PHARMACOGENOMICS INFORMATION-SEEKING BEHAVIOR AND THE OPENINFOBUTTON SOLUTION

by

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ABSTRACT

Lack of information is a serious concern for clinicians. Information resources can address this problem, leading to improvements in decision making and patient outcomes. Genomics is an information-rich domain where searching for information can be complex. For example, most physicians agree that pharmacogenomics can be used to improve the quality of care, and there is evidence that many patients harbor actionable pharmacogenomic variation. However, surveys have shown that physicians feel their knowledge of pharmacogenomics to be inadequate. This represents an information need. A natural approach to meet this need is to provide context-aware access to the precise information needed. The Health Level 7 Context-Aware Knowledge Retrieval Standard, a.k.a the Infobutton, offers a modality to deliver context-aware knowledge into electronic health record (EHR) systems. OpenInfobutton is a reference implementation of this standard that offers an open-source instantiation. In this thesis, we aimed to provide insight into pharmacogenomics information needs and an automated mechanism for addressing these needs. Such work can aid the design of tools that support clinical decisions in genomics.

This work is dedicated to God, my family, my mentor, and the faculty of the Department. They have answered all my requests with patience, and kindness. Their efforts have provided for an awesome opportunity to be a part of the changing face of Medical Informatics. Don't lose the faith.
Keep Watch. Take Heart.

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CHAPTER 1

INTRODUCTION

Lack of information is a serious concern for clinicians. Information resources can address this problem, leading to improvements in decision making and patient outcomes [1]. Our overall goal is to provide insight into pharmacogenomics information needs (AIM 1) and an automated mechanism for addressing these needs (AIM 2). Such work can aid the design of tools that support clinical pharmacogenomics decisions. Current systematic reviews have reinforced the need for research on innovative use of technology in the clinical setting to bring pharmacogenomics information to healthcare providers [2–4]. Underscoring the importance of pharmacogenomics in personalized medicine, an estimated 2 million people in the US [5] are documented to have adverse drug effects. In addition, adverse effects was the second highest rank among drug topics searched by clinicians in a randomized control trial of information delivered by infobuttons [6]. Most physicians (98%) agreed in a 2008 survey that pharmacogenomics data can improve the quality of care [7]. Indeed, in a recent study, one of five actionable pharmacogenomics variants was identified in 90% of patients due to whole-genome-sequencing [8]. However, surveys have shown that physicians feel their knowledge of pharmacogenomics to be inadequate [7,9], indicating a need for information.

In assessments of what information should be considered to meet clinicians'

information needs, three questions typically serve as a focus of pharmacogenomics action: “What to test?,” “When is testing recommended?,” “How does the result impact treatment?” [10–14]. The impact of specific test results on treatment is a common goal of many efforts [3,4], and is an important aspect of the Clinical Pharmacogenetics Implementation Consortium (CPIC) mission integrated in PharmGKB [15,16]. The question of “When is testing recommended?” is also valid, as adoption of whole-genome-sequencing has yet to become universal, and as too many tests [17] or too few tests [18] are linked to improper care and increased financial costs. In this thesis, we conducted an in-depth exploration of pharmacogenomics information needs of clinicians to see if they have needs beyond the three focal needs. Specifically, we aimed to isolate what kinds of information are most frequently sought in the clinical setting.

Attempts have been made to address the perceived three focal information needs. Providing answers for “What to test?” and “How does the result impact treatment?” is the goal of several efforts [3,4], but less has been done to provide a seamless answer to the question “When is testing recommend?” To answer their pharmacogenomics questions, physicians often turn to web resources, like UpToDate [19–21] and FDA labels [22]. Anticipating this observation, Overby et al. implemented a pharmacogenomics clinical decision support (CDS) tool using the infobutton modality that provide answers for check “What to test?” and “How does the result impact treatment?” [23]. While part of the development of CDS pharmacogenomics tools, documentation on the availability and accessibility of answers for “When is testing recommended?” is difficult to find. One approach has been to avoid the question, “When is testing recommended?,” by using a committee to provide a directive [12,24] or scheduling a consult with a clinical geneticist.

However, these solutions do not scale well, becoming burdensome as more guidelines accumulate (currently there are 17 published CPIC guidelines), and leave open questions regarding interactions yet to be considered. A scalable and natural approach is to explore automatic context-aware retrieval of recommendations found in resources such as UpToDate, a key web resource often used by clinicians [19–21]. The Health Level 7 Context-Aware Knowledge Retrieval Standard, a.k.a the Infobutton Standard, offers a modality to deliver context-aware knowledge into electronic health record (EHR) systems. We sought to use the HL7 Infobutton Standard to enable context-aware information retrieval from genomic knowledge resources. The aims of this current work are the following:

- Aim 1 of this work is to determine the pharmacogenomics information needs and seeking behavior of clinicians. Questions investigated are: "What themes are emergent?" and "How do physicians search for information?" To accomplish this aim we will use case vignettes to probe the pharmacogenomics information needs and seeking patterns of clinicians.
- Aim 2 of this work is to enable standards-based context-aware information retrieval of current pharmacogenomics knowledge. The main question investigated is: "Are current standards and technology sufficient for integration of genomics knowledge with electronic health records?" To achieve this aim we will:
    - Assess the readiness of pharmacogenomic resources for adoption of the Health Level 7 (HL7) Infobutton (IB) Standard.

- Implement a public search interface for genomic knowledge that utilizes the HL7 Infobutton (IB) Standard.

CHAPTER 2

BACKGROUND

2.1 Need for Clinical Pharmacogenomics Information

Pharmacogenomics information is increasingly important in patient care decisions. Used correctly, pharmacogenomics tests can alleviate hospitalizations due to adverse drug effects of treatment, improve quality of patient care, and reduce financial costs [25–30]. Additionally, there is growing evidence that pharmacogenomics testing can improve patient adherence to treatment regimens [31,32]. The critical importance of pharmacogenomics in personalized medicine is further highlighted in that adverse drug events are estimated to affect 2 million people in the US [5]. More specifically, in the treatment of asthma with beta-adrenergic receptor agonists, there are several studies that recommend that patients who have specific genetic variants, in some cases with specific genetic backgrounds, be given an alternative treatment [26,29,30,33]. Current National Heart, Lung, and Blood Institute guidelines recommend beta-adrenergic receptor agonists as the "drug of choice" [34] for acute asthma symptoms (e.g., asthma attacks). Asthma affects around 23 million Americans, and it is estimated that 12 million of US asthma sufferers will experience acute symptoms [35]. Thus, the cost of misuse of beta-adrenergic receptor agonists, only one of many medications with pharmacogenomics implications, is likely to be highly significant.

2.2 Clinicians' Need for Pharmacogenomics Information

Physicians have a self-identified lack of pharmacogenomics knowledge and low self-efficacy in use of pharmacogenomics tests. Only 10% of physicians nation-wide, based on the 2008 National Survey [7], feel that they have adequate understanding of pharmacogenomics tests, while 98% believe that pharmacogenomics tests will be beneficial to their patients [7]. The lack of understanding suggests low self-efficacy. In regards to the theory of self-efficacy, Bandura states that "(e)fficacy beliefs in part determine outcome expectations" and that "(m)ost people engage in tasks in which they feel competent and confident and avoid those in which they do not" [36]. A more recent survey had similar results. Selkirk et al. surveyed physicians at the NorthShore University HealthSystem. They found that 11% of physicians considered themselves to have "above average to expert knowledge" of pharmacogenomics, while about 51% had no to minimal knowledge [9]. Similar results were found for "When and how to incorporate genomic medicine into practice." Thus, physicians may avoid pharmacogenomics testing because they feel their pharmacogenomic knowledge is inadequate. In response, attempts have been made to better integrate pharmacogenomics information into medical education [37], including moves to include personal genomic testing in education [38,39]. Also, several consortiums and organizations have been formed to promote usage of pharmacogenomics data [28]. However, physicians still feel that they are not adequately informed. A more recent survey by Selkirk et al. found that only 11% of physicians at the NorthShore University HealthSystem considered themselves to have "above average to expert knowledge" of pharmacogenomics, while about 51% had no to minimal knowledge [9]. Similar results were found for "When and how to incorporate genomic

medicine into practice."

Of note, a recent study provided a sense of clinicians' information needs in response to case simulations that included a pharmacogenomics clinical decision support system [14]. Devine et al. used a mixed-method approach that included mapping subject statements to heuristics and deriving themes from these mappings. The authors found that clinicians suffered from a lack of training, but also reported that subjects recommended alerts with "dosing guidelines and recommendations." Three important themes were a need for phenotypic interpretations, credibility of the source of information, and clinically relevant information.

2.3 Additional Barriers to Using Pharmacogenomics

In addition to self-efficacy, further barriers to usage of guidelines have been studied as documented in a systematic review by Cabana et al. They found a significant number of articles concerning "awareness (n = 46), familiarity (n = 31), agreement (n = 33), self-efficacy (n = 19), outcome expectancy (n = 8), ability to overcome the inertia of previous practice (n = 14), and absence of external barriers to perform recommendations (n = 34)" [40]. A more recent meta-analysis generally agrees and found that for studies published after Cabana et al., "in most of the studies, GPs referred to a lack of time to read and assess the guidelines" [41]. Typically, clinicians will spend no more than 2 minutes pursing questions at the point of care [42]. Similarly to medical guidelines in general, following recommendations for "when is testing necessary" for pharmacogenomics is impacted by a lack of time, awareness of recommendations, lack of self-efficacy, and lack of pharmacogenomics knowledge.

2.4 Medical Education

Education is one approach for reducing a knowledge gap and improving self-efficacy. Attempts have been made to integrate pharmacogenomics data into medical education [37] and several consortiums and organizations have been formed to promote usage of pharmacogenomics data [28]. However, pharmacogenomics education in medical school is still inadequate and physicians still feel that they are not adequately informed. For example, in a survey of 10,303 physicians in 2012, only 15% of US physicians noted that pharmacogenomics was included in their medical education curriculum, while 23% received instruction during their postgraduate medical education, and only 10% of 10,303 surveyed US physicians are confident that they have adequate understanding of pharmacogenomics testing [7].

Two studies represent a move in medical education to include personal genomic testing. An initial attempt was made to educate physicians by offering personal genome testing and the study resulted in over 50% of physicians stating that they felt better able to advise their patients [39]. However, the utility of the effort was not fully measured. A more recent study also saw student interest in genetic testing increase with personal genome testing [38]. Both of these efforts were focused on testing in general, not on pharmacogenomics nor a specific test.

2.5 Dealing with Information

Knowledge gaps are a significant concern for clinicians that can be addressed through seamless access to information resources [43,44], with reported improvements in patient outcomes [1,21,45]. Lack of time can also be addressed [6,46–48]. Current systematic reviews have further reinforced the need for research on electronic ways to

bring pharmacogenomics information into clinical settings [2–4]. To answer their pharmacogenomics questions, physicians often turn to web resources, like UpToDate [19–21] and FDA labels [22]. Specifically in regards to pharmacogenomics, when asked about sources of information for genetic testing and the application in the context of drug therapy, 39% of physicians use drug labels [22] and 75% highly valued evidence from scientific journal publications [22]. While reasonable sources, FDA drug labels and the scientific literature can still lead to incomplete information, confusion, and a lack of action evidenced by the fact that of 10,303 physicians surveyed in 2008 only 12% had ordered a pharmacogenomics test within the prior six months [7,22]. Thus, a more seamless means of providing information is needed. One important consideration for effective injection of information into the clinical process is to avoid disrupting it [48]. It is not likely that a clinician will be able to process several sources of information, such as several electronic resources, at one time. A. Miller emphasizes that the human mind can process only seven chunks of information at a time [49,50], and Cohen et al. suggest the number is actually four [51]. And for high-stress situations, such as air-traffic controlling, a single instruction has been recommended [52]. Thus, prefiltering of electronic resources to reduce the bits of information that must be considered supports human information processing limitations. Infobuttons are an effective modality for delivering precise information content as evidenced by a randomized control trial of information delivered by infobuttons [6] carried out by Del Fiol and colleagues. In this trial, the topic of "adverse effects" had the second highest rank among topics searched by clinicians, and a "high positive clinical impact" was reported by study subjects in 62% of their infobutton sessions [6]. Infobuttons can enable more rapid searching for pharmacogenomics

information [53,54], and an infobutton manager, tooling that uses the context of an information request to choose appropriate resources, can also be used to to reduce the amount of information that must be considered.

2.6 Automated Context-Aware Information Retrieval (Health Level 7 Infobutton) in Genomics

As mentioned, streamlined access to genomic knowledge in the context of patient care can be provided through context-aware information retrieval applications called infobuttons. This has been proposed by eMERGE [55] and implemented in EHR systems [14,53,56]. Implementation of the Health Level 7 Context-Aware Information Retrieval application (HL7 Infobuttons) [57] is particularly attractive as it is required in the Meaningful Use EHR certification criteria [58]. The Meaningful Use program also includes financial incentives to providers who adopt certified EHR products. To date, over a thousand EHR products have been certified under the Meaningful Use program [59]. Infobuttons translate the context of a patient encounter into a query for information to answer specific questions. The answers are retrieved form internet resources, and in the HL7 IB standard, the context is provided to the resource in a computable fashion. Use of infobuttons has been shown to produce improvements in the speed with which clinicians find answers to clinical questions [6], producing a perceived positive impact on decision making [6,46,47]. Thus, the use of automated context-aware information retrieval is an attractive option to provide the clinician more confidence and time to focus on drugs where recommendations are more likely to be present, thus reducing the potential for cognitive disruption.

2.7 Clinical Pharmacogenomics Implementation Consortium (CPIC)/PharmGKB.org an Exemplar Online Resource for Meeting Information Needs

As an example of an online resource for pharmacogenomics, the Clinical Pharmacogenomics Implementation Consortium has the purpose of providing actionable recommendations in pharmacogenomics [60]. They have published several guidelines and partnered with the Pharmacogenomics Knowledgebase (PharmGKB.org) to deliver their content [60]. The CPIC guidelines provide details on the interpretation of specific genetic tests as the test result relates to a specific medication. The discussion is often focused on the disease most relevant to the medication. Thus, content from a specific guideline could be delivered relative to a specific gene/drug/disease context to answer questions on genetic testing.

2.8 Efforts to Meet Perceived Needs

For pharmacogenomics, providing automated accessible information to the questions of "What to test?" and "How does the result impact treatment?" is a focus for several efforts [3,4], including the Emerge network. But other needs may exist. Addressing the question "When is testing recommend?" is especially vital as testing too often [17] or not often enough [18] adds significant costs both in patient outcomes and financially. Several nonautomated solutions are currently being used to handle the question of "When is testing recommend?" For some hospitals and CDS pharmacogenomics tool designers, the solution has been to use a committee to decide which tests will be implemented [12,24]. Another solution is to consult with a clinical geneticist. ARUP has shown that for general genetic testing questions, consult can save $48,000 per month [61]. While demonstrating the impact of having an informed answer

to the question “When is testing recommended?,” requiring the service of a genetic counselor for every pharmacogenomics decision does not scale well. Critically, not enough is known of the ability to meet clinician’s needs beyond “What to test?” and “How does the result impact treatment?,” nor what those needs are.

Our work addresses the question of what information clinicians seek in pharmacogenomics. Also, we provide an implementation of the HL7 IB that delivers retrieval from both pharmacogenomics, gene-based, and genetic disease-based content. This implementation could be tailored to meet the needs we have uncovered.

CHAPTER 3

PHYSICIANS' PHARMACOGENOMICS INFORMATION NEEDS AND SEEKING BEHAVIOR: A STUDY WITH CASE VIGNETTES

3.1 Abstract

Genetic testing, especially in pharmacogenomics, can have a major impact on patient care. However, most physicians do not feel that they have sufficient knowledge to apply pharmacogenomics to patient care. Online information resources can help address this gap. Thus, we sought to investigate clinicians' pharmacogenomics information needs and information-seeking behavior and to provide guidance to improve the design of pharmacogenomics information resources. To accomplish this objective, we carried out a mixed-method assessment of clinicians' information-seeking process for three pharmacogenomics case vignettes. Clinicians' interactions with online pharmacogenomics resources were recorded, transcribed, and analyzed for prominent themes. Quantitative data included information-seeking duration, page navigations, and pre- and poststudy questionnaires. We found that physicians searched on average for 8 minutes for pharmacogenomics information and spent less than 30 seconds considering content before navigating away. The information needs exhibited by clinicians can be summed up by a needs for phenotypic descriptions of test interpretations, molecular basis

for the clinical effect of drug variation, information on the logistics of carrying out a genetic test (including questions related to cost, availability, test turn-around time, insurance coverage, and accessibility of expert support), and an indication of the choice of an alternative therapy, along with clear demographic prevalence data. Also, we found that when navigating, clinicians were as likely to return to the case vignette as to navigate to new content – emphasizing a requirement to retain the search within the context of care. To conclude, 8 minutes is longer than can be expected for physicians to search for information at the point of care. Also, a pharmacogenomics resource should strive to address the themes noted here with topical hyperlinks that lead to information presentation consumable in less than 30 seconds.

3.2 Introduction

Pharmacogenomics information is increasingly important in patient care decisions. Used correctly, pharmacogenomics testing has the potential to alleviate complications due to adverse drug events, improve quality of patient care, and reduce financial costs [25–30]. Additionally, there is growing evidence that pharmacogenomics testing can improve patient adherence to treatment regimens [31,32]. The critical importance of pharmacogenomics in personalized medicine is further highlighted in that adverse drug events are estimated to affect 2 million people in the US [5]. For example, in the treatment of asthma with beta-adrenergic receptor agonists, studies recommend that patients who have specific genetic variants be given an alternative treatment [26,29,30,33]. Asthma affects around 23 million Americans, and it is estimated that 12 million will experience acute symptoms [35]. Thus, the cost of misuse of beta-adrenergic receptor agonists, only one of many medications with pharmacogenomics implications, is

likely to be highly significant.

Despite the potential benefits of pharmacogenomics, there are significant barriers to the optimal adoption of pharmacogenomics information in routine patient care decisions. Physicians have a self-identified lack of pharmacogenomics knowledge and low self-efficacy in use of pharmacogenomics tests. Only 10% of physicians nation-wide, based on the 2008 National Survey [7], feel that they have adequate understanding of pharmacogenomics tests, while 98% believe that pharmacogenomics tests will be beneficial to their patients [7]. In response, attempts have been made to better integrate pharmacogenomics information into medical education [37], including education on personal genomic testing [38,39]. Also, several consortiums and organizations have been formed to promote usage of pharmacogenomics data [28]. However, physicians still feel that they are not adequately informed. A more recent survey by Selkirk et al. found that only 11% of physicians at the NorthShore University HealthSystem considered themselves to have "above average to expert knowledge" of pharmacogenomics, while about 51% had no to minimal knowledge [9]. Similar results were found for "When and how to incorporate genomic medicine into practice."

Knowledge gaps are a significant concern for clinicians that can be addressed through online information resources [43,44], which have demonstrated improvements in provider decisions and patient outcomes [1,45,62] [6,46–48]. Recent systematic reviews have further reinforced the need for research on electronic ways to bring pharmacogenomics information into the clinical setting [2–4]. To answer their pharmacogenomics questions, physicians often turn to Web-based resources, such as UpToDate [19,20,62] and US Food and Drug Administration (FDA) drug labels [22].

Additionally, groups such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published guidelines on pharmacogenomics testing [60]. Despite the availability of these resources, a survey of 10,303 physicians in 2008 showed that only 12% had ordered a pharmacogenomics test within the prior six months [7,22]. This low use may be partially due to barriers that limit seamless access to information that can help guide physicians in the use of pharmacogenomics. To help guide the design of delivery of content from clinical pharmacogenomics resources, we investigated physicians' information needs and information seeking behavior when exposed to pharmacogenomics case vignettes.

3.3 Methods

A mixed-methods study with case vignettes was designed to capture physicians' information needs and information-seeking behavior related to genetics. The study consisted of a prestudy survey, three case vignettes to prompt information seeking, a poststudy survey, and a short poststudy interview.

3.3.1 Case Vignette Design

Three case vignettes were designed through examining existing case vignettes (case 1: [63–66]), guidelines (case 1: [67]; case 2: [30,68,69]; case 3: [70,71]) and iteratively refined and validated by a clinical domain expert. Each vignette consisted of a case narrative and prompted for a pharmacogenomics information search. Vignettes can be found in the online supplement. Table 3.1 summarizes the cases.

Table 3.1 Case vignette summary

Case Vignette	Disease or Condition	Medication Focus	Problem	Patient	Main Information-Seeking Driver
1	Guacher's disease	Enzyme Replacement Therapy	Hereditary risk	Prospective child of at risk parents	Parents desire to be prepared
2	Asthma	Albuterol	Worsening symptoms while on treatment	Pediatric male, no apparent environmental factors, twin sister with same problem	Father's concern
3	Percutaneous coronary intervention	Clopidogrel	Loading dose prescription	65 –year old male, past smoker, no history of bleeding or increased clotting	Patient's concern

3.3.2 Data Collection

The data collection instruments are included in the online supplement. Subjects were first asked to fill out a prestudy survey, which asked for demographic data, experience with internet resources, as well as attitudes about and experience with pharmacogenomics. The prestudy survey included questions from a survey previously used by Stanek et al. [7] and questions used by Del Fiol [72]. Next, subjects were presented each of the vignettes and were asked to search for relevant information from UpToDate (all cases) and PharmGKB (case 3). Subjects were asked to think aloud and share their thoughts as they sought information. Audio and computer screen interactions were recorded while subjects sought information in response to each case vignette. While subjects sought information, one of the authors (BH) took notes to help with the short postsession interview. After the second and third cases, subjects filled out a brief post-study survey adapted from Del Fiol et al. The survey included seven questions. Three

questions were open-ended: “What is your final answer to the case vignette?,” “Could you please summarize in 1-2 sentences the gist of the evidence that guided your decision?,” and “What other types of information could have helped you?” Four questions were Likert scale questions, two on the complexity and experience with the case vignette, and two regarding the information found. After the third case, BH carried out a short interview using the audio/computer screen recording and notes to elicit details of the information seeking experience. Each session lasted between 50 to 90 minutes.

3.3.3 Qualitative Data Analysis

The think aloud audio and poststudy interviews were transcribed and time-stamped. Then a process consistent with content analysis as described in Berg et al. [73] was carried out. Initially, BH performed open coding for one subject using both the audio transcripts and the computer screen recordings. “Berry-Picking,” as described in the following section, was used as a theoretical framework. After the initial open coding, BH and GDF refined the initial codes for inclusion into a study code book for further use. For reliability and validity, BH and AK coded each subject independently and iteratively reconciled disagreements through consensus with a third researcher (GDF). Overall, there were 42 need codes identified. These can be found in the appendix. In the last stage, BH and AK performed a thematic analysis by merging similar codes into higher level themes. A candidate set of themes was then refined through discussions among BH, GDF, and BS. Thematic analysis was also carried out on the open-ended questions from the post-study survey.

3.3.4 Theoretical Framework Guiding Data Analysis

Coding was guided by a model of information seeking called "Berry-Picking" [74]. According to the "Berry-Picking" model, an information-seeking experience starts with an information need. Then the subject exercises strategies to satisfy the information need, seeking locations of information that are compared to "berry" patches. As the subject finds relevant "berries," the understanding of the problem improves, leading to more refined and specific information-seeking strategies. The process continues iteratively with the subject posing progressively more sophisticated inquiries. Berry-picking is applicable in situations where the information seeker is not an expert in the subject of interest, which may be the case when primary care physicians seek new information on pharmacogenomics for a specific patient. We used the strategies, locations, and information berries to determine subjects' information needs.

3.3.5 Quantitative Data Analysis

To describe quantitatively the information-seeking behavior of clinicians in our study, we computed median, average, range, and standard deviation for the following measurements: the time spent by each physician on information seeking, the time between navigational actions such as clicking links or tabs, number of tabs or links clicked, and the number of searches entered. The time between clicks represents the time subjects spent on content before leaving to other content.

3.3.6 IRB approval

This study was reviewed and approved by the University of Utah Institutional Review Board as exempt (IRB_00075761).

3.4 Results

Six physicians, five males and one female, participated in the study. Three subjects were in the 30-39 years of age category, two were 40-49 years-old and one was 60-69 years old. In general, subjects were pediatricians and internists. Years in clinical practice ranged from 2 to 36 years, with an average of 13.8 years.

3.4.1 Prestudy Survey - Pharmacogenomics Experience and Attitudes

Subjects were proficient in using the internet and UpToDate, but none were familiar with PharmGKB. All subjects felt that genetics can influence response to treatment, but only one of six felt adequately informed about genetic testing. Only one subject had education in pharmacogenomics. Five subjects stated that colleagues were the source of routine pharmacogenomics information. Only two subjects indicated that the internet was their routine source of pharmacogenomics information and had actual pharmacogenomics testing experience within the previous six months. All subjects indicated that private, state, and federal health insurers should provide full coverage for pharmacogenomics tests, at least in some cases.

3.4.2 Themes

The qualitative analysis revealed 11 themes that could be further merged into 6 categories (Table 3.2).

3.4.2.1 Alternative Therapy Options

Subjects indicated that, prior to proceeding to ordering a genetic test; they needed evidence and recommendations for alternative treatments to consider. Subjects sought evidence that alternative treatments could be used effectively and safely without

Table 3.2 Information needs and information seeking categories and themes

Category	Theme
Is there an alternative therapy that obviates the need for genetic testing?	Alternative therapy options
Clear, reliable guidance on genetic testing: when and how	Specific, actionable, clinical guidance from authoritative sources
	Guidance on optimal approach to genetic testing
	Logistics of testing
How often might genetic testing be indicated?	Prevalence of genetic variation
	Indications for genetic testing
How important is genetic testing to care of my patient and what is the evidence?	Clinical impact of genetic testing
	Practice changing evidence
Help in understanding genetic effects	Role of genetics in the manifestation of the disease
	Understanding general molecular effect of genetic variant
Aid in searching for information	Help with search terms

requiring a genetic test or they wished to have evidence that such an alternative therapy was not available.

For example, subject 5 sought a recommendation "…telling you to just be using another option in him or does [the patient] have a particular contraindication to just doing alternate therapy [that] I'm supposed to pick up on, instead of doing any testing on him." Similarly, a different subject expressed that "ideally, what I am thinking is to maybe just change the therapy and regimen… just switch to something else."

3.4.2.2 Specific, Actionable, Clinical Guidance from Authoritative Sources

Subjects need an authoritative, "bottom-line" recommendation. For example, subject 3 stated, "with the authorities, with the experts, with the review of the literature, American Heart Association and the rest, where they will be saying, "You know, you

know guys you ought to test these guys, because you are [going to] lower your risks related to putting that stent in and the clotting stuff that might mess you up." That's what I was looking for." Similarly, subject 3 was "going for a bottom-line." Additionally, consult with a specialist was considered as evidenced by subjects navigating to and examining available "Genetic Counseling" sections.

3.4.2.3 Guidance on Optimal Approach to Genetic Testing

Subjects wanted know the best genetic test to use. For example, subject 3 mentioned "I'm not finding anything that is like a straightforward test…," and subject 5 stated they were "looking for if there were any indication that I should select a particular genetic test option."

They were also curious about choosing one approach over the other, evidenced by subject 6 stating "genotyping may miss some of those loss of function alleles. And, I just find it interesting that it is a footnote because it seems rather important to me."

3.4.2.4 Logistics of Testing

Subjects also wanted information on whether or not they could order a test in their system, the test turn-around time, and considered both cost and proximity of an expert. For example, subject 4 mentioned "first, I'd have to find out if a test even exists and how much it costs." And subject 4 asked "how fast can we make the genomic test actually be available?" Getting a test result in time to make decisions was a concern. For example, subject 3 asked "But can they turn [the genetic test] around? You would have to know, I mean, if the guy is going to have the stent the next day." Subject 3 wondered if the result could be achieved "in half an hour with DOT-Blot-PCR."

Other cost considerations were expressed by subject 3 during the postsession interview: “Other information that could have helped me? Ah, knowing the prevalence of the CYP2C19 mutations in the general population and in subset populations, knowing if the patient had had family members with known difficulty in metabolizing medications, cost of the test, availability of the test, turnaround time of the test.” Subject 1 voiced a perception that the financial cost is high by indicating that the subject would order a test “if this guy is rich and wants to be parted with some of his money…”

Subject 6 also mentioned concern regarding the proximity to a specialist “but if you have implications to a child’s wellbeing and maybe mortality …and I have the resources here, I use them…that’s sort of a bit harder if you are asking your family to drive 400 miles to a pharmacogenetic counselor.”

3.4.2.5 Prevalence of Genetic Variation

Information on prevalence of genetic variation was also sought; both for the population in general, for the ethnic group the patient belonged too, and in the patient’s family. For example, subject 4 stated “it doesn't really tell me what percentage of the population has an issue with CYP2c19.” Along these lines, subject 6 stated “…just how many individuals do I need to test before I find…individuals who either metabolize rapidly or poorly.” And for the case on Gaucher’s disease, subject 6 remarked “But of course, there are Ashkenazi ethnicities that live in Scandinavia.”

The following demonstrates subject 4’s use of family history. When asked “is that important?” in relation to highlighting autosomal co-dominant during case 2, subject 4 responded “It is important because… if there had been a pure autosomal dominant, maybe you would actually have a family history of something that would be relevant.”

3.4.2.6 Indications for Genetic Testing

Subjects sought information on the patient characteristics that indicate a benefit or imperative for testing. For example, subject 5 remarked, “the information that I was looking for the whole time that I didn’t feel like I really found in a really concentrated way, was here are the risk factors that you as the clinician [want to] be looking for in your own patient that is [going to] send you over the edge to actually get genetic testing.” Subject 5 stated that they wanted “a bulleted list that says risk factors for testing.” Additionally, subject 3 stated “…some instance group where you were to tell me that that gentleman needed to be tested before he had a stent put in. That’s what I was searching for.” Also, when subject 5 was asked what they were looking for when they highlighted “select populations” in the CPIC guidelines, subject 5 responded “same thing that I wanted the whole time…what is this selected patient population…“

3.4.2.7 Clinical Impact of Genetic Testing

Subjects wanted to know if carrying out a genetic test would have clinical impact. Impact was indicated by the manifestation of treatment failure. For example, subject 6, after having entered in a search term containing a drug and gene name, focused on the sections of UpToDate that defined “resistance” and “nonresponsiveness” to treatment. When asked about this focus, subject 6 said they were “trying to understand the relevance of the HPR [high on-treatment platelet reactivity] to the therapeutic intervention.” HPR is an indication of treatment failure.

Impact was measured by the actions needed to address treatment failure. For example, in case 2 while looking at information on asthma exacerbation, subject 3 remarked “asthma exacerbation in children, that might be a good start…I'm looking for

something that…oh, management criteria..."

Also, impact was understood from the change in treatment course that could result from the genetic test, for example, subject 3 exclaimed "…so, they're suggesting another drug for intermediate metabolizers."

Further, impact was measured by the effect of ignoring genetic testing in specific situations, i.e., the effect of a genetic variation on the likelihood of treatment failure, and likelihood of severe side-effects. This was evidenced by subject 3 examining the effects of medication resistance and treatment failure, and by subject 1 remarking, "I like this failure thing because I wonder if that might have something to do with...if the genetics might have something to do with failure…severity of." Additionally, subject 2 stated "I wanted to look at what information there was about patients with asthma and albuterol and how their genetic profile affects albuterol. And I just wasn't seeing a search that was really jumping out at me at the time." Subject 2 went on to say "I was hoping that I would see something like albuterol failure in asthma, or issues associated with treatment, or treatment failure in asthma, or something like that. And then when I clicked on that link, there [would be] a sub-tab like genetic issues or genetic variance or something like that."

Finally, impact of genetic testing was measured by an explicit connection between the test result and a phenotype of the patient. Subject 6 stated, "UpToDate suggested ah, at least based on my reading that um, that ah, ah, genotypic testing is in most cases um, not helpful or difficult to interpret. Whereas here [Clinical Pharmacogenomics Implementation Consortium guideline] I'm seeing, you know, recommendations that are strong… you know, based on a genotypic classification suggesting, well, a phenotype that has relevance to your therapeutic intervention."

3.4.2.8 Practice Changing Evidence

Subjects were looking at evidence not only for assurance that an association existed but also for assurance that the association was practice changing. Subjects looked for succinct, strongly worded statements from authoritative sources as practicing changing evidence. This idea is typified by the statement from subject 6, “But essentially you know whenever [the] clinical literature says “data suggests” or “maybe relevant,” that sort of thing, you realize that the evidence basis is still in its nascence. It may still be weak.”

Evidence could also be drawn from the phenotypic explanation of manifestations of resistance or disease. For example, subject 6 while using the mouse to highlight implications for clopidogrel treatment of poor metabolizers in Table 2 of the CPIC guidelines, where it also says the level of evidence is strong, stated “briefly reading this, this group suggests that there is benefit to looking at CYP2C19 status.” Further, indications for treatment made subject 4 “hopeful that that meant the guideline updates were down there somewhere that directed the actual testing recommendations.”

Additionally, evidence came in the form of evidence-based routine recommendation for testing. For example, subject 5 while browsing the results of the ARTIC-Monitoring trial noted “almost 2500 patients” and later read-aloud “do not recommend routine testing.” Also, subject 3 noted “it is not completely clear in my mind yet about the evidence for doing the testing for the variants…how standard that is and how clear that is.” Finally, subject 1 was left to conclude “the summary did not have any recommendations. It had a summary of the data but the data was too far removed from me actually being able to take one step or another,” and subject 6 stated “I liked that it

was, for the clinical question we had, simpler and more succinct than UpToDate. But it seemed that…they [Clinical Pharmacogenomics Implementation Consortium guideline] were more confident in the evidence base than the final summary recommendation in UpToDate."

Interestingly, subject 1 commented that it was important to know how often the patient's specific demographic was included in the evidence for genetic testing interpretations, "if they are unrepresented in the studies, then how am I going to know how …to interpret this. I am liable to come back with something that says "we do not have enough information."

Finally, evidence was sought from randomized controlled trials supporting the hypothesis that a specific genetic test improves patient outcomes compared to alternatives. For example, subject 2 highlighted through reading aloud "then on the RAPID GENE study, 200 patients undergoing PCI were randomly assigned to either a rapid point of care genotyping for the CYP2C allele given..." when looking for information.

3.4.2.9 Role of Genetics in the Manifestation of the Disease

In looking at drug-disease pairs and genetics, subjects sought to determine if genetics had been associated with the symptoms and prognosis of the disease. For example, subject 3 stated "I would want to know about the genetic variant effects that are associated with worsening asthma symptoms" and was looking for a statement that "might have said that there was a genetic predisposition to worsening symptoms."

In the case of Gaucher's disease, a subject found that the manifestation of disease is inherited, "So it says Gaucher is divided into types and I wanted to know what the

types are, because each type is associated with a genetic variant, and certain genotypes or a descent ancestry are more common in others. So I wanted to know with Ashkenazi Jews what type of Gaucher's disease do they have and in terms of severity, I looked at the severity based upon critical manifestations of these diseases."

3.4.2.10 Understanding General Molecular Effect of Genetic Variant

Subjects needed to know how to understand the molecular change and the ramification on protein activity. For example, subject 6 remarked "…trying to recall my molecular biology…and ah, what is a missense mutation."

3.4.2.11 Help with Search Terms

Subjects sought guidance on constructing search terms, such as the correct spelling of a gene name, useful synonyms, or medication specific detail. Key search terms were considered gateways to satisfying information needs. For example, subject 4 copied and pasted the CYP2C19 as a search term to aid the process. Similarly, subject 5 remarked on the difficulty of gene names, "I can remember clopidogrel as an entire word, and CYP2C19, whatever the numbers are, I had way harder time keeping in my brain… I can remember a word much better than a random function of a gene." Additionally, subject 6 reflected "I should have put in β2-agonist in front of pharmacogenomics or something like that." Finally, as subject 6 put it, "98 times out of 100, I get a couple of search terms that I can screen down, I can find out exactly what I want to go to very quickly."

3.4.3 Time spent on Case Vignettes/ Query Entry

Subjects spent a median of 7 minutes per case searching for information (Table 3.3). During the search for information, subjects used browser tabs and hyperlinks (median of 8.5 clicks per case) to navigate to different pages or different sections within a page. The median time interval before navigating was 28 seconds, but it ranged widely from 3 seconds to 8:27 minutes. In 9 out of the 18 information-seeking sessions (3 sessions per subject), subjects performed only one search, but could perform as many as 8 searches.

3.5 Discussion

We investigated physicians' pharmacogenomics information needs and information-seeking behavior when presented with three case vignettes on pharmacogenomics testing. Strengths include a mixed-method approach, with rigorous thematic analysis of recorded information-seeking interactions and deepening interviews. Overall, the analyses revealed that clinicians posed a wide variety of information needs and had significant challenges finding answers to these needs in online clinical resources,

Table 3.3 Measures of information seeking time and effort.

Measurement	Range	Median	Average +/- sd
Information seeking session duration (minutes)	2:41 to 15:08	7:14	8:22 +/- 3:57
Time prior to page navigation (minutes)	0:03 to 8:27	0:28	0:53 +/- 1:10
Number of page navigation events per subject	1 to 18	8.5	8 +/- 4.8
Number of Searches	1 to 8	1.5	2.3 +/- 1.9

spending an average of 8 minutes seeking information for each case vignette. Previous studies have shown that clinicians will not spend more than 2 minutes searching online resources at the point of care [42]. Thus, our results suggest that seeking pharmacogenomics guidance in today's online resources may not be feasible for most clinicians. Our study findings provide guidance to improve the design of online resources in order to reduce barriers to using pharmacogenomics information in patient care decisions.

As expected, subjects looked for evidence on the clinical impact of genetic testing. In addition, physicians were interested in how genetic variants affect their patients' health, such as phenotypic descriptions of test interpretations, similarly to Devine et al. [14]. This also agrees with the finding that 80% of physicians would include information on how genetic variation alters drug activity in their ideal pharmacogenomic resource [75]. Less expected, subjects also sought information to address knowledge gaps in genomics, such as understanding the molecular basis for the clinical effect of drug variation.

In addition to clinical evidence, clinicians also showed a need for information on the logistics of carrying out a genetic test, including questions related to cost, availability, test turn-around time, insurance coverage, and accessibility of expert support. In general, this finding is in agreement with both a recent American Medical Association (AMA) survey [75] and a study on a pharmacogenomics clinical decision support system [14]. Interestingly, 63% of the physicians in the AMA survey agreed that a list of the laboratories offering testing and indications of insurance coverage are features of an "ideal pharmacogenomic educational resource" [75].

We also observed that clinicians sought alternative approaches, which would obviate the need to consider genetic testing. It is possible that a sense of low self-efficacy and information overload may lead physicians to avoid genetic testing decisions. This is not unexpected, as "escape" is a known strategy for dealing with information overload [44,76]. This is further highlighted by the themes of "Prevalence of genetic variation " and "Indications for genetic testing." Subjects wanted to know if genetic testing was something they would need to worry about on a regular or irregular basis, in addition to tailoring care to their current patient. Interestingly, 77% of respondents of the AMA survey would include "demographics of populations likely to carry variations" in their ideal information system [75]. Thus, our results indicate that clear indication of the choice of an alternative therapy, along with clear demographic prevalence data, would be very useful in a pharmacogenomics information resource.

On average, subjects navigated to eight different content sections or pages per case vignette. This finding is consistent with the "berry-picking" information seeking pattern, in which searchers "pick" pieces of information in different locations to form a mental "picture" of the situation. Information resources could be designed in a way that facilitates the berry-picking approach in one content view, rather than requiring users to navigate to multiple pages.

Rather than refining search terms, subjects preferred to rely on hyperlinks to navigate to content in different pages or sections. This finding may suggest the need for improvements both in the search process, since clinicians are less likely to refine their search strategy, and in the provision of more meaningful content headings and hyperlink labels. Also, it is notable that subjects often navigated back and forth between the case

vignette narrative and online resources. The case vignette is a surrogate for an electronic health record (EHR), suggesting that subjects will need to refer back to patient data almost as often as new content. For design, this indicates that merging the display of online resources with the EHR can reduce navigation effort and reduce short-memory overload. Additionally, subjects typically spent less than 30 seconds considering a specific piece of content before navigating to other content. This suggests that information presented to clinicians should be consumable in less than 30 seconds.

3.6 Limitations

Limitations include a convenience sample of six physicians, most of them in pediatrics. In addition, subjects were not imposed any time constraints in the information-seeking sessions. Searching under the time pressure of typical clinical settings would likely affect search behavior. Yet, not imposing time constraints allowed us to observe a wide range of clinicians' information needs and the entire information-seeking process. Finally, by constraining to UpToDate (all cases) and PharmGKB (for case 3), we focused the subjects on the search for information within a resource and not on the choice of which resource to search.

3.7 Conclusion

Correct application of pharmacogenomics testing can avoid complications of adverse drug events, improve care, reduce financial costs [25–30], and improve patient adherence [31,32]. However, most physicians, including those in our study, do not feel confident in their knowledge of pharmacogenomics. Searching for information is quite challenging, as evidenced in our study. Physicians searched for information for an

average of 8 minutes, far exceeding the 2 minutes expected to be spent at the point of care to purse questions [42]. We found that physicians' information needs fall into eleven themes: 1) Alternative therapy options, 2) Specific, actionable, clinical guidance from authoritative sources, 3) Guidance on optimal approach to genetic testing, 4) Logistics of testing, 5) Prevalence of genetic variation, 6) Indications for genetic testing, 7) Clinical impact of genetic testing, 8) Practice changing evidence, 9) Role of genetics in the manifestation of the disease, 10) Understanding general molecular effect of genetic variant, and 11) Help with search terms. Based on our themes, we would recommend that a clinical decision support system, or pharmacogenomics resource, provide topically labeled hyperlinks that lead to brief snippets on: phenotypic descriptions of test interpretations, molecular basis for the clinical effect of drug variation, the logistics of carrying out a genetic test (including questions related to cost, availability, test turn-around time, insurance coverage, and accessibility of expert support), an indication of the choice of an alternative therapy, and demographic prevalence data. This information should be consumable within 30 seconds and be provided with the clinical context in view. Further study is needed to learn to what extent the themes found generalize, as our formative evaluation was limited to six physicians primarily with pediatric experience, and case vignettes. Lastly, it would be very interesting to learn how incorporation of our themes into a CDSS would lead to more effective use of pharmacogenomics.

CHAPTER 4

INTEGRATING GENOMIC RESOURCES WITH ELECTRONIC HEALTH RECORDS USING THE HL7 INFOBUTTON STANDARD[1]

4.1 Abstract

The Clinical Genome Resource (ClinGen) Electronic Health Record (EHR) Workgroup aims to integrate ClinGen resources with EHRs. A promising option to enable this integration is with the Health Level Seven (HL7) Infobutton Standard. Our objective in this study is to integrate genomic knowledge resources using the HL7 Infobutton Standard. Two tactics to achieve this objective were creating an HL7-compliant search interface for ClinGen, and proposing guidance for genomic resources on achieving HL7 Infobutton Standard accessibility and compliance. To meet our objective, a search interface was built utilizing OpenInfobutton, an open source reference implementation of the HL7 Infobutton Standard. Additionally, ClinGen resources were assessed for readiness towards HL7 compliance. Finally, based upon our experiences, we provide recommendations for publishers seeking to achieve HL7 compliance. As a result, eight genomic resources and two sub-resources were integrated with the ClinGen search engine via OpenInfobutton and the HL7 Infobutton Standard. Also, we found that

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resources have varying levels of readiness towards HL7-compliance, and that adoption of standard terminologies used by EHR systems is the main gap to achieve compliance. In conclusion, EHR systems that are certified according to the US Meaningful Use program provide HL7-compliant infobutton capabilities, which can be leveraged to support clinical decision-making in genomics. Further, genomic resources can be integrated with EHR systems via the HL7 Infobutton Standard using OpenInfobutton. Finally, full compliance of genomic resources with the Infobutton Standard would further enhance interoperability with EHR systems.

4.2 Background and Significance

Clinical genomics is considered an important, complex, rapidly increasing knowledge domain [77]. Integration of clinical genomics into medical practice is highly desirable, but the need for clinical guidance is significant, as indicated by the US National Human Genome Research Institute (NHGRI) director [78] and the American College of Medical Genetics and Genomics Board of Directors [79]. Further, the President of the United States highlighted the importance of genomics in precision healthcare in his 2015 State of the Union address. The challenging juxtaposition of complexity, growth, and importance in clinical genomics can lead to difficulty in knowledge management, producing gaps in information. When the need for information is not satisfied, this can result in medical error or reduced quality of care [80,81]. Online medical knowledge resources offer a possible solution for satisfying information needs [44,78]. It has been demonstrated that online resources provide answers for greater than 90% of clinicians general patient care questions [82], and there is good evidence that searching electronic resources for information can have positive effects on clinical

decision making [6,45,62,83].

To support information needs in clinical genomics, the Clinical Genome Resource (ClinGen) was established to "provide high quality, curated information on clinically relevant genes and variants" [84]. The ClinGen Electronic Health Record Work Group (EHR WG) has been tasked with providing integration between EHRs and genomics resources, including future ClinGen resources. As such, the ClinGen EHR WG in conjunction with other ClinGen domain experts has produced a website containing links to several genomics resources thought to be of value in particular contexts. Specifically, the links are organized for different end users (Clinician, Researcher, Laboratory, and Patient) under a clinical activity classification, such as point of care or "just in time" education. Many of these resources are developed by or are accessible through the National Center for Biotechnology Information (NCBI) at the National Institutes of Health [85]. The NCBI offers a rich aggregation of clinical genomics resources, supporting a wide-range of specialization. However, searching many genomic resources and learning how to optimally use each resource is time-consuming and unfeasible for most busy clinicians. Importantly, in pursuing answers to clinical questions, clinicians note that lack of time and seamless access to resources at the point of care are the main barriers [86]. Thus, a solution is needed to streamline point of care access across the landscape of genomic resources.

As discussed by the eMERGE network in its efforts to aid content authoring [55], and previous implementations within EHR systems [14,53,56], infobuttons are an information retrieval modality that can address the need for streamlined access to genomic knowledge in the context of patient care. In the clinical setting, infobuttons are

used to translate the context of a particular patient encounter into a request for information related specifically to that context from the web's plethora of electronic resources (e-resources). Infobuttons have been shown to improve the speed with which clinicians find answers to clinical questions [6], producing a positive impact on decision making [6,46,47]. Thus, infobuttons offer an attractive tool to improve clinicians' access to genomic knowledge, even at the point of care.

Further motivation to pursue infobuttons for dissemination of genomic knowledge is linked to the US Meaningful Use EHR certification criteria, which includes a requirement [58] for implementation of the HL7 Infobutton Standard [57]. The Meaningful Use program also includes financial incentives to providers who adopt certified EHR products. To date, over a thousand EHR products have been certified under the Meaningful Use program [59].

4.3 Objective

EHR In order to facilitate EHR access to genomic resources, the ClinGen EHR WG decided to develop an infobutton-enabled search interface, compliant with the HL7 Infobutton Standard (HL7 IB). The overall goal of the present study is to describe the implementation of the search interface, which leverages an open source, HL7-compliant, infobutton platform called OpenInfobutton. Specifically we aimed to: 1) develop an OpenInfobutton enabled search engine; 2) configure OpenInfobutton to access a subset of ClinGen genomic resources; 3) analyze readiness of this set of genomics resources regarding the HL7 IB standard; and 4) provide recommendations for publishers to achieve HL7 IB compliance.

4.4 Methods

4.4.1 HL7 Infobutton Standard and OpenInfobutton

An infobutton is a context-aware information retrieval tool that anticipates the information needs of a clinician in a specific clinical context and provides automated links to relevant e-resources [87]. For example, in the context of prescribing clopidogrel in the outpatient setting for a 67 year-old female with a history of stroke, a simple infobutton could provide access to a statement from the American College of Cardiology related to clopidogrel treatment for female patients with a history of stroke.

Infobuttons are typically implemented with a web service known as an "Infobutton manager" (IM) [88,89]. Infobutton managers match the context conveyed in an EHR request to a set of relevant resources and automatically create infobutton requests for each of the selected e-resources. Importantly, IMs match contextual parameters to specific resources to ensure 1) optimal resources are offered to users, and 2) the order of returned links reflects the relevance of each resource in a particular context. As an example, an infobutton connecting to an IM within the context of computerized provider order entry (CPOE) and containing the term "clopidogrel" could return a link to the FDA approved label for clopidogrel, a link to the common conditions for which clopidogrel may be indicated, and a link to a genomic resource page on testing for clopidogrel resistance. Alternatively, if the infobutton were placed within a patient problem list, then the IM might reorder the links reflecting the difference between the contexts of medication ordering versus problem list review. For example, in the context of problem list review, the IM may return the link to the common conditions indicating clopidogrel as the first link, and might not return the link to the FDA label.

The HL7 IB standard is designed to reduce the effort required to integrate e-resources with EHR systems. The standard contains a context information model, a standard set of terminologies to maximize interoperability with EHR systems, and RESTful web-based implementation approaches [90]. The context information model defines a set of context parameters according to four dimensions: the patient, the infobutton user, the care setting (e.g., inpatient, outpatient), and the task undertaken by the user within the EHR task (e.g., a medication order entry, a diagnosis, a laboratory test result). The patient dimension can include a main clinical concept of interest, patient's age, gender, medications, and additional patient conditions/diagnoses. The user dimension allows the distinction between a healthcare provider and a patient user as well as the preferred language of the target information recipient. Importantly, the HL7 IB standard parameters aids semantic interoperability by providing coded data, and the terminology from which the code is derived. The example shows how a compliant request may appear (Table 4.1). The name of the parameter appears after an ampersand ('&') and the value after an equals sign ('='). The role of each component of the example is explained to the right. Object Identifiers (OIDs), are globally unique identifiers set by the International Organization for Standardization (ISO) and used by HL7 to identify organizations and code systems. Several HL7 IB compliant e-resources have taken advantage of the context within a HL7 IB compliant request to deliver specialized navigation pages that are tuned to support clinical decision making [88].

OpenInfobutton is an open source implementation of the HL7 IB standard, and is intended to streamline adoption of infobutton capabilities by healthcare organizations. To date, several large healthcare organizations, including the Veterans Health

Table 4.1 HL7 IB example request implemented as a URL.

Example of Infobutton Request Syntax	**Explanation of Component**
http://clingen.org/tools-resources/web-resources/?searchType=HL7	Base URL of knowledge resource
&representedOrganization.id.root=1.3.6.1.4.1.3768	OID of requesting organization
&patientPerson.administrativeGenderCode.c=F	Patient gender (code)
&age.v.v=67	Patient age (value)
&age.v.u=a	Patient age (units)
&mainSearchCriteria.v.c=749196	Search term (code)
&mainSearchCriteria.v.cs=2.16.840.1.113883.6.88	Search term (OID of code system)
&mainSearchCriteria.v.dn=Clopidogrel	Search term (display name)
&performer=PROV	Role of person performing request (code)
&taskContext.c.c=MLREV	Context of the EHR task (code)
&informationRecipient=PROV	Role of person consuming results (code)
&knowledgeResponseType=application/json	Defines syntax of response

Administration [90], have deployed OpenInfobutton. Included in OpenInfobutton is a reference implementation of an IM, and several tools including the resource profile configuration tool known as LITE (Librarian Infobutton Tailoring Environment) [91]. Currently, configured resource profiles allow OpenInfobutton to provide EHRs access to over 40 e-resources. Resource profiles describe the context covered by the resource and, for resources not compliant with HL7, provide mappings to the resource proprietary search engine application program interface (API). Figure 4.1 describes the OpenInfobutton architecture and information flow.

The full specification of the parameters available for clinical context can be found

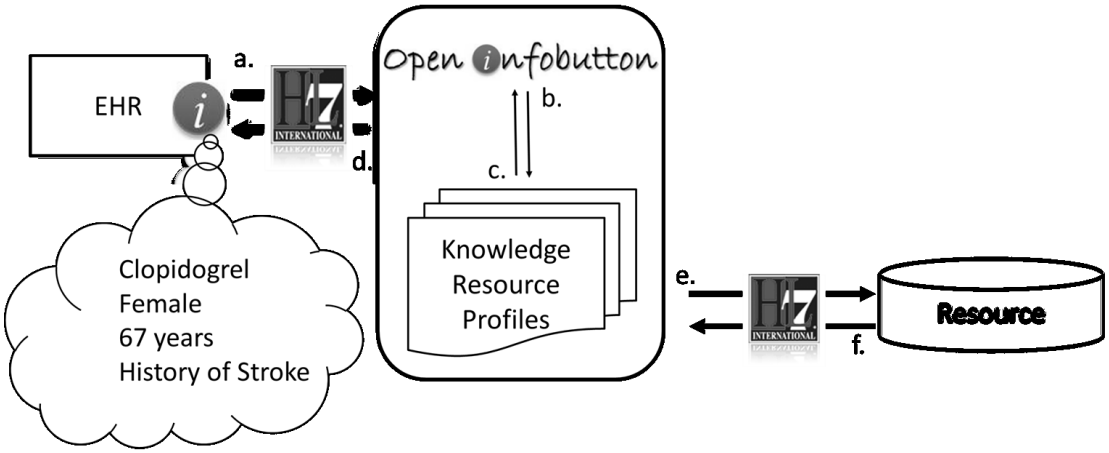

Figure 4.1. OpenInfobutton architecture and information flow. (a) An HL7-compliant URL request that contains context parameters is sent from the EHR to OpenInfobutton. (b) Resource profiles are selected which match the EHR context, and (c) an infobutton response is produced with links to those resources. (d) OpenInfobutton responses can take the form of non-HL7 IB HTML and as HL7 IB XML/JSON. (e) Additionally, if a resource is HL7 IB compliant, OpenInfobutton can send the resource an HL7 IB request and (f) process HL7 IB responses.

in the HL7 IB specification [22]. The parameters we focus on here are the main clinical concept of interest, clinical role, and the identifier for the organization making the request, called the organization id. These parameters are included in HL7 IB compliant URLs.

4.4.2 Selection of Genomic Resources

A list of resources was compiled by surveying attendees of a ClinGen educational session at the 2015 annual American College of Medical Geneticists meeting (ClinGen web-resources page: https://www.clinicalgenome.org/tools/web-resources/). The resources were organized by the ClinGen EHR WG based upon the role that the resource was expected to satisfy. For example, the patient tab has resources for patient education, but not resources that provide variant level details. In contrast, the clinician tab has resources such as The Pharmacogenomics Knowledgebase (PharmGKB), a clinician-

facing pharmacogenomics resource. From the list, resources chosen for the patient and clinician role context were examined for integration using the HL7 IB. Special emphasis was placed on the NCBI resources as they actively maintain an extensive collection of genetic and genomic resources and are closely collaborating with ClinGen.

4.4.3 OpenInfobutton Enabled Search Engine

We created a search interface to explore providing genomic resource access to EHRs using the HL7 IB. Though the genomics resources themselves are not compliant with HL7 IB, OpenInfobutton resource profiles allow EHRs to access noncompliant resources through an HL7 IB request. OpenInfobutton accomplishes this through configuring custom API calls.

4.4.4 OpenInfobutton Configuration for Genomic Resources

OpenInfobutton resource profiles for genomic resources were configured to match the context of the organization making the request (ClinGen), the role of the information recipient (clinician or patient) and the terminology of the search concept. ClinGen was specified as the “requesting organization” given that OpenInfobutton requests are made through the ClinGen search interface. We found that this implementation choice would lower the barriers for EHRs to implement genomic infobutton searches. By only matching ClinGen as the requesting organization, rather than matching any organization, we provide a means to control when links to genomics content are returned by an OpenInfobutton request. This feature can be easily changed to accommodate EHR systems wishing to directly access the resource profiles. We configured Openinfobutton through the LITE application [91].

4.4.5 Genomics Resources and Readiness for HL7 IB Compliance

According to the HL7 IB specification, compliant resources should provide a RESTful interface that can receive HL7 IB requests and provides HL7 IB responses. The request contains a syntax that presents search context using standard terminologies. Proper semantic understanding of the context requires support of the terminologies used by the request. Further, the HL7 IB specifies syntax for the resource response, including XML and JSON data types, and semantics according to the Atom standard (https://tools.ietf.org/html/rfc4287). We evaluated resource readiness based on the presence of a URL- based API, support for HTTP/HTTPS GET and POST protocols, support for standard terminologies, and support for response formats in XML and JSON. The evaluation was carried out by reading the web-accessible documentation for each resource as well as conducting test searches using the resource search API. The results were confirmed by contacting resource representatives.

4.5 Results

4.5.1 Genomic Resources Configured for Searching

We selected eight genomic resources and two sub-resources for integration by the ClinGen OpenInfobutton search interface. The resource names and urls are found in Table 4.2.

4.5.2 OpenInfobutton Enabled Search Engine

The search user interface consists of a search bar with auto-complete functionality that is populated by a controlled list of relevant genomic terms and concepts (e.g., gene names, genetic conditions) from specific terminologies (Figure 4.2).

Table 4.2 Resources chosen for configuration.

Resource name*	**Resource web-site**
1000 Genomes project	http://browser.1000genomes.org/
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Accessed through PharmGKB and NCBI
ClinVar	http://www.ncbi.nlm.nih.gov/clinvar/
GeneReviews	http://www.ncbi.nlm.nih.gov/books/NBK1116/
Genetic Practice Guidelines	Accessed through MedGen
Genetic Testing Registry (GTR)	http://www.ncbi.nlm.nih.gov/gtr/
Genetics Home Reference (GHR)	http://ghr.nlm.nih.gov
MedGen	http://www.ncbi.nlm.nih.gov/medgen/
Online Mendelian Inheritance in Man (OMIM)	http://www.omim.org/
The Pharmacogenomics Knowledgebase (PharmGKB)	https://www.pharmgkb.org/

*Genetic Practice Guidelines and CPIC guidelines are examples of specific content accessed as sub-resources of other resources, MedGen and PharmGKB respectively.

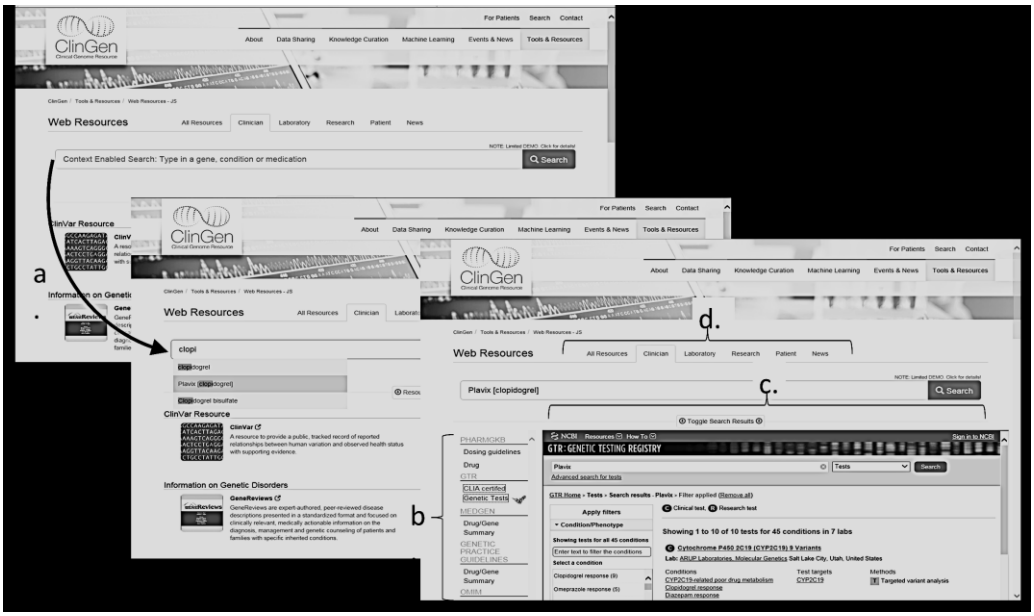

Figure 4.2 A screenshot of the ClinGen EHR WG OpenInfobutton search interface. (a) As text is typed into the search bar, suggestions for autocompleting are provided from the controlled vocabulary. (b) After search initiation, context dependent links to resources are provided in a menu (c) with the first resource link displayed in a frame. (d) Tabs for clinician or patient provider are found above the search bar.

We used the terminology of the search term as an indicator of the genomic domain of inquiry. The three domains used are: Gene (HUGO Gene Symbol), Genetic Disorders/Conditions (OMIM), and Medication (RxNorm). HUGO Gene Symbols is an established international gene name terminology that is required by the HL7 Clinical Genomics Implementation Guide [92]. OMIM was chosen by the ClinGen steering committee to be used to represent genetic disorders within ClinGen, and it is accepted by HL7 as an optional terminology in the HL7 Clinical Genomics Implementation Guide [92]. Further, OMIM currently provides better coverage for rare and genetic diseases than ICD-9, ICD-10, and SNOMED-CT. We use RxNorm to represent drugs given that it is required for EHR certification in the Meaningful Use program [21]. Yet, the use of specific terminologies can be extended according to the HL7 IB specification and within OpenInfobutton's architecture.

The interaction between the search interface and Openinfobutton (Figure 4.3) begins when the ClinGen EHR search interface takes the role of an EHR system and prepares an infobutton request based on search input. The request is sent to OpenInfobutton, which responds using the HL7 Infobutton JSON format. The search interface parses the JSON response, presents the user with a list of indexed links from the matching resources, and loads the first resource into a frame within the ClinGen Web site. The order of the e-resource links is based on the context of the terminology used for the search. For example, when an RxNorm (medication terminology) concept is used, it is inferred that a clinician has an interest in pharmacogenomics. PharmGKB is a pharmacogenomics specialized resource, thus links for PharmGKB content appear at the top of the list.

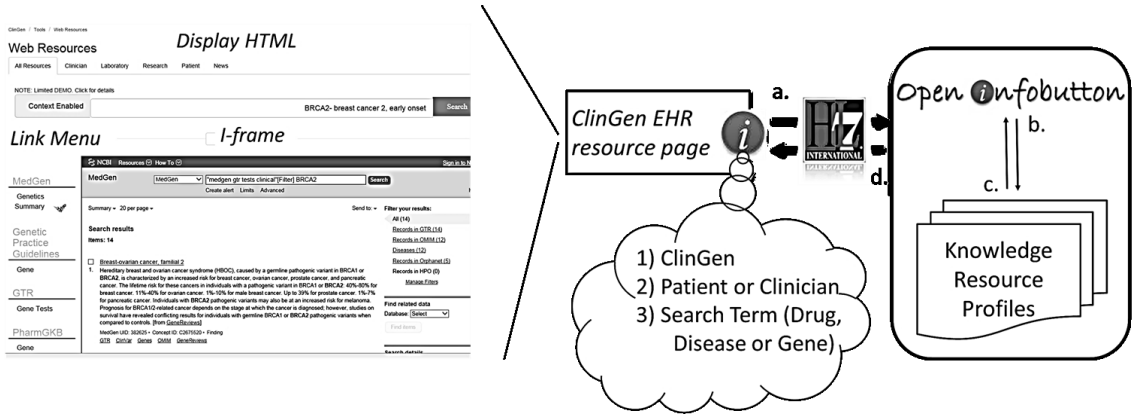

Figure 4.3. Data flow from the ClinGen search interface to OpenInfobutton. (a) When the search button is selected the ClinGen EHR resource page creates an HL7 Infobutton request that sends the context of the search to OpenInfobutton, similarly to an EHR generated infobutton request. The context includes the search term (i.e., main clinical concept of interest, selected from a controlled vocabulary through a drop-down list), the user's role (clinician, laboratorian, researcher or patient) and the identifier for ClinGen, the organization making the request. (b) Next, the context is matched to the resource profiles within OpenInfobutton. (c) URLs from resources matching the context parameters are collated (d) and sent as a response to the ClinGen EHR Resource. As seen on the left side of the figure, the ClinGen resource page parses the OpenInfobutton response and displays the context sensitive links on a menu to the left of a frame containing the web-site of the first listed resource link.

An important additional context we implemented was the "role" parameter which is set based on the tab selected by the user in the ClinGen EMR page. As an example, when the patient tab is selected in the ClinGen search interface, only GHR is returned for genetic disorder (OMIM) concepts.

4.5.3 OpenInfobutton Configuration for Genomic Resources

Most resources were configured through OpenInfobutton profiles to respond to the context of all three search term domains (Gene, Genetic Disorders/Conditions, and Medications). The exception is Gene Reviews, which is retrieved only when the search term is in the Gene domain. For search terms in the Gene and Medications domains, we

configured OpenInfobutton to use the text label associated with the search. We followed a similar strategy for the Genetic Disorder domain. However, for OMIM, we were able to use the OMIM code (called a MIM number) with some resources. At present, only GHR was configured to respond to the patient role.

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4.5.4 Genomics Resources and Readiness for HL7 IB Compliance

Table 4.3 describes the readiness of eight genomic resources for compliance with the HL7 IB specification, as of September 14th, 2015. Except for CPIC, all resources provide a URL-based API that supports the HTTP/HTTPS GET and POST protocols. CPIC guidelines were made retrievable as a subset of the links returned using the PharmGKB resource.

Within PharmGKB, CPIC guidelines are directly accessible only using PharmGKB's internal proprietary codes. But, in general, PharmGKB supports searches using a proprietary identifier for medications as well as free-text medication terms. Access to concepts defined by MIM numbers was well supported by the NCBI genomic resources (ClinVar, GeneReviews, Genetic Practice Guidelines, Genetic Testing Registry, MedGen), GHR, and OMIM itself. Not surprisingly, all resources supported the use of HUGO Gene Nomenclature Committee (HGNC) gene symbols, but not HGNC code-based searching. Additionally, OMIM supported retrieval of XML/JSON. Aside from direct URL access, the five NCBI resources can also be accessed through an application program interface (API) called e-utilities [30]. The tool-set provides programmatic access including a URL-based request for XML and JSON. Support for infobutton response using the XML and JSON data types is part of the HL7 IB RESTful

Table 4.3 Readiness of genomic resources for HL7 IB compliance.

Resource	**Response Types**	**Specific Terminologies used to index the content**	**Code-based searching support for Specific Terminologies**
NCBI Resources: ClinVar, GeneReviews, Genetic Practice Guidelines, Genetic Testing Registry, MedGen	HTML/Text XML/JSON (with e-utilities)	OMIM, HGNC Approved Gene Symbol, UMLS, SNOMED-CT	OMIM*
GHR (National Library of Medicine)	HTML	OMIM, HGNC Approved Gene Symbol , UMLS, SNOMED-CT	OMIM
OMIM	HTML/XML/JSON /JSONP (with Key)	OMIM, HGNC Approved Gene Symbol, UMLS, SNOMED-CT	OMIM
PharmGKB	HTML	OMIM, HGNC Approved Gene Symbol, UMLS, SNOMED-CT, NDFRT	None
CPIC guidelines	None	None	N/A

* While code-based searching with OMIM MIM numbers is supported by the www.ncbi.nlm.nih.gov resources, in some cases, we choose to use the search term itself to maximize coverage.

specification [22].

4.5.5 Search Interface Go-live and Sample HL7 Infobutton Requests

As of October 2015, the first iteration of the OpenInfobutton search interface was available to the public. And, integration with EHRs was enabled with support of HL7 IB requests by the search interface. Additionally, resources within ClinGen such as gene dosage and variant evidence annotations are included in the genomic search and HL7 infobutton response. Supplement A contains examples HL7 IB requests for clinical

questions regarding Genes, Genetic disorders/conditions, and pharmacogenomics.

4.6 Discussion

We have successfully enabled infobutton access to eight genomic resources and two sub-resources through OpenInfobutton and the HL7 IB standard. This brings access to many EHR systems as compliance with the HL7 IB is required for EHR certification in the US Meaningful Use program. Any EHR system that is HL7 IB compliant can use OpenInfobutton to access the configured genomic resources via context-specific infobuttons located in EHR modules such as problem list, laboratory test results, medication prescriptions, and computerized provider order entry. A next step towards interoperability of genomic resources with EHR systems is for resources themselves to become HL7 IB compliant. HL7 compliance would bring additional benefits, such as the ability to tailor the search results according to the EHR clinical context, more precise information retrieval due to the use of standard terminologies, tuning of resource API results for use by clinicians at the point of care, and the ability to integrate directly with any EHR that is compliant with the HL7 IB standard.

The use of OpenInfobutton has allowed us to configure access to several non-HL7 IB compliant genomic resources by EHR systems. However, there are important caveats that resulted in suboptimal results with non-HL7 IB compliant resources. For example, OpenInfobutton access to non-HL7 IB compliant resources will return a URL for the resource even when the URL results in the resources “no results found” page. Furthermore, the resource search URLs used in the resource profiles required manual optimization. After consultation of resource provided documentation, we iteratively optimized the search configurations based on available filters. We chose resource URL

search configurations which maximized coverage of the terms and concepts used in the auto-complete functionality of our search interface, but potentially at the expense of precision. Since the IB standard requires EHR systems to send both codes and labels, resource search engines can use a combination of strategies in real time to optimize retrieval. This approach is used by several HL7-compliant resources, such as MedlinePlus and UpToDate. Finally, EHR integration for noncompliant resources is dependent on OpenInfobutton.

4.6.1 General HL7 IB Compliance Considerations

We found that many resources required additional work to facilitate HL7 compliance. We therefore provide recommendations to facilitate scalable access to resources using the HL7 IB standard. In general, toward adopting the HL7 IB standard, genomics resources should consider supporting the following requirements in their search APIs:

a. Support HTTP/HTTPs POST and GET.
b. Support standard terminologies that are required for EHR certification, such as RxNorm and SNOMED-CT.
c. Support the syntax of standard HL7 IB requests and use context parameters to tailor the search response.
    i. Example of a request: ‘http://clingen-resource.org/tools-resources/web-resources/?searchType=HL7&representedOrganization.id.root=1.3.6.1.4.1.3768&patientPerson.administrativeGenderCode.c=F&age.v.v=67&age.v.u=a&taskContext.c.c=MLREV&mainSearchCriteria.v.c=749196&mainSearchCriteria.v.cs=2.16.840.1.113883.6.88&mainSearchCriteria.v.dn=

Clopidogrel&performer=PROV&informationRecipient=PROV &knowledgeResponseType=application/json'. In the example, the base URL is 'http://clingen-resource.org/tools-resources/web-resources/?searchType=HL7' and the text following the base URL contains the contextual parameters. Briefly, the contextual parameters of the example are:

1. 'representedOrganization.id.root' is the requesting organization
2. 'patientPerson.administrativeGenderCode.c' is the code for patient Gender
3. 'age.v.v' and 'age.v.u' are the age value and units
4. 'taskContext.c.c' has the code for the context of the Task
5. 'mainSearchCriteria.v.c', 'mainSearchCriteria.v.cs' and 'mainSearchCriteria.v.dn' contain the code of the search term, the code system of the search term, and a text-version of the search term.
6. 'performer' contains a code indicating the role of the person performing the request
7. 'informationRecipient' indicates the role of the person the information is intended to be used by.
8. 'knowledgeResponseType' indicates the form the client system is expecting the resource response to be in.

d. Support HL7 IB compliant response including both XML and JSON data types (see the HL7 IB standard specification for examples).

4.6.2 Recommendations for ClinVar, Gene Reviews, Genetic Practice Guidelines, Genetic Testing Registry, MedGen, and GHR

We found that the NCBI resources have many of the foundational components required for HL7 IB compliance, including a URL accessible API that can handle HTTP/HTTPs GET and POST requests, and content indexed with standard terminologies that are required for EHR certification (SNOMED-CT and RxNorm). Although the NCBI APIs do not provide the ability to search using RxNorm and SNOMED-CT codes, NCBI can leverage its ability to search with UMLS codes to provide RxNorm and SNOMED-CT code-based searches. One potential solution is to map incoming requests in RxNorm and SNOMED-CT to UMLS codes and use these codes for searching. Another recommendation regarding terminology support is to support searching with HUGO codes for genes as approved gene symbols change over time.

As mentioned, the NCBI provides a tool called e-utilities for programmatic searches of its databases, with support for XML/JSON responses. E-utilities could be a starting point for an HL7 IB interface to NCBI sites (ClinVar, Gene Reviews, Genetic Practice Guidelines, Genetic Testing Registry, MedGen).

Further, the domain www.ncbi.nlm.nih.gov offers many high-quality genomic resources with specialized content. We suggest that the domain consider enabling a single HL7 IB API for access across all the resources of the domain. The feasibility of this approach is evidenced by the success of our search interface. One request is sent to OpenInfobutton and links to multiple resources are returned, with additional higher level categorization possible using the HL7 IB response format.

Finally, NCBI has the potential to extend accessibility to other e-resources. For

example, both the 1000 Genomes resource and the text of CPIC guidelines are currently accessible through NCBI. NCBI adoption of the HL7 IB standard would make, support HL7 IB context-aware responses from these resources possible.

4.6.3 Recommendations for OMIM

OMIM provides two APIs, one requiring an authentication key with the base URL http://www.omim.org/api , which has many of the same foundational components as the NCBI resources. The API accessed through http://www.omim.org/api could be a starting point for an HL7 IB interface. The HL7 IB interface should handle the HL7 IB syntax for responses and requests (as noted in the general considerations section).

4.6.4 Recommendations for PharmGKB

PharmGKB has implemented some of the foundational features towards HL7 IB compliance, especially a URL-based search mechanism. As a drug reference resource, the most important gap in PharmGKB towards HL7 compliance is support for RxNorm code-based searching. PharmGKB already uses drug names for content indexing. These drug names could be used to automatically identify RxNorm codes via the RxNorm RESTful API provided by the National Library of Medicine[31]. PharmGKB informed the authors that it is extending an API to support JSON/XML data types and code-based searching with RxNorm.

4.6.5 Limitations

We did not test implementation of all the possible parameters of the HL7 IB standard and only looked at providing responses for Medications, Genetic Diseases/Conditions, and Gene queries. Secondly, we did not consider allelic or genetic

sequence-level-based searches. Accessing allele-specific or sequence-level information to offer clinical recommendations based on a patient's specific genotype is a complex but highly important issue for EHR systems, not to mention a key goal of the ClinGen project. Efforts to access clinical assertions based on allelic data are frustrated by the absence of widely accepted standards for exchange or storage. As a result, we did not support sequence-level searches other than an attempt using free-text with the 1000 Genomes resource. As a first step toward addressing this issue, the ClinGen Resource is working with key stakeholders to define a common data model to unambiguously describe genetic alleles at the sequence level. ClinGen is also working with NCBI to design and implement a system for assigning unique Allele Identifiers and for providing Registry Web Services (provided by the ClinGen data modeling working-group) that will facilitate linking of genetic test results to HL7 IB compliant resources.

4.6.6 Future for ClinGen EHR OpenInfobutton Enabled Search Interface and ClinGen Genomics Resource Access

The ClinGen EHR WG is pursuing a formal usability study to improve the user-interface and content provided by the genomic search. Also, we are in discussion with the resources mentioned here to improve access to resource content. Additionally, efforts are underway in HL7 to improve guidance for use of infobuttons in genomic information retrieval.

In the future, the OpenInfobutton-enabled search interface will be expanded to other genomic resources found within ClinGen, including individual sequence variant pathogenicity. As standards for representing structured genomic data in the EHR are developed, it will be possible to create links into ClinGen curated variant information

from the EHR based on an individual patient's genotype. ClinGen is actively involved in efforts to establish such standards; the project contributes to the emerging HL7 Fast Healthcare Interoperability Resources FHIR standard for reporting genetic test results, as well as contributing Logical Observation Identifiers Names and Codes LOINC codes appropriate for representing genetic test results.

Further, Geisinger has recently enabled HL7 Infobutton requests within its genomic testing reporting system using HL7 requests.

4.7 Conclusions

We have produced the functional architecture needed to perform context-based searching of genomics e-resources using an OpenInfobutton implementation of the HL7 IB standard. OpenInfobutton successfully enabled access to genomic e-resources using HL7 IB standard requests and provided response messages that complied with the standard. This demonstrates that OpenInfobutton can reduce the barrier for genomic e-resource providers to utilize the HL7 IB standard for integrating their content with EHR systems. The process of creating the interface also provided an opportunity to evaluate e-resource readiness for HL7 IB standard compliance, and to create recommendations for paths to EHR accessibility and compliance. We found that the genomic resources have many foundational features needed for HL7 IB readiness. To become compliant, the resources generally need to adapt their existent interfaces to handle the syntax of an HL7 IB request and return an HL7 IB compliant response. A major feature of handling HL7 requests, that resources should adopt, is support of terminologies used in EHRs, including concept code-based searching. To accomplish this, the resources investigated can take advantage of their current usage of codes for other terminologies. Thus, the largest effort

will be to determine how the resources wish to use the context provided by EHR systems. Tailored, precise access to genomics information relevant to a specific patient's context may soon be available at the touch of a button—a crucial function to enhance the value of the anticipated ClinGen resource.

4.8 Clinical Relevance Statement

This paper outlines how the Clinical Genomic Resource (ClinGen) made use of the widely adopted HL7 Infobutton Standard and OpenInfobutton to facilitate integration of genomic knowledge into EHRs. The use of the HL7 standard reduces the barrier for EHR systems to support clinical decision making in genomics by providing clinicians with access to precise, context-aware genomics knowledge. Also, guidance is given to aid online knowledge resources in adopting the standard to streamline access to their genomics content.

4.9 Conflicts of Interest

The authors declare that they have no conflicts of interest in the research.

4.10 Protection of Human and Animal Subjects

Human and/or animal subjects were not included in the project.

4.11 Acknowledgements

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4.12 Supplement A. Examples of HL7 Infobutton Requests to ClinGen for Genomics Information

The following are sample HL7 Infobutton requests to ClinGen for a genomics search. In order to implement HL7 IB requests within an institutions' EHR system, the main-search criteria should be populated with a gene (HGNC symbol), genetic disorder/condition (OMIM MIM), or medication (RxNorm ID). The 'knoweldgeResponseType' parameter can have values of application/json, text/xml or be excluded to request JSON, XML, or HTML responses respectively.

4.13 Requests

A) This request specifies a search for the gene symbol AGTR2 and a provider as both the information requestor and recipient. Note, we have chosen to enable the use of the HGNC gene symbol as the HGNC code as a pragmatic choice based on personal communication with EHR vendors and potential implementers.
https://www.clinicalgenome.org/tools/web-resources/?searchType=HL7&representedOrganization.id.root=1.3.6.1.4.1.5884&patientPerson.administrativeGenderCode.c=F&age.v.v=47&age.v.u=a&taskContext.c.c=PROBLISTREV&mainSearchCriteria.v.c=AGTR2&mainSearchCriteria.v.cs=2.16.840.1.113883.6.281&mainSearchCriteria.v.dn=AGTR2&performer=PROV&informationRecipient=PROV&knowledgeResponseType=application/json

B) This request specifies a 47-year-old female patient and information on genetics related to Breast Cancer using the OMIM code for Breast Cancer.
https://www.clinicalgenome.org/tools/web-resources/?searchType=HL7%20&representedOrganization.id.root=1.3.6.1.4.1.5884

%20&patientPerson.administrativeGenderCode.c=F%20&age.v.v=47%20&age.v.u=a&taskContext.c.c=PROBLISTREV%20&mainSearchCriteria.v.c=114480%20&mainSearchCriteria.v.cs=2.16.840.1.113883.6.174%20&mainSearchCriteria.v.dn=BREAST%20CANCER%20&performer=PROV%20&informationRecipient=PROV%20&knowledgeResponseType=text/xml

C) This request specifies a search for pharmacogenomics information based on the RxNorm code for a 20MG dose of Plavix (clopidogrel), for a 47-year-old female patient.

https://www.clinicalgenome.org/tools/web-resources/?searchType=HL7&representedOrganization.id.root=1.3.6.1.4.1.5884&patientPerson.administrativeGenderCode.c=F&age.v.v=47&age.v.u=a&taskContext.c.c=MLREV&mainSearchCriteria.v.c=573094&mainSearchCriteria.v.cs=2.16.840.1.113883.6.88&mainSearchCriteria.v.dn=clopidogrel%2075%20MG%20[Plavix]&performer=PROV&knowledgeResponseType=application/json

CHAPTER 5

CONCLUSION

This work addressed the problem of physicians' perceived lack of knowledge in genomics by deepening understanding of physicians' information seeking behavior in pharmacogenomics and producing a genomics search interface that provides HL7 Infobutton access to genomics resources through use of Openinfobutton. Together, our studies provided the foundation for future work to meet clinicians' perceived lack of knowledge in genomics.

Effective use of pharmacogenomics testing can avoid complications of adverse drug events, improve care, reduce financial costs [25–30], and improve patient adherence [31,32]. However, most physicians, including those in our study, do not feel confident in their knowledge of pharmacogenomics. A lack of confidence and understanding can be addressed by successfully meeting information needs [36,93,94]. But, searching for information is quite challenging, as evidenced in our study. We found that physicians searched for information for an average of 8 minutes, far exceeding the 2 minutes expected to be spent at the point of care to purse questions [42]. Thus, similarly to guidelines in general [40], effective use of pharmacogenomics is impacted by awareness of recommendations, lack of self-efficacy, lack of pharmacogenomics knowledge, and a lack of time.

The themes uncovered in our study provide a foundation for what information should be delivered to aid effective use of genetic testing, and how it should be delivered. Important themes we uncovered included a need for concise information on each test for the cost (both hospital and patient), test turn-around time, insurance coverage, and accessibility to an expert (i.e., domain experts or colleagues who have used the test frequently). Also, we saw that clinicians wanted to know about the existence of alternative therapies that do not require genetic testing. In particular, the feature of financial cost is an addressable need. While hospital systems maybe unable to provide specific costs, a ball-park estimate such as comparison to the cost of a MRI could meet this need. Additionally, providing an indication of the presence of a local expert, either an experienced colleague or a trained specialist, is an indication of the level of support the physician can expect when making a decision. Interestingly, we saw that physicians were likely to navigate back to case vignette during their information search. This suggests that clinicians also need to consume new information juxtaposed to patient information.

Additionally, rather than refining search terms, subjects preferred navigational strategies such as hyperlinks. Thus, information resources could improve navigation support such as through the provision of meaningful content headings and hyperlink labels. The theory of information foraging, which premises that humans are "informavores" seeking rich information patches [95], suggests that content headings and labels with strong "information scent" are key to attracting users to the correct content.

Finally, our study results were consistent with the model of information behavior called berry-picking [74]. The majority of subjects chooses one search query and then proceeded to navigate from information patch to information patch, sampling information

in 30-second bites. The berry-picking strategy could be facilitated by guiding a user through the information gathering process by providing basic pharmacogenomics information, followed by an indication of the level of clinical importance of the pharamacogenomic effect and applicability to particular patient population, then evidence of the utility of available tests (sensitivity/specificity), prior to providing logistical details (such as time to test result, cost, access to expertise, insurance coverage). Thus, meeting physicians needs maybe best done with a modality that provides topical hyperlinks that ink to specific 30-second information bytes, merged with pertinent patient information.

To deliver content to meet clinical information needs, the HL7 Infobutton Standard offers a useful solution. Our genomics search interface is a successful first step towards having the infrastructure to meet physicians' genomics information needs, including pharmacogenomics. Adoption of the standard can decrease the barrier to providing genomics at the point of care. When resources use the contextual parameters of the information response, they have an opportunity to minimize the time it takes to answer information needs. However, most of the genomic resources are in the early stages of adoption. Also, Electronic Healthcare systems (EHRs) while adopting the HL7 IB standard are not yet generally utilizing genomic nomenclatures, terminologies, or ontologies. This hinders the effective delivery of content to resources. As genomic resources begin to fully utilize the HL7 IB standard, and EHRs adopt genomic terminologies, there is an expectation that the information needs of physicians in genomics will be met.

While we focused on physicians, future investigations should extend the study of pharmacogenomics information needs and information-seeking to additional

stakeholders, and incorporate tactics within a genomics infobutton response to meet those needs. For example, there is a trend of increasing interest in direct-to-consumer genetic testing [96–98]. The authors of one study cite evidence that people who search the internet "increasingly" want their genomic data and concluded that patients themselves will be more likely to be faced with understanding genomics results [99]. Thus patients' pharmacogenomics information needs may become more prominent. Further, there is also discussion of moving pharmacogenomics decisions fully into the purview of pharmacists [100]. A future study should include these two important groups, patients and pharmacists, and determine tactics to meet their needs.

In conclusion, pharmacogenomics is an area where improved access to information may reduce physicians sense of low self-efficacy and thus improve the effective use of pharmacogenomics testing. The HL7 Infobutton modality can be used not only to meet pharmacogenomics information needs but also general genomics information needs. As a step towards meeting general information needs in genomics, the work of this thesis has enabled context-aware retrieval of actionable, curated evidence on the gene and disease level from genomics information resources, including ClinGen, by Electronic Healthcare systems. Coupling this information with patient information and logistics information, such as cost, test-turnaround time, and accessibility of an expert, will provide a tool that meets the information needs we uncovered. A next step is to learn if such a tool actually improves both physicians' level of comfort with genomics and patient outcomes.

REFERENCES

1. Goodman K, Grad R, Pluye P, Nowacki A, Hickner J. Impact of knowledge resources linked to an electronic health record on frequency of unnecessary tests and treatments. J Contin Educ Health Prof. 2012 Mar 1;32(2):108–15.

2. Sheldon J, Ou W. The real informatics challenges of personalized medicine: not just just about the number of central processing units. Pers Med. 2013 Sep;10(7):639–45.

3. Overby CL, Tarczy-Hornoch P. Personalized medicine: challenges and opportunities for translational bioinformatics. Pers Med. 2013 Jul 1;10(5):453–62.

4. Manolio TA, Chisholm RL, Ozenberger B, Roden DM, Williams MS, Wilson R, Bick D, Bottinger EP, Brilliant MH, Eng C, Frazer KA, Korf B, Ledbetter DH, Lupski JR, Marsh C, Mrazek D, Murray MF, O'Donnell PH, Rader DJ, Relling MV, Shuldiner AR, Valle D, Weinshilboum R, Green ED, Ginsburg GS. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013 Apr;15(4):258–67.

5. Pharmacogenomics and Personalized Medicine | Learn Science at Scitable [Internet]. [cited 2014 Mar 14]. Available from: http://www.nature.com.ezproxy.lib.utah.edu/scitable/topicpage/pharmacogenomics-and-personalized-medicine-643

6. Del Fiol G, Haug PJ, Cimino JJ, Narus SP, Norlin C, Mitchell JA. Effectiveness of topic-specific Infobuttons: A randomized controlled trial. J Am Med Inform Assoc JAMIA. 2008 Nov 1;15(6):752–9.

7. Stanek EJ, Sanders CL, Taber KAJ, Khalid M, Patel A, Verbrugge RR, Agatep BC, Aubert RE, Epstein RS, Frueh FW. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clin Pharmacol Ther. 2012 Mar;91(3):450–8.

8. Van Driest S, Shi Y, Bowton EA, Schildcrout JS, Peterson JF, Pulley J, Denny JC, Roden DM. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther [Internet]. 2014 Jan 22 [cited 2014 Feb 12]; Available from: http://www.nature.com/clpt/journal/vaop/ncurrent/full/clpt2013229a.html

9. Selkirk CG, Weissman SM, Anderson A, Hulick PJ. Physicians' preparedness for

integration of genomic and pharmacogenetic testing into practice within a major healthcare system. Genet Test Mol Biomark. 2013 Mar;17(3):219–25.

10. Lubin IM, McGovern MM, Gibson Z, Gross SJ, Lyon E, Pagon RA, Pratt VM, Rashid J, Shaw C, Stoddard L, Trotter TL, Williams MS, Amos Wilson J, Pass K. Clinician perspectives about molecular genetic testing for heritable conditions and development of a clinician-friendly laboratory rReport. J Mol Diagn. 2009 Mar;11(2):162–71.

11. Ramos EM, Din-Lovinescu C, Berg JS, Brooks LD, Duncanson A, Dunn M, Good P, Hubbard TJP, Jarvik GP, O'Donnell C, Sherry ST, Aronson N, Biesecker LG, Blumberg B, Calonge N, Colhoun HM, Epstein RS, Flicek P, Gordon ES, Green ED, Green RC, Hurles M, Kawamoto K, Knaus W, Ledbetter DH, Levy HP, Lyon E, Maglott D, McLeod HL, Rahman N, Randhawa G, Wicklund C, Manolio TA, Chisholm RL, Williams MS. Characterizing genetic variants for clinical action. Am J Med Genet C Semin Med Genet. 2014;n/a–n/a.

12. Williams MS. Genomic medicine implementation: Learning by example. Am J Med Genet C Semin Med Genet. 2014;n/a–n/a.

13. Scheuner MT, Hilborne L, Brown J, Lubin IM, members of the RAND Molecular Genetic Test Report Advisory Board. A report template for molecular genetic tests designed to improve communication between the clinician and laboratory. Genet Test Mol Biomark. 2012 Jul;16(7):761–9.

14. Devine EB, Lee C-J, Overby CL, Abernethy N, McCune J, Smith JW, Tarczy-Hornoch P. Usability evaluation of pharmacogenomics clinical decision support aids and clinical knowledge resources in a computerized provider order entry system: a mixed methods approach. Int J Med Inf. 2014 Jul;83(7):473–83.

15. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012 Oct;92(4):414–7.

16. Caudle KE, Klein TE, Hoffman JM, Müller DJ, Whirl-Carrillo M, Gong L, McDonagh EM, Sangkuhl K, Thorn CF, Agundez JA, Schwab M, Freimuth RR, Huser V, Lee MTM, Iwuchukwu OF, Crews KR, Scott SA, Wadelius M, Swen JJ, Tyndale RF, Stein CM, Roden D, Relling MV, Williams MS, Johnson SG. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014 Feb;15(2):209-17

17. Cohen DA, Shirts BH, Jackson BR, Parker LS. Laboratory informatics based evaluation of methylene tetrahydrofolate reductase C677T genetic test overutilization. J Pathol Inform. 2013;4:33.

18. Leandro B, Paneque M, Sequeiros J, Porto G. Insufficient referral for genetic counseling in the management of hereditary haemochromatosis in Portugal: a

study of perceptions of health professionals requesting HFE genotyping. J Genet Couns. 2014 Oct 1; 23(5):770-7

19. Cimino JJ, Overby CL, Devine EB, Hulse NC, Jing X, Maviglia SM, Del Fiol G. Practical choices for infobutton customization: experience from four sites. AMIA Annu Symp Proc. 2013 Nov 16;2013:236–45.

20. Del Fiol G, Rocha RA, Clayton PD. Infobuttons at Intermountain Healthcare: utilization and infrastructure. AMIA Annu Symp Proc. 2006;2006:180–4.

21. Isaac T, Zheng J, Jha A. Use of UpToDate and outcomes in US hospitals. J Hosp Med Off Publ Soc Hosp Med. 2012 Feb;7(2):85–90.

22. Stanek EJ, Sanders CL, Frueh FW. Physician awareness and utilization of Food and Drug Administration (FDA)-approved labeling for pharmacogenomic testing information. J Pers Med. 2013 Jun 10;3(2):111–23.

23. Overby CL, Devine EB, Tarczy-Hornoch P, Kalet IJ. Deriving rules and assertions from pharmacogenomics knowledge resources in support of patient drug metabolism efficacy predictions. J Am Med Inform Assoc. 2012 Sep 1;19(5):840–50.

24. Bell GC, Crews KR, Wilkinson MR, Haidar CE, Hicks JK, Baker DK, Kornegay NM, Yang W, Cross SJ, Howard SC, Freimuth RR, Evans WE, Broeckel U, Relling MV, Hoffman JM. Development and use of active clinical decision support for preemptive pharmacogenomics. J Am Med Inform Assoc. 2013 Aug 26;21(e1):e93–9.

25. Sayers I, Hall IP. Pharmacogenetic approaches in the treatment of asthma. Curr Allergy Asthma Rep. 2005 Mar;5(2):101–8.

26. Sayers I. A tailored approach to asthma management: Arg16 holds the key? Clin Sci. 2013 Apr 1;124(8):517–9.

27. Stallings SC, Huse D, Finkelstein SN, Crown WH, Witt WP, Maguire J, Hiller AJ, Sinskey AJ, Ginsburg GS. A framework to evaluate the economic impact of pharmacogenomics. Pharmacogenomics. 2006 Sep;7(6):853–62.

28. Madian AG, Wheeler HE, Jones RB, Dolan ME. Relating human genetic variation to variation in drug responses. Trends Genet. 2012 Oct;28(10):487–95.

29. Kazani S, Wechsler ME, Israel E. The role of pharmacogenomics in improving the management of asthma. J Allergy Clin Immunol. 2010 Feb;125(2):295–302.

30. Lipworth BJ, Basu K, Donald HP, Tavendale R, Macgregor DF, Ogston SA, Palmer CNA, Mukhopadhyay S. Tailored second-line therapy in asthmatic children with the Arg ^{16} genotype. Clin Sci. 2013 Apr 1;124(8):521–8.

31. Charland SL, Agatep BC, Herrera V, Schrader B, Frueh FW, Ryvkin M, Shabbeer J, Devlin JJ, Superko HR, Stanek EJ. Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. Pharmacogenomics J [Internet]. 2013 Aug 27 [cited 2014 Feb 5]; Available from: http://www.nature.com/tpj/journal/vaop/ncurrent/abs/tpj201327a.html

32. Dolgin E. Pharmacogenetic tests yield bonus benefit: better drug adherence. Nat Med. 2013 Nov;19(11):1354–5.

33. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J, Kraft M, Kunselman SJ, Lazarus SC, Lemanske Jr RF, Liggett SB, Martin RJ, Mitra N, Peters SP, Silverman E, Sorkness CA, Szefler SJ, Wechsler ME, Weiss ST, Drazen JM. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004 Oct 29;364(9444):1505–12.

34. Section 3, Component 4: Medications. In: National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma [Internet]. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. p. 235. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/07_sec3_comp4.pdf

35. Slejko JF, Ghushchyan VH, Sucher B, Globe DR, Lin S-L, Globe G, Sullivan PW. Asthma control in the United States, 2008–2010: Indicators of poor asthma control. J Allergy Clin Immunol. 133(6):1579–87.

36. Bandura A. Self-efficacy. In: Ramachaudran VS, editor. Encyclopedia of human behavior. New York: Academic Press; 1994. p. 77–81.

37. Gurwitz D, Weizman A, Rehavi M. Education: teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. Trends Pharmacol Sci. 2003 Mar;24(3):122–5.

38. Vernez SL, Salari K, Ormond KE, Lee SS. Personal genome testing in medical education: student experiences with genotyping in the classroom. Genome Med. 2013 Mar 19;5(3):24.

39. Sharp RR, Goldlust ME, Eng C. Addressing gaps in physician education using personal genomic testing. Genet Med. 2011 Aug;13(8):750–1.

40. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR.. Why don't physicians follow clinical practice guidelines?: A framework for improvement. JAMA. 1999 Oct 20;282(15):1458–65.

41. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. Br J Gen Pract. 2007 Dec 1;57(545):971–8.

42. Del Fiol G, Workman TE, Gorman PN. Clinical questions raised by clinicians at the point of care: a systematic review. JAMA Intern Med. 2014 May;174(5):710–8.

43. Davidoff F, Miglus J. Delivering clinical evidence where it's needed: Building an information system worthy of the profession. JAMA. 2011 May 11;305(18):1906–7.

44. Smith R. Strategies for coping with information overload. BMJ. 2010 Dec 15;341:c7126–c7126.

45. Pluye P, Grad RM, Dunikowski LG, Stephenson R. Impact of clinical information-retrieval technology on physicians: A literature review of quantitative, qualitative and mixed methods studies. Int J Med Inf. 2005 Sep;74(9):745–68.

46. Maviglia SM, Yoon CS, Bates DW, Kuperman G. KnowledgeLink: impact of context-sensitive information retrieval on clinicians' information needs. J Am Med Inform Assoc JAMIA. 2006 Feb;13(1):67–73.

47. Cimino JJ. Use, usability, usefulness, and impact of an infobutton manager. AMIA Annu Symp Proc AMIA Symp AMIA Symp. 2006;151–5.

48. Weir CR, Nebeker JJ, Hicken BL, Campo R, Drews F, LeBar B. A cognitive task analysis of information management strategies in a computerized provider order entry environment. J Am Med Inform Assoc. 2007 Jan 1;14(1):65–75.

49. Miller GA. The magical number seven, plus or minus two: some limits on our capacity for processing information. Psychol Rev. 1994 Apr;101(2):343–52.

50. Miller GA. Human memory and the storage of information. IRE Trans Inf Theory. 1956 Sep;2(3):129–37.

51. Cowan N. The magical number 4 in short-term memory: A reconsideration of mental storage capacity. Behav Brain Sci. 2001;24(1):87–114.

52. Farris C, Farris C. The effects of message length, L2 proficiency and cognitive workload on performance accuracy and speech production in a simulated pilot navigation task [Internet] [masters]. Concordia University; 2007 [cited 2014 Apr 16]. Available from: http://spectrum.library.concordia.ca/975449/

53. Overby CL, Tarczy-Hornoch P, Kalet IJ, Thummel KE, Smith JW, Fiol GD, Fenstermacher D, Devine EB. Developing a prototype system for integrating pharmacogenomics findings into clinical practice. J Pers Med. 2012 Nov 20;2(4):241–56.

54. Overby CL, Tarczy-Hornoch P, Hoath JI, Kalet IJ, Veenstra DL. Feasibility of incorporating genomic knowledge into electronic medical records for

pharmacogenomic clinical decision support. BMC Bioinformatics. 2010 Oct 28;11(Suppl 9):S10.

55. Overby CL, Rasmussen LV, Hartzler A, Connolly JJ, Peterson JF, Hedberg RE, Freimuth RR, Shirts BH, Denny JC, Larson EB, Chute CG, Jarvik GP, Ralston JD, Shuldiner AR, Starren J, Kullo IJ, Tarczy-Hornoch P, Williams MS. A template for authoring and adapting genomic medicine content in the eMERGE Infobutton Project. AMIA Annu Symp Proc AMIA Symp AMIA Symp. 2014;2014:944–53.

56. Del Fiol G, Williams MS, Maram N, Rocha RA, Wood GM, Mitchell JA. Integrating genetic information resources with an EHR. AMIA Annu Symp Proc AMIA Symp AMIA Symp. 2006;904.

57. HL7 Standards Product Brief - HL7 Version 3 Standard: Context Aware Knowledge Retrieval Application ("Infobutton"), Knowledge Request, Release 2 [Internet]. [cited 2015 Sep 8]. Available from: http://www.hl7.org/implement/standards/product_brief.cfm?product_id=208

58. Health Information Technology: standards, implementation specifications, and certification criteria for electronic health record technology. 2014 edition, final rule, 171. [Internet]. 2012. Available from: http://www.gpo.gov/fdsys/pkg/FR-2012-09-04/pdf/2012-20982.pdf

59. Certified Health IT Product List (CHPL) | Policy Researchers & Implementers | HealthIT.gov [Internet]. [cited 2015 Sep 17]. Available from: http://www.healthit.gov/policy-researchers-implementers/certified-health-it-product-list-chpl

60. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011 Mar;89(3):464–7.

61. Miller CE, Krautscheid P, Baldwin EE, Tvrdik T, Openshaw AS, Hart K, LaGrave D. Genetic counselor review of genetic test orders in a reference laboratory reduces unnecessary testing. Am J Med Genet A. 2014 Jan 1;n/a-n/a.

62. Isaac T, Zheng J, Jha A. Use of UpToDate and outcomes in US hospitals. J Hosp Med. 2012 Feb;7(2):85–90.

63. Gaucher Disease | Diagnostic Case Study of Gaucher Disease [Internet]. [cited 2014 Jun 6]. Available from: http://www.gauchercare.com/en/healthcare/diagnosing/DiagnosticCaseStudy.aspx

64. 15. Gaucher's Disease > Laboratory Medicine | Yale School of Medicine [Internet]. [cited 2014 Jun 6]. Available from: http://labmed.yale.edu/education/cme/casestudies/1/15.aspx

65. Case study- Gaucher Disease | Biochemistry for Medics – Lecture Notes [Internet]. [cited 2014 Jun 6]. Available from: http://www.namrata.co/case-study-gaucher-disease/

66. Larsen EC, Connolly SA, Rosenberg AE. Case 20-2003. N Engl J Med. 2003 Jun 26;348(26):2669–77.

67. gaucher VEN_Gaucher_Web - GaucherPNDS-FRenPro644.pdf [Internet]. [cited 2014 Jun 6]. Available from: https://www.orpha.net/data/patho/Pro/en/GaucherPNDS-FRenPro644.pdf

68. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm (Accessed on March 21, 2011). In.

69. Management of Acute Asthma Exacerbations - American Family Physician [Internet]. [cited 2014 May 14]. Available from: http://www.aafp.org/afp/2011/0701/p40.html

70. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV, Ritchie JL, Gibbons RJ, Cheitlin MD, Eagle KA, Gardner TJ, Garson A, Russell RO, Ryan TJ, Smith SC. ACC/AHA/ACP–ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). Circulation. 1999 Jun 1;99(21):2829–48.

71. Fox K, Garcia MAA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, Backer GD, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc J-J, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Zamorano JL, Andreotti F, Becher H, Dietz R, Fraser A, Gray H, Antolin RAH, Huber K, Kremastinos DT, Maseri A, Nesser H-J, Pasierski T, Sigwart U, Tubaro M, Weis M. Guidelines on the management of stable angina pectoris: executive summary The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006 Jun 1;27(11):1341–81.

72. Fiol GD, Mostafa J, Pu D, Medlin R, Slager S, Jonnalagadda SR, Weir CR. Formative evaluation of a patient-specific clinical knowledge summarization tool. Int J Med Inf. 2016 Feb 1;86:126–34.

73. Berg BL. Qualitative research methods for the social sciences. 4th ed. Boston: Allyn and Bacon; 2001. 304 p.

74. Bates MJ. The design of browsing and berrypicking techniques for the online search interface. Online Rev. 1989;13(5):407–24.

75. Johansen Taber KA, Dickinson BD. Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. Pharmacogenomics Pers Med. 2014 Jul 10;7:145–62.

76. Hollnagel E, Woods DD. Joint cognitive systems: foundations of cognitive systems engineering. CRC Press; 2005. 236 p.

77. Zook J, Salit M. Chapter 23 - Genomic Reference Materials for Clinical Applications. In: Pfeifer SK, editor. Clinical Genomics [Internet]. Boston: Academic Press; 2015 [cited 2015 Sep 15]. p. 393–402. Available from: http://www.sciencedirect.com/science/article/pii/B978012404748800023X

78. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014 Jun 19;370(25):2418–25.

79. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2015 Jun;17(6):505–7.

80. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, Hallisey R, Ives J, Laird N, Laffel G. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995 Jul 5;274(1):35–43.

81. Institute of Medicine (U.S.), Committee on Quality of Health Care in America. Crossing the quality chasm a new health system for the 21st century [Internet]. Washington, D.C.: National Academy Press; 2001 [cited 2015 Sep 21]. Available from: http://site.ebrary.com/id/10032412

82. Del Fiol G, Workman TE, Gorman PN. Clinical questions raised by clinicians at the point of care: a systematic review. JAMA Intern Med. 2014 May;174(5):710–8.

83. Bonis PA, Pickens GT, Rind DM, Foster DA. Association of a clinical knowledge support system with improved patient safety, reduced complications and shorter length of stay among Medicare beneficiaries in acute care hospitals in the United States. Int J Med Inf. 2008 Nov;77(11):745–53.

84. Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, Ledbetter DH, Maglott DR, Martin CL, Nussbaum RL, Plon SE, Ramos EM, Sherry ST, Watson MS, ClinGen. ClinGen—the clinical genome resource. N Engl J Med. 2015 Jun 4;372(23):2235–42.

85. NCBI Resource Coordinators. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2015 Jan;43(Database issue):D6-17.

86. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999 Oct 20;282(15):1458–65.

87. Cimino JJ, Elhanan G, Zeng Q. Supporting infobuttons with terminological knowledge. Proc Conf Am Med Inform Assoc AMIA Annu Fall Symp AMIA Fall Symp. 1997;528–32.

88. Del Fiol G, Huser V, Strasberg HR, Maviglia SM, Curtis C, Cimino JJ. Implementations of the HL7 Context-Aware Knowledge Retrieval ("Infobutton") Standard: challenges, strengths, limitations, and uptake. J Biomed Inform. 2012 Aug;45(4):726–35.

89. Cimino JJ, Li J, Bakken S, Patel VL. Theoretical, empirical and practical approaches to resolving the unmet information needs of clinical information system users. Proc AMIA Annu Symp AMIA Symp. 2002;170–4.

90. Del Fiol G, Curtis C, Cimino JJ, Iskander A, Kalluri ASD, Jing X, Hulse NC, Long J, Overby CL, Schardt C, Douglas DM. Disseminating context-specific access to online knowledge resources within electronic health record systems. Stud Health Technol Inform. 2013;192:672–6.

91. Cimino JJ, Jing X, Del Fiol G. Meeting the electronic health record "meaningful use" criterion for the HL7 infobutton standard using OpenInfobutton and the Librarian Infobutton Tailoring Environment (LITE). AMIA Annu Symp Proc AMIA Symp AMIA Symp. 2012;2012:112–20.

92. HL7 Standards Product Brief - HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model (US Realm) [Internet]. [cited 2015 Sep 17]. Available from: http://www.hl7.org/implement/standards/product_brief.cfm?product_id=23

93. Dey A. Consumer health informatics: an overview of patient perspectives on health information needs. HIM J. 2004;33(4):121–6.

94. Bass SB, Ruzek SB, Gordon TF, Fleisher L, McKeown-Conn N, Moore D. Relationship of Internet health information use with patient behavior and self-efficacy: experiences of newly diagnosed cancer patients who contact the National Cancer Institute's Cancer Information Service. J Health Commun. 2006 Mar;11(2):219–36.

95. Pirolli P, Card S. Information foraging. Psychol Rev. 1999;106(4):643–75.

96. Frueh FW, Greely HT, Green RC, Hogarth S, Siegel S. The future of direct-to-consumer clinical genetic tests. Nat Rev Genet. 2011;12(7):511–515.

97. Goldsmith L, Jackson L, O'Connor A, Skirton H. Direct-to-consumer genomic testing: systematic review of the literature on user perspectives. Eur J Hum Genet.

2012;20(8):811–816.

98. Sturm AC, Manickam K. Direct-to-consumer personal genomic testing: a case study and practical recommendations for “genomic counseling.” J Genet Couns. 2012;21(3):402–412.

99. Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013 May 17;14(6):415–26.

100. Owusu-Obeng A, Weitzel KW, Hatton RC, Staley BJ, Ashton J, Cooper-Dehoff RM, Johnson JA. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacother J Hum Pharmacol Drug Ther. 2014 Oct;34(10):1102–12.