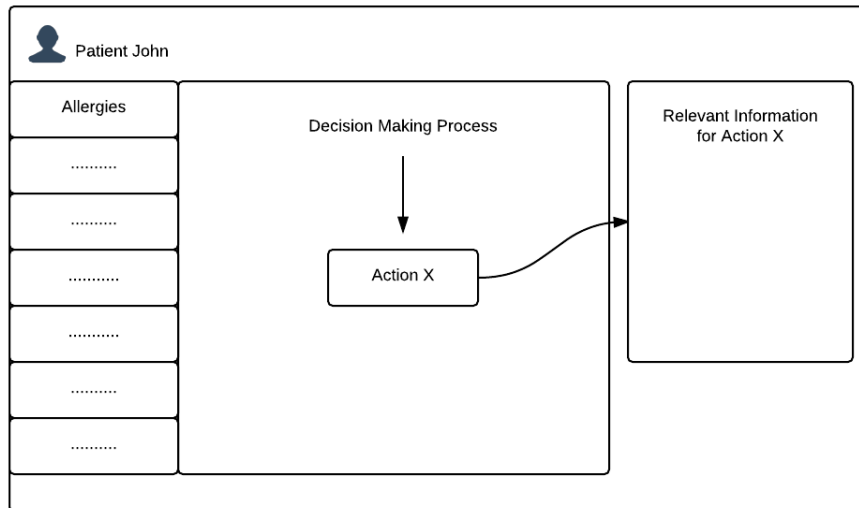


Figure 3 Display of context-based information

C. Prototype

In the prototype phase, we used Adobe Illustrator to sketch the PGx-CDS. We designed

Page 1: List of Medications

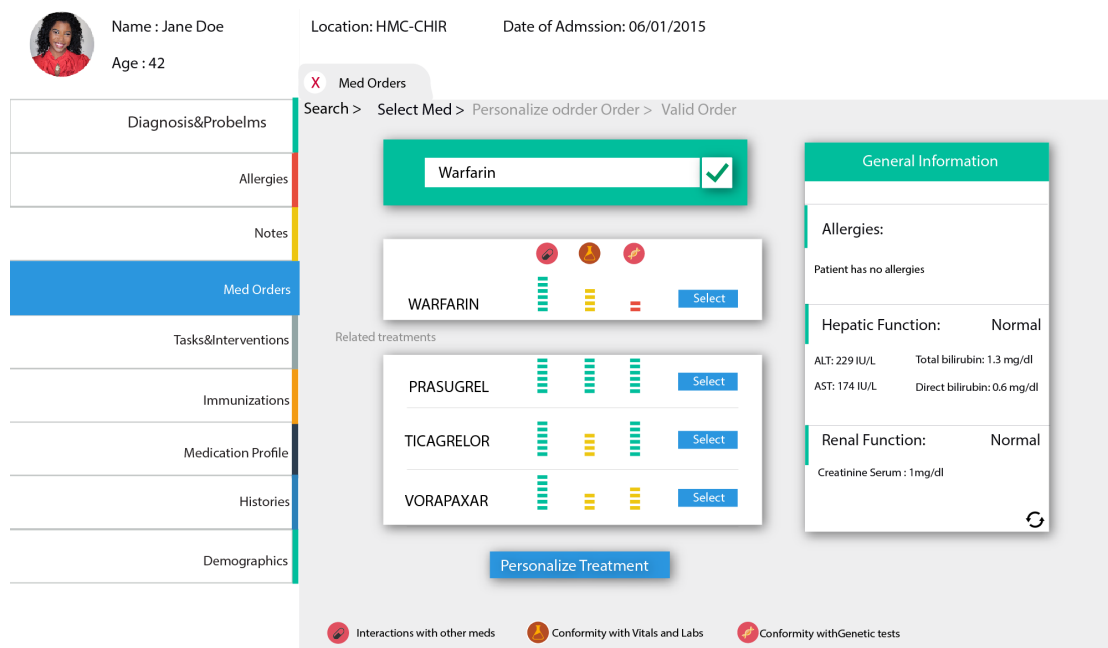


Figure 4: Prototype page 1 “List of medications”

- ❖ **General Information Box** : at this point, the information box shows general information about the patient. Allergies, Hepatic Function and Renal Function.

- ❖ **Personalize treatment:** We intend to change the physician’s direction of choosing warfarin (which is not recommended to this patient based on her genetic information). Therefore, we propose other medication that can substitute for warfarin.
- ❖ **Comparing Different Drugs** We present a new option for the physician of comparing different treatments and evaluate their outcomes for his/her patient. We present a visual way to compare the different drugs based on 3 Categories:
 - Genetic Information
 - Drug-Drug interaction
 - Vitals and labs

Page 2 : Personalize Treatment

Med Orders

Name: Jane Doe Location: HMC-CHIR Date of Admssion: 06/01/2015
Age: 42

Search > Select Med > Personalize Order > Valid Order

Search & Order

Top Recommended

Drug	Interactions with other meds	Conformity with Vitals and Labs	Conformity with Genetic tests
1. PRASUGREL	High (3 bars)	Medium (2 bars)	Low (1 bar)
2. TICAGRELOR	Medium (2 bars)	High (3 bars)	Low (1 bar)
3. VORAPAXAR	Low (1 bar)	Medium (2 bars)	High (3 bars)
4. WARFARIN	Low (1 bar)	Medium (2 bars)	High (3 bars)

Least Recommended

Ignore

General Information

Allergies: Patient has no allergies

Hepatic Function: Normal
ALT: 229 IU/L Total bilirubin: 1.3 mg/dl
AST: 174 IU/L Direct bilirubin: 0.6 mg/dl

Renal Function: Normal
Creatinine Serum: 1mg/dl

Interactions with other meds Conformity with Vitals and Labs Conformity with Genetic tests

Figure 5: Prototype page 2 "Personalize treatment"

After choosing “Personalize treatment”, the different drugs will be classified based on their scores in the 3 categories (Genetic information, Drug-drug Interaction, and Vitals and labs). Drugs will be listed from the top recommended to the least recommended.

➔ We intend to present different treatment options and help the clinician choose among them. We ranked medications from the least recommended to the most recommended.

Page 3: Relevant Vitals and labs

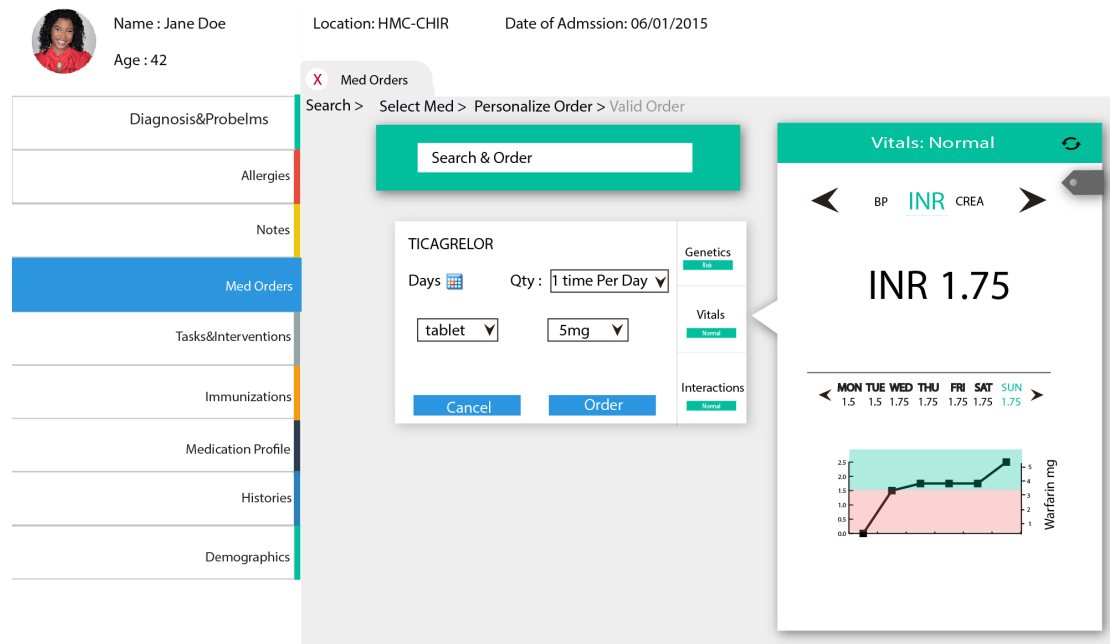


Figure 6: Prototype page 3 "Relevant vitals and labs"

Once the clinician chooses a medication, he/she can check the interactions of this medication with :

- Genetic information (PGx tests),
- Vitals and labs that are relevant for this medication
- Drug-Drug interactions

More information about these 3 topics are available for the clinician in the Information Box.

➔ We aim to encourage the physician to verify vitals and labs related to the drug that he intends to prescribe. This will help the clinician to have an overview of the relevant information without adding burden to his workflow.

Page 4 : Drug-Drug Interactions

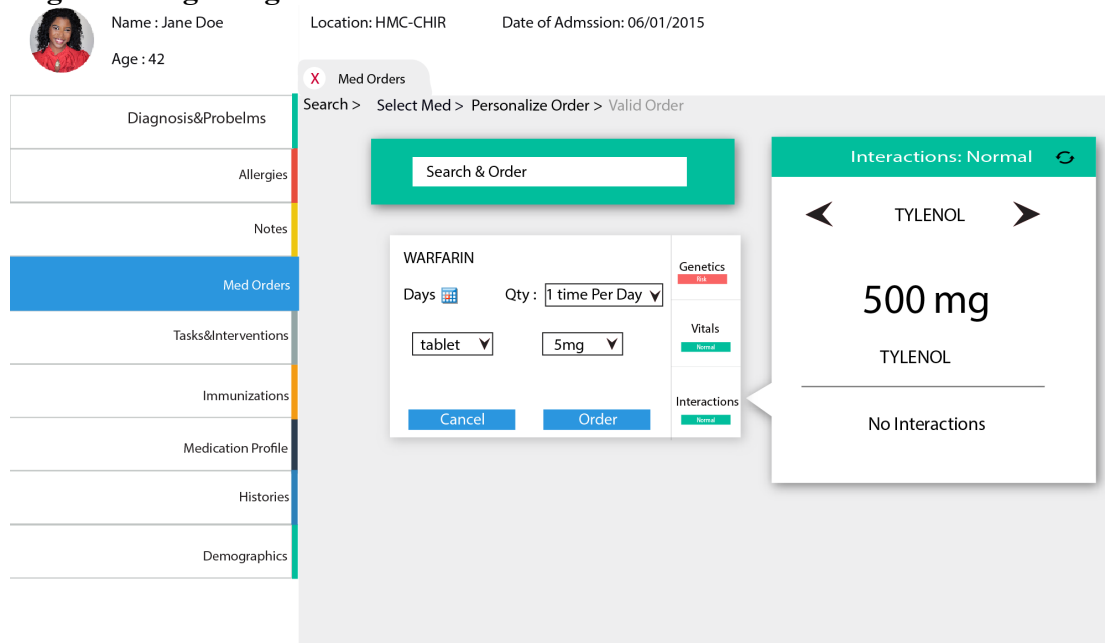


Figure 7: Prototype page 4 "Drug-Drug Interactions"

By clicking on the “Interactions button”, the clinicians can check the interaction of the medication that he/she is trying to prescribe with existing medications that the patient is already taking.

→ We aim to encourage the physician to check the drug-drug interactions before prescribing the medication.

Page 5 : Genetic Information

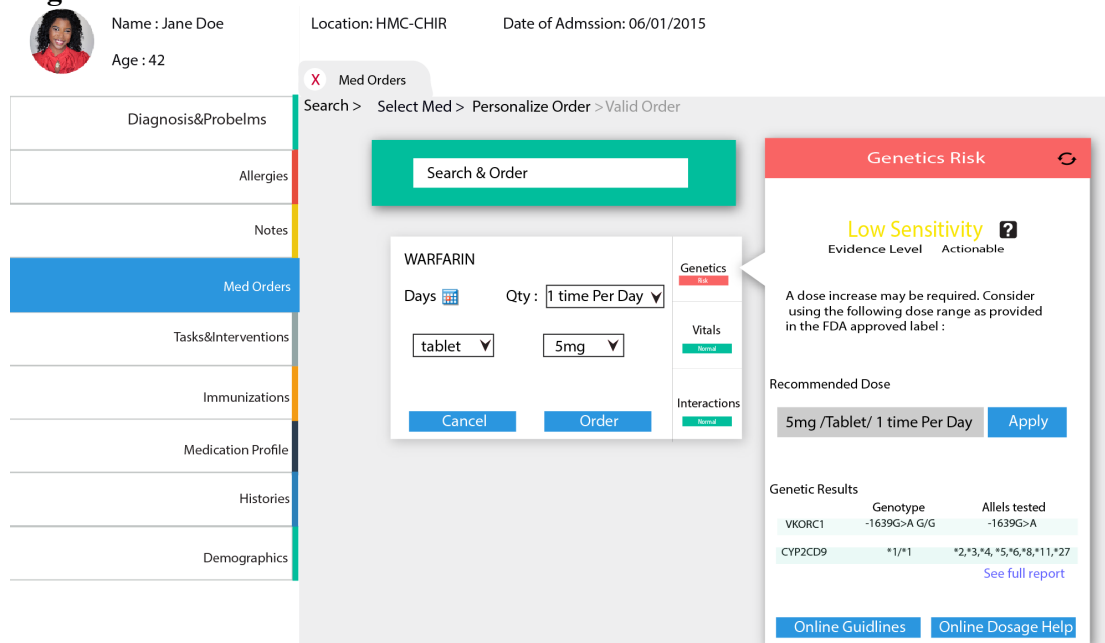







Figure 8: Prototype page 5 "Genetic Information"

This table illustrates the features presented in the box of information related to the PGx test.

Table 2 List of design features provided with the PGx results

Features and role	Design									
Online Guidelines: “Online guidelines” button will help the clinician pull external relevant guidelines										
Dosage recommendations : The physician can auto-populate the dosage boxes with the recommended dosage	Recommended Dose 									
Genetic Results: An overview of the genetic test results. This can save the clinician the time of reading the whole report	Genetic Results <table border="1"> <thead> <tr> <th></th> <th>Genotype</th> <th>Allels tested</th> </tr> </thead> <tbody> <tr> <td>VKORC1</td> <td>-1639G>A G/G</td> <td>-1639G>A</td> </tr> <tr> <td>CYP2CD9</td> <td>*1/*1</td> <td>*2,*3,*4, *5,*6,*8,*11,*27</td> </tr> </tbody> </table>		Genotype	Allels tested	VKORC1	-1639G>A G/G	-1639G>A	CYP2CD9	*1/*1	*2,*3,*4, *5,*6,*8,*11,*27
	Genotype	Allels tested								
VKORC1	-1639G>A G/G	-1639G>A								
CYP2CD9	*1/*1	*2,*3,*4, *5,*6,*8,*11,*27								
Interpretation of Genetic results: The interpretation of the results can help the clinician understand the relationship between the genetic results and the drug response										
General Information about Genetic results: If needed, this button will provide more information about the genetic results.										
Link for the Full Summary: In addition to the overview of the results, we kept a link for the full report.										

V. Heuristic Evaluation:

After finishing the prototype phase, we started planning for the evaluation.

We picked the heuristic evaluation developed by Nielson & Molich in 1990 to capture heuristic problems in our design. Nielsen calls this usability the discount usability since it is inexpensive, fast and easy to use. Heuristic evaluation involves having a small set of evaluators evaluate a prototype, or product against a brief list of

heuristics. One of the strengths of the heuristic evaluation is that it does not need a large number of participants. 3 or 5 participants is a reasonable number.

We chose “the task-based approach” for the conduct of our heuristic evaluation sessions, where evaluators are asked to identify usability problems while they walk-through specific tasks.(34)(35)

Table 3: Neilson's Heuristics (1994)

Example List of Heuristics Visibility of system status Match between system and the real world User control and freedom Consistency and standards Error prevention Recognition rather than recall Flexibility and efficiency of use Aesthetic and minimalist design Help users recognize, diagnose, and recover from errors Help and documentation
--

A. Evaluation plan:

1. Evaluators

The evaluators were 16 evaluators who had not been involved with the design of the interface. Feedback was solicited from experts in two rounds of heuristic evaluation. The first round was realized with experts with a design background. The second round was realized with experts with a medical background.

We were able to recruit evaluators who had two domains of expertise.

The first group of evaluators: (11 evaluators) participants are members of a research group focusing on the development of new technology for patient-centred purposes.

The second group of evaluators (5 members) are experts in personalized medicine and informatics.

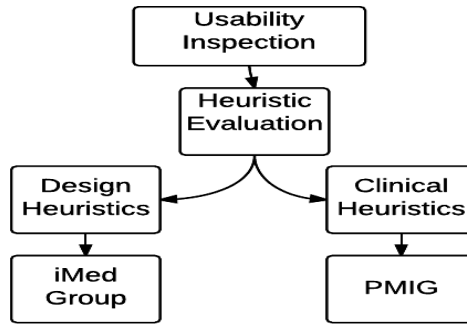


Figure 9: Usability inspection plan

Participants were recruited by word of mouth and contacted by email for more information about the evaluation session.

2. Evaluation Sessions:

We presented the prototype of a PGx Clinical Decision Support system using a web application that allows the user to interact with the prototype. The web application connects the different pages using hyperlinks, which allowed us to simulate the use of CDS.

The focus of this heuristic review is evaluating design interfaces, such as text display, buttons, and links.

The evaluation is comprised of 4 parts: Introduction of the tool to provide a context of use, informal walk-through of designs in a self-directed manner, heuristic criteria review based on Neilson's criteria and other criteria, and a group open-ended wrap-up session for design feedback.

Both rounds lasted up to 60 minutes each. (30 minutes for individual tasks + 30 minutes for group discussion)

Participants did walk-through the CDS-PGx prototype and wrote down their comments. The evaluators were asked to find as many problems as possible.

After the completing of the individual testing, participants were asked to participate in a 30 minute debriefing session to discuss their findings. They were also invited to propose changes for the redesign phase.

B. Summary of recommendations and lessons learned:

1. Lists of Medication Design:

To design the list of medication, we followed the Microsoft guidance for CDS design. This report proposed that CDS should have a graded display of the different options. Medications would be graded, then displayed accordingly. An icon to suggest preference ratings is also recommended.(31)

In our heuristic evaluation, users with a clinical background raised some points concerning this type of display:

- By classifying the medications, we might be sharing legal and ethical responsibility with the physicians.
- Physicians would avoid considering this classification. Because they are ethically and legally responsible for the decision, they would trust their own judgment ,rather trusting the CDS classification

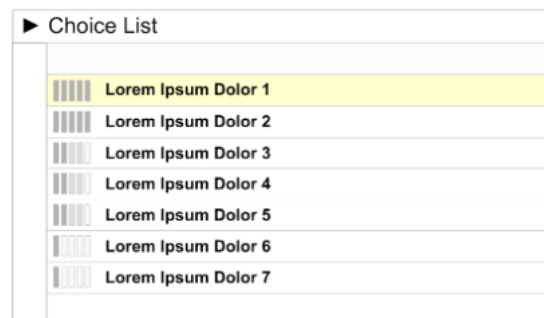


Figure 10: Microsoft recommendations for "Choice Lists with Preferences" 1



Figure 11 PGx-CDS medications' list

- ⇒ We will avoid classifying the different options. Instead, we will just propose a comparison.
- ⇒ We will provide a mouse-over explanation to help the user understand our comparison.

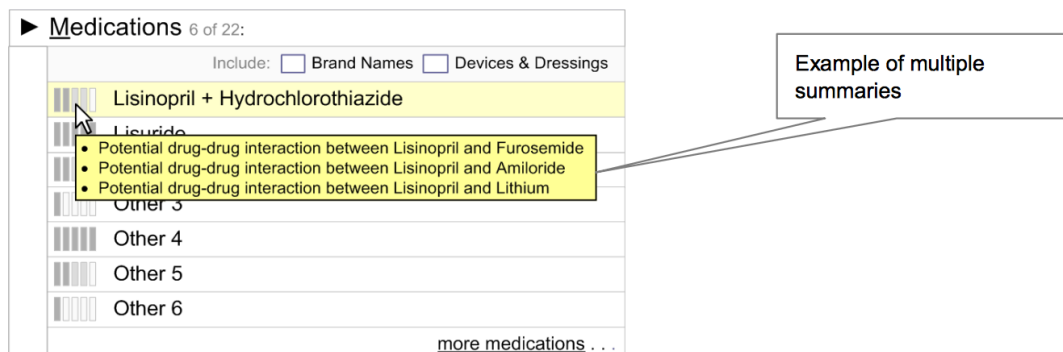


Figure 12 Microsoft recommendations for "Choice Lists with Preferences" 2

Recommendation for the "List of Medications" Design

- Present a list of different medications that the physician may consider.
- Provide a comparison of the different medications presented to the clinician
- Display a summary of relevant information for comparison on Mouse-Over

2. Genetic Information




Figure 13 “Genetic Information” box

We summarized the evaluation concerning the “Genetic Information” box in the next table.

Table 4 “Genetic information “box: Heuristic evaluation results

		Results
Online Guidelines. A link for guidelines resources.		Approved But with a pop-up window. Do not create a new tab. The user can get lost
Dosage recommendations	Recommended Dose 	Approved
Overview of Genetic Results	Genetic Results 	Approved
Interpretation of Genetic results		Still confusing. Both groups said that they want something more intuitive.

General Information about Genetic results.		A link for more information was approved
Link for the Full Summary	See full report	Providing a link for the Genetic full report was highly recommended by the clinicians group.

Recommendations for the “Genetic Information display” design

- Provide dosage help and guidelines.
- Use pop-up windows. Do not open a new tab for resources and external links
- Deliver an interpretation of the Pharmacogenomics test
- Offer a link for the Full report

3. **Context-based Display:**

- Users were not sure if the display was personalized to the drug or not.
- Add the time of the last update of the displayed information
- Drug-Drug interactions: We choose to display the interaction One drug at a time: Users preferred to have an overview of drug-drug interactions
- The Visual display of the Vitals was approved. A visual summary is helpful to have a quick overview of the vitals.

4. **Other General recommendations**

- Give the user the possibility to cancel at any time
- Indicate the progress of the process:
 - Choose medication> Set-up dosage>Confirm>Summary of the order.

VI. Limitations & Future Work

A. Limitations

1. Interoperability with Existing EHR:

According to Zhang et al, the implementation of CDS in EHR remain a challenging task. They state that one of the different barriers facing the adoption of CDS in clinical settings is to connect the CDS to the existing system. CDS will need to be connected to specific modules in clinical information systems to be functioning.

To realize this connection, Rodriguez Loya, Kawamoto, Chatwin , and Huser identified the use of service-oriented architecture (SOA) as a promising approach for implementing CDS in existing EHR systems. (36)(37)

SOA was identified as: *“an open, agile, extensible, federated, composable architecture comprised of autonomous, Quality of Service (QoS)-capable, vendor diverse, interoperable, discoverable, and potentially reusable services, implemented as Web services”*.(36)

SOA has been proposed as a solution to facilitate the transfer of information between different applications:

They mention 3 other benefits of SOA that can affect CDS implementation:

- Facilitate knowledge maintenance by centralizing the CDS content
- Reduce costs by adoption existing systems
- Ease the implementation of new CDS functionalities

Unfortunately, SOA remains as a vision. Hopefully, it will be part of our reality.

B. Future work

1. Build an ontology for the context-based display

To realize a context-based display, we will face a challenge of identifying relevant information for every drug and every task. Hervas and Bravo proposed to build an ontology that can facilitate identifying the relevant topics to be presented to the user.(38) In addition to this ontology, we need to identify rules that can help us prioritize the display of information to avoid overwhelming the clinicians with too many details.

In our future work, we will build an ontology for medication-related information.

According to the proposed CDS design, this ontology should contain 3 main classes:

- Genetic information
- Related Lab results and vitals
- Drug-Drug Interactions.

We will proceed for a literature review to identify rules to prioritize the display of information.

2. **Improve the design of Genetics results**

During the heuristic evaluation, evaluators did not approve the display of genetic results. To resolve this usability problem, we need to find a more intuitive way to present genetic data for the clinician. We will gather focus groups of experts. These groups will focus on optimizing the presentation of genetic results.

VII. Contribution:

A. 1. Methodological Contributions

Based on our experience in designing a PGx-CDS ,we propose this methodological process be followed for future work. We divided the process into 4 major phases: Define, Analyse, Prototype and Evaluate. These steps will help to capture the most relevant information related to the design of PGx-CDS, optimize the prototype based on the gathered information, and iterate the design process after evaluating the prototype.

- **Define:**

As a preliminary step, we should define the needs in PGx in general. During this phase, we reviewed articles from the literature. We tried to capture milestones, challenges and barriers that the PGx is facing from Lab to the bedside of the patient. These details should be captured to identify the goals that the CDS system should accomplish.

- **Analyse:**

We need to review the literature and previous projects to identify the different features proposed to be involved in the design of CDS. We need to analyse these features to decide which ones should be included in the design.

- **Prototype:**

After summarizing the findings from the two first steps-define needs and analyse features to be included in the CDS- we can start sketching the CDS design. The

sketching should be compliant with existing design recommendations for clinical settings. Microsoft proposed a set of recommendation for CDS that are useful in this step.

- **Evaluate:**

To realize the evaluation, we choose the Heuristic Evaluation. It was easy and not expensive. We decided to have evaluators with a design background and evaluators with a clinical background. Evaluators with a design background will be able to find design-related problems. Evaluators with a clinical background will be able to capture more clinical-related problem. We proceeded to iterate between the different steps to optimize the outcome of the process.

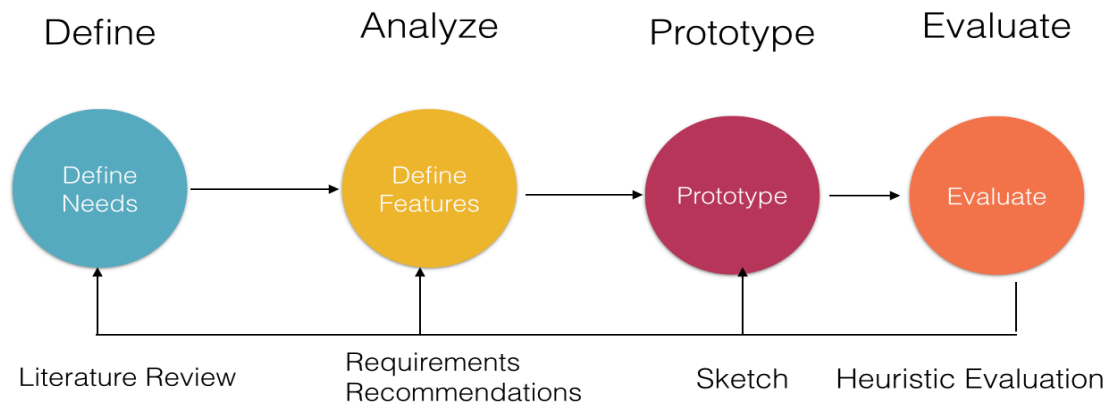


Figure 14 Design process

B. Design contributions: Context-based display

We propose a new approach to replace CDS alerts. Context-based display can be a promising solution to solve the alerts overriding problem. By providing context based information we will avoid to stop the physician. Instead, we will provide him/her with relevant information that should be taken in consideration. This process will help the clinician consider other options that should be more compliant with the patient profile.

- We propose to present different medications-that can substitute the original order without changing the clinical benefit. A table of comparison between different treatments will help the physician make the right decision.

Medication	Genetic Interaction 1	Genetic Interaction 2	Genetic Interaction 3	Action
WARFARIN	Normal	Normal	Interaction with CYP2C9*	Select
TICAGRELOR	Normal	Normal	Normal	Select
VORAPAXAR	Normal	Normal	Normal	Select
PRASUGREL	Normal	Normal	Normal	Select

[Ignore](#)

Figure 15 Table of comparison

- For each medication, we need to present relevant information about the compliance of this drug with the patient genetic profile.

Genetics Risk ↻

Low Sensitivity ?
Evidence Level Actionable

A dose increase may be required. Consider using the following dose range as provided in the FDA approved label :

Recommended Dose

5mg /Tablet/ 1 time Per Day Apply

Genetic Results

	Genotype	Allels tested
VKORC1	-1639G>A G/G	-1639G>A
CYP2CD9	*1,*1	*2,*3,*4, *5,*6,*8,*11,*27

[See full report](#)

[Online Guidelines](#) [Online Dosage Help](#)

Figure 16 Genetic information

VIII. Conclusion:

Implementing PGx in clinical care is revolutionizing the health care system. It is changing the way we approach the patient and the way we prescribe medications. As an emerging field, PGx is still facing several challenges. Once we have PGx tests and guidelines fully functioning, we will be able to solve more of the unknown facts about the patient response to treatments.

In addition to that, information technology is capturing more and more details from the patient's environment. By integrating these data, with the genetic profile and the medical history, we will be able to optimize the prediction of the patient's response to every treatment he takes. Using machine learning and mathematical models, we will be able to test a medication virtually before prescribing it for a patient. Implementing PGx in clinical settings is just a small step in the upcoming journey of modern medicine.

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