A Template for Authoring and Adapting Genomic Medicine Content in the eMERGE Infobutton Project

Casey L. Overby, PhD[1,2]; Luke V. Rasmussen[3]; Andrea Hartzler, PhD[4]; John J. Connolly, PhD[5]; Josh F. Peterson, MD MPH[6,7]; RoseMary E. Hedberg, MA[3]; Robert R. Freimuth, PhD[8]; Brian H. Shirts, MD PhD[9]; Joshua C. Denny, MD MS[6,7]; Eric B. Larson, MD MPH[10]; Christopher G. Chute, MD DrPH[8]; Gail P. Jarvik, MD PhD[11]; James D. Ralston, MD MPH[10]; Alan R. Shuldiner, MD[1]; Justin Starren, MD PhD[3,12]; Iftikhar J. Kullo, MD[13], Peter Tarczy-Hornoch, MD[14], Marc S. Williams, MD[15]

[1]Program for Personalized and Genomic Medicine and Department of Medicine, [2]Center for Health-related Informatics and Bioimaging, University of Maryland, Baltimore, MD; [3]Department of Preventive Medicine, [12]Medical Social Sciences, Northwestern University, Chicago, IL; [4]The Information School, [9]Laboratory Medicine, [14]Biomedical Informatics and Medical Education, [11]Department of Medical Genetics, University of Washington, Seattle, WA; [5]Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA; [6]Department of Biomedical Informatics, [7]Department of Medicine, Vanderbilt University, Nashville, TN; [10]Group Health Research Institute, Seattle, WA; [8]Department of Health Sciences Research, [13]Division of Cardiovascular Diseases, Mayo Clinic, Rochester MN; [15]Genomic Medicine Institute, Geisinger Health System, Danville, PA

Abstract

The Electronic Medical Records and Genomics (eMERGE) Network is a national consortium that is developing methods and best practices for using the electronic health record (EHR) for genomic medicine and research. We conducted a multi-site survey of information resources to support integration of pharmacogenomics into clinical care. This work aimed to: (a) characterize the diversity of information resource implementation strategies among eMERGE institutions; (b) develop a master template containing content topics of important for genomic medicine (as identified by the DISCERN-Genetics tool); and (c) assess the coverage of content topics among information resources developed by eMERGE institutions. Given that a standard implementation does not exist and sites relied on a diversity of information resources, we identified a need for a national effort to efficiently produce sharable genomic medicine resources capable of being accessed from the EHR. We discuss future areas of work to prepare institutions to use infobuttons for distributing standardized genomic content.

Introduction

The Electronic Medical records and Genomics (eMERGE) Network[1] is a national consortium funded by the National Human Genome Research Institute (NHGRI) to develop methods and best practices for using the electronic health record (EHR) for genomic medicine and research. Methods and best practices span from using EHR data to discover genotype-phenotype associations, to incorporating genotype data into the EHR for clinical use. There are however significant challenges to using genotype data to make informed healthcare decisions. These include lack of evidence-based clinical guidelines for using genotype data and barriers to implementation (i.e., practice change).

In collaboration with the Pharmacogenomics Research Network[2], the eMERGE network is using clinical guidelines prepared by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[3, 4] in patients who are preemptively genotyped and who have an increased probability of receiving target drugs including clopidogrel, warfarin and simvastatin in the next 3 years. In order to achieve impact, however, changes in healthcare practices are critical. Institutions participating in this eMERGE Pharmacogenomics (PGx) project are therefore establishing various implementation strategies that encourage healthcare providers to individualize drug therapy using CPIC guidelines.

While implementation strategies must be localized[5-7], developing sharable tools and resources increases the likelihood of a successful local implementation. To this end, the eMERGE Network is exploring use of infobuttons[8-10] as a decision support tool to provide context-specific links within the EHR to relevant genomic

medicine content about drug-gene associations. A previous study showed providing infobuttons that link to specific content topics was more effective than links that point to general overview content[11]. We therefore aimed to design an infobutton-compatible information resource[12] that is likely to impact decision-making. Our goal was to: (a) characterize the diversity of information resource implementation strategies among eMERGE-PGx project participants; (b) develop a master template containing content topics important for genomic medicine practices; and (c) assess the coverage of content topics among information resources developed by eMERGE sites.

Methods

Characterize the diversity of eMERGE-PGx information resource implementation strategies

Through early research team discussions, we found that many eMERGE-PGx project participants had already established local approaches to synthesize evidence and manage content for healthcare providers and/or patients. We therefore characterized implementation strategies among eMERGE-PGx project participants by assessing the target audience, purpose and format for their information resources. We also assessed authoring, editing and reviewing, and updating processes. In addition to efforts related to eMERGE-PGx, for comparison purposes, we evaluated resources from three national efforts: two to synthesize genomic medicine evidence (GeneReviews®[13-15] and PLoS Currents Evidence on Genomic Tests[16, 17]) and one to publish clinical guidelines (CPIC guidelines). In order to design an information resource that accounts for diverse implementation strategies, we developed a master template for authoring and adapting genomic medicine content from existing resources.

Develop a master template for eMERGE-PGx content using DISCERN-genetics criteria

The research team developed an initial list of content topics based on the quality assessment tool, DISCERN-genetics.[18, 19] The DISCERN criteria was developed for assessing information on treatment[20, 21], and is widely used for both appraisal[21-25] and to guide the production of health information on treatment for the public[26, 27]. The DISCERN methodology was more recently used to develop the DISCERN-genetics criteria to assess the quality of information on genetic screening and testing for a lay audience.[18] We chose to use this tool given the criteria were developed to facilitate applying information covering a broad range of genetic screening and testing situations to a variety of settings and conditions. The DISCERN-genetics criteria have also undergone an extensive evaluation involving testing with health information consumers, producers and providers. Moreover, the focus of DISCERN-genetics is on information content, rather than the way information is packaged, presented and made accessible. These characteristics are appropriate given the diversity of implementation strategies among eMERGE institutions.

One author (CO) developed a master template from the initial list of content topics. Initial revisions were then made to the template based upon discussions among three authors on this manuscript with expertise in clinical and biomedical informatics (CO, LR, AH). Following revisions, we piloted the template by adapting content from one information resource (MyResults.org[28]) developed by the Children's Hospital of Philadelphia. Specifically, three authors (CO, LR, JC) each adapted content for one of three drug-gene pairs (clopidogrel/*CYP2C19*, warfarin/*CYP2C9* & *VKORC1* and simvastatin/*SLC01B1*) to the master template. Pilot efforts informed our approach to provide training to eMERGE network participants interested in using the master template.

Assess the coverage of template content topics among eMERGE institutions

One author (CO) led a 20 minute training session that provided eMERGE participants with an overview of the master template, the process for adapting content, and study questions. At the conclusion of this session we identified individuals from eMERGE institutions interested in contributing to this study and each identified one or two PGx scenarios for which they would either author or adapt content from an existing information resource to the master template.

We used the Qualtrics online survey platform (http://qualtrics.com/) to collect descriptive data (i.e., institution, name of existing information resource, topic/scenario), content that was adapted to the master template and that was uploaded as an attachment, data on the adaption process, and data that was useful for configuring information resources for infobuttons (e.g.,where in the EHR should the resource be accessed). Quantitative data were downloaded and saved as an Excel file, and then read into STATA[29] for summary statistics. We report summary statistics for descriptive data and data on the adaption process. Two questions about the adaption process were asked for each content topic (i.e., "Please indicate how you were able to adapt text from the original resource?" and "Was there an equivalent section in the original resource?"). Data collected for questions relevant for configuring information resources were not within the scope of this manuscript and therefore were not analyzed.

We also included an open-ended comment field for each content topic. Qualitative narrative responses were used to provide a more thorough understanding of challenges faced when using the master template.

Results

Diversity of eMERGE PGx resource implementation strategies

We characterized seven information resources, including four developed by eMERGE institutions and three from national efforts to synthesize genomic medicine evidence. **Table 1** summarizes the target audience, purpose and format of the information resource. With the exception of MyResults.org that targets a patient audience, all of the resources we reviewed target healthcare professionals. Other target audiences among the resources we evaluated include researchers, public health professionals and decision-makers (providers, patients, managers and policy makers). The purpose of two information resources (MyDrugGenome.org and MyResults.org) was to provide education. The purpose of five information resources (AskMayoExpert, CPIC Guidelines, GeneReviews, MyDrugGenome.org, and Northwestern Clopidogrel Fact Sheet) was to allow healthcare providers to manage and treat patients that have specific genetic conditions or genetic test results. One information resource (PLoS Currents Evidence on Genomic Tests) aimed to provide a forum for sharing genomic medicine content with a wide audience.

Table 1. Scope of existing genomic medicine resources.

Information Resource (Institution)	Target audience	Purpose	Format (how information is made accessible)
AskMayoExpert* (Mayo Clinic)	Mayo Clinic healthcare providers	To provide access to expert clinical information on a wide variety of topics related to patient care including prevention, diagnosis and treatment.	Custom web-based content system; in the context of pharmacogenomics, the content is also used to develop clinical decision support logic.
CPIC Guidelines (PGRN and PharmGKB)	Clinical professionals (MD, PharmD, NP), other healthcare professionals, researchers and genetics professionals.	To provide guidance to healthcare providers about how genetic tests should be interpreted to improve drug therapy.	Published in the journal *Clinical Pharmacology and Therapeutic*s and made available at PharmGKB[30, 31]
GeneReviews® (University of Washington)	Genetics professionals (MD, PhD, MS), and other healthcare professionals.	To allow healthcare providers who are not experts in a given disorder to manage the first encounter with a patient with a given diagnosis.	Online web-based resource publically accessible on the National Center for Biotechnology Information (NCBI) Bookshelf website[32]
MyDrugGenome.org* (Vanderbilt University)	Clinical professionals (MD, NP), other healthcare professionals, Researchers and genetics professionals	To educate healthcare providers on pharmacogenetics and to allow healthcare providers to interpret the impact of specific pharmacogenetic diplotypes on target medications.	Online web resource linked to implemented clinical decision support available in order entry and e-prescribing applications
MyResults.org* (Children's Hospital of Philadelphia)	Patients in the eMERGE network, resources for professionals planned for future implementation.	To educate patients on the purpose of the eMERGE network and eMERGE projects relevant to their healthcare.	Online web-based resource
Northwestern Clopidogrel Fact Sheet* (Northwestern University)	Northwestern University clinical professional (MD, NP), other healthcare professionals, researchers and genetics professionals.	To allow healthcare providers to interpret new genomic test results.	Custom web-based content system accessible through infobuttons in the EHR
PLoS Currents Evidence on Genomic Tests	Public health and healthcare practitioners and decision-makers.	To bring together data from multiple sources (e.g., basic research, clinical trials, epidemiological and clinical studies), and provide a forum for sharing data, with the goal of making it actionable.	Published using the PLOS Currents Annotum publishing platform[33] and archived at PubMed Central[34]

*Resources developed by eMERGE institutions

Table 2 (on the next page) summarizes content management processes for these resources including authoring, editing and reviewing, and updating processes. Four different approaches to authoring materials are described among the seven resources we reviewed. For four resources (CPIC Guidelines, GeneReviews, MyDrugGenome.org[35], and MyResults.org) content is team-authored, for one resource (Northwestern Clopidogrel Fact Sheet) a single individual authors materials, and for two resources (AskMayoExpert and PLoS Currents Evidence on Genomic Tests) one or more individuals author materials. In terms of editing and reviewing, three resources are externally peer-reviewed (CPIC Guidelines, GeneReviews and PLoS Currents Evidence on Genomic Tests). In all three instances reviewers are provided detailed guidance on how to review the materials. Conversely, a team of individuals reviews content for the four information resources that are developed by eMERGE institutions (AskMayoExpert, MyDrugGenome.org, MyResults.org and Northwestern Clopidogrel Fact Sheet). Prior to

publishing, some institutions require a formal approval (e.g., as with AskMayoExpert) and some require team consensus (e.g., as with MyDrugGenome.org). Three resources we evaluated, CPIC Guidelines, GeneReviews and MyResults.org, have established a formal process to regularly update their content.

Table 2. Content management processes for genomic medicine resources

Information Resource (Institution)	Authoring	Editing and reviewing	Updating
AskMayoExpert* (Mayo Clinic)	Internally authored by one primary author. Additional authors/contributors to information are optional.	The Mayo Clinic Pharmacogenomics Task force, comprised of a multidisciplinary team of subject experts reviews and approves pharmacogenomics modules. (Internal review)	A formal review is conducted 1 year from publication, unless stated otherwise by the authors.
CPIC Guidelines (PGRN and PharmGKB)	Distributed (international); a multidisciplinary writing committee composed of scientists, pharmacologists, and healthcare providers that have expertise in the topic area; a PharmGKB scientific curator; and a biomedical informatics professional.	The writing committee and members of CPIC review the guideline manuscript internally. The manuscript then undergoes external scientific peer-review by the journal *Clinical Pharmacology and Therapeutics* prior to publication. (Internal and external review)	A formal review is conducted every two years or as needed based on important new information that would modify prescribing recommendations. All versions are archived and separately citable.
GeneReviews® (University of Washington)	Distributed (international); experts include at least one healthcare provider (target audience member).	Editors with expertise in clinical genetics, laboratory genetics, and genetic counseling review disease descriptions for accuracy. Descriptions are then peer-reviewed by internationally acknowledged subject experts. (Internal and external review)	A formal review is conducted every two or three years, depending on the topic. The editorial staff or authors initiate time-critical revisions when a clinically significant development needs to be published.
MyDrugGenome.org* (Vanderbilt University)	Internally authored by members of the Vanderbilt pharmacogenomics implementation team.	The Vanderbilt pharmacogenomics team, made up of a multidisciplinary group of subject experts, review clinical and pharmacogenomics content related to each drug-gene interaction. (Internal review)	Updates are concurrent with release of new drug-gene interactions within the PREDICT program.[36]
MyResults.org* (Children's Hospital of Philagelphia)	Led the research/outreach team at Children's Hospital of Philadelphia and supported by other eMERGE members.	A genetic counselor from Northwestern University reviews the content. (External review)	Several components are still under development. The website is updated every three weeks. There is a formal review by two individuals that occurs annually.
Northwestern Clopidogrel Fact Sheet* (Northwestern University)	Primarily developed by one genetic counselor as a synthesis of existing resources.	A physician reviews the content to ensure wording is succinct, informative and actionable. Genetic counselors also review content for accuracy and appropriate wording. (Internal review)	No formal process is established at this time.
PLoS Currents Evidence on Genomic Tests	Manuscript submission. Most authors are researchers in genetics, knowledge synthesis, or related fields.	A board or reviewers determine whether contribution is intelligible, relevant, ethical and scientifically credible. The reviewers focus on 5 criteria: Methodology, Results and interpretation, Quality of the written English, Data availability, and Ethical standards. (External review)	Revisions to contributions are possible with approval by the Reviewer Board. All versions are archived and separately citable.

*Resources developed by eMERGE institutions

Master template developed for eMERGE-PGx content

Following discussions among three research team members, 19 DISCERN-genetics question themes[19], were translated into 13 content topics that comprise the eMERGE master template (see **Box 1**). All content topics correspond to DISCERN-genetics question themes, with the following exceptions: (1) five themes about testing ("purpose of the test," "testing procedure," "test accuracy," "after the test," and "access to test results") were translated into three content topics (see **Box 1**, #5-7); (2) three themes ("discrimination," "psychosocial consequences," and "consequences for others") were collapsed into one content topic (see **Box 1**, #9); (3) two themes ("aims are clear" and "sources of information used") were replaced (see **Box 1**, #1 and #12, respectively); and (4) two themes ("aims achieved," and "balance

Box 1. Content topics captured by eMERGE template

1. Clinical scenario/Overview
2. Background and effects of the condition
3. Treatment and management choices for the condition
4. Risk of developing, carrying or passing on the condition
5. Types of tests available or being offered
6. Testing procedure
7. Test accuracy and reliability
8. Shared decision making
9. Potential risks (psychosocial consequences, implications of discrimination, potential consequences for others)
10. Local information
11. Additional sources of support and information
12. Content contributors
13. Date of the information

and bias") were dropped all together. We also used hints provided for questions in the DISCERN-genetics questionnaire in the master template to help individuals identify relevant content to adapt from another information resource (e.g., Question #1: Are the aims clear?; Hints: What is it about? What is it meant to cover [and what topics are excluded]? Who might find it useful?).

Piloting the master template with the MyResults.org resource informed the design of reference material used in our training session. This material was shared by email to all individuals who volunteered to adapt content to the master template. In addition, our pilot effort informed changes to MyResults.org format and content. The MyResults team continues to revise their template to align with the 13 content topics listed in **Box 1**, in an effort to achieve consistency across eMERGE informational projects.

Individuals from six eMERGE institutions contributed pharmacogenomics information resources. Resources and drug-gene pairs we covered are summarized in **Table 3**. All together we assessed eleven information resource/drug-gene pair combinations (e.g. AskMayoExpert/Clopidogrel[*CYP2C19*] is one information resource/drug-gene pair combination). One resource provided clinical guidelines for using pharmacogenomics data (CPIC guidelines). The other six resources summarized evidence and recommendations from systematic reviews and evidence-based clinical guidelines. Five were existing information resources prepared by eMERGE institutions (AskMayoExpert, MyDrugGenome.org, MyResults.org, Northwestern Patient Handout, Northwestern Clopidogrel Fact Sheet). One resource contained content that was authored using the master template (Geisinger-authored).

Table 3. Information resources and sample of pharmacogenomic drug-gene pairs adapted to the eMERGE template

Information Resource	**Pharmacogenomics Drug-Gene Pairs Adapted to the Master Template**				
	Carbamazepine (HLA-B)	***Clopidogrel (CYP2C19)***	***Simvastatin (SLC01B1)***	***Thiopurine (TPMT)***	***Warfarin (CYP2C9 & VKORC1)***
AskMayoExpert		X	X		
CPIC Guidelines on PharmGKB	X				X
Geisinger-authored			X		
MyDrugGenome.org		X		X	
MyResults.org			X	X	
Northwestern Patient Handout		X			
Northwestern Clopidogrel Fact Sheet		X			

NOTE: empty cells denote that they were not included in this study (not that they do not exist for a given information resource).

Coverage of template content topics among eMERGE institutions

We assessed the coverage of content topics in our template by authoring or adapting content for seven resources (eleven information resource/drug-gene pair combinations). **Table 4** summarizes for each content topic whether relevant text existed and whether a specific sub-section existed in the resource for the drug-gene pair.

All information resources contained text relevant for four content-topics ("Clinical scenario/Overview", "Background and effects of the condition", "Treatment and management choices for the condition", and "Additional sources of support and information"). All but one information resource contained text relevant for the "Risk of developing, carrying or passing on the condition" content topic. Text on "Types of tests available or being offered," "Testing procedure," "Test accuracy and reliability" existed for seven (64%), eight (73%), and eight (73%) of the information resource/drug-gene pair combinations, respectively. Text on "Content contributors" existed for eight (73%) of information resource/drug-gene pair combinations.

Less than half of the information resource/drug-gene pair combinations covered each of the remaining content topics: 45% covered "Shared decision making," 45% covered "Potential risks (psychosocial consequences, implications of discrimination, potential consequences for others)," 45% covered "Local information" (e.g., information about re-imbursement), and 45% covered "Date of the information."

Two resources had only a few sub-sections (Northwestern Patient Handout and Northwestern Clopidogrel Fact Sheet). The remaining five resources (AskMayoExpert, CPIC Guidelines on PharmGKB, Geisinger-authored, MyDrugGenome.org, MyResults.org) included a minimum of eight sub-sections that corresponded to template content topics. For MyDrugGenome.org we also assessed other local resources for content (e.g., the PREDICT project Smarter Prescriptions webpage[37], See [a] in **Table 4**).

Table 4. Resource text and sub-sections corresponding with eMERGE template content topics.

Resource (Drug-gene pair)	Content topic number (See Box 1 for a brief description)												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
AskMayoExpert (Clopidogrel/CYP2C19)	T S	T S	T S	T S	T S	T S				T S	T S	T S	S
AskMayoExpert (Simvastatin/SLC01B1)	T S	T S	T S	T S	T S	T S				T S	T S	T S	S
CPIC Guidelines on PharmGKB (Warfarin/CYP2C9 & VKORC1)	T S	T S	T S	T	T S		T S	T	T S		T S	T S	T S
CPIC Guidelines (Carbamazepine/HLA-B)	T S	T S	T S	T	T S		T S		T S		T S	T S	T S
Geisinger-authored[b] (Simvastatin/SLC01B1)	T S	T S	T S	T S	T S	T S	T S	T S	T S	S	T S	T S	T S
MyDrugGenome.org (Clopidogrel/CYP2C19)	T S	T S	T S	T S	T S[a]	T S[a]	T S			T	T S	T S[a]	
MyDrugGenome.org (Thiopurine/TPMT)	T S	T S	T S	T S	T S[a]	T S[a]	T S				T S	T S[a]	
MyResults.org – (Simvastatin/SLC01B1)	T S	T S	T S	T S		T S	T S	T S	T	T	T S		
MyResults.org (Thiopurine/TPMT)[c]	T S	T S	T S	T S		T S	S	S			T S		
Northwestern Patient Handout (Clopidogrel/CYP2C19)	T	T	T				T S	T			T S		T
Northwestern Clopidogrel Fact Sheet (Clopidogrel/CYP2C19)	T	T	T	T S	T	T	T S	T	T	T	T S	T	T

T=text relevant for the content topic exists; S: sub-section relevant for the content topic exists; [a]content exists within another related webpage; [b]authored materials using the master template; [c]content had not yet been published to MyResults.org at the time of this analysis.

Discussion

This work characterized the diversity of information resource implementation strategies among eMERGE-PGx project sites; developed a master template containing content topics important for genomic medicine practices (as identified by the DISCERN-Genetics tool); and assessed the coverage of content topics by authoring and adapting content to our master template at six eMERGE institutions.

Implementation strategies were diverse, despite our common start and end points. While the target audience and purpose for information resources we reviewed were comparable across sites, we found that authoring, reviewing and editing processes were different. In addition, with the exception of CPIC Guidelines, GeneReviews and MyResults.org, updating processes were largely informal and in one case had not yet been established. This finding is consistent with the finding that despite adopting a common sequencing platform among Clinical Sequencing Exploratory Research (CSER) institutions[38], there were a range of approaches to annotate and prioritize genomic variants and generating whole-genome clinical reports for integration into the EHR.[6]

The master template contains 13 content topics that are important for genomic medicine practices. We successfully demonstrated our ability to adapt content to this template for a range of pharmacogenomics scenarios and information resources in this study. This task, however, did not come without challenges. Given we kept the language general for a broad range of genomic medicine scenarios, we found that the hints and content sections did not always appear directly relevant for pharmacogenomics scenarios (e.g., "genetic condition" implies a "*disease-causing* genetic condition"). This finding is not surprising given the DISCERN-genetics questionnaire was evaluated previously with a sample of information on cystic fibrosis, Down's syndrome, familial breast cancer, familial colon cancer, hemochromatosis, Huntington's disease, sickle cell disease and thalassemia.[18] To these authors knowledge, however, the DISCERN-genetics criteria is the only criteria that has been assessed with such a broad range of genetic conditions that represent different populations, disease pathways and treatment decisions, and that has been evaluated with a diverse audience including health information consumers, producers and providers.

When assessing the coverage of content topics among information resources developed by eMERGE institutions we found that many existing resources have sections or sub-sections that map directly to the content topics we defined in our template. These findings reinforce the appropriateness of our decision to use the DISCERN-genetics criteria

as the basis for our master template, given the criteria focus on information content, rather than the way information is packaged, presented and made accessible. For example, MyResults.org and AskMayoExpert both have structured templates for content relevant for drug-gene pairs of interest to eMERGE. The MyResults.org template is organized into tabs that allow patients to explore answers to common questions and resources (e.g., the video titled "Does Everyone Respond to Statins in the Same Way?"[39] under the "Media and Recommended" tab). Alternatively, the AskMayoExpert template provides content on a single document organized into major sections including "FAQs", "Key Facts", "Guidelines", "Publications and Resources", and "Patient Education". Even though the templates are quite different from each other, they both include sections or sub-sections that align with the content topics listed in **Box 1** (see **Table 4** e.g., "Pub/Resources" and "Patient Education" sections of AskMayoExpert and the "Media and Recommended" tab of MyResults.org map to the "Additional sources of support and information" eMERGE template content topic).

We also identified important aspects of genetic testing that are not addressed well by existing information resources in their current form. For example, "Shared decision making," and "Potential risks (psychosocial consequences, implications of discrimination, potential consequences for others)," were covered by fewer than half of the information resource/drug-gene pair combinations we reviewed. In addition, we found that few resources captured content on "Date of the information," which directly impacts our ability to define formal processes for updating materials. We also identified aspects of genetic testing that are covered very well by the resources we analyzed. For example, content relevant for "Clinical scenario/Overview", "Background and effects of the condition", "Treatment and management choices for the condition", and "Additional sources of support and information" template content topics were available in all of the resources we evaluated. These findings help guide areas of focus for developers of genomic medicine content. Toward improving the coverage of important content areas and achieving consistency across eMERGE informational projects, the MyResults team has already made revisions to their template to align with the 13 content topics included in the master template. At the time of our analysis, MyResults targeted a patient audience, and is now being considered for expansion to a healthcare provider audience.

Conclusions and Future Directions

Overall, we gathered genomic medicine information resources in preparation for a network-wide infobutton implementation across eMERGE institutions. Given that a standard implementation does not exist and sites relied on a diversity of information resources, there is a need for methods and approaches to help institutions efficiently produce sharable genomic medicine resources. Our findings highlight two potential areas for developing tools as part of the eMERGE infobutton project: (a) collaborative authoring and (b) adapting existing information resources. Exploring both areas, in turn, there are several considerations and opportunities to collaborate with existing projects.

First, our finding that teams of individuals often author and review information resource content motivates future work to design a collaborative writing application. We also suspect that the primary literature, clinical guidelines, and systematic reviews that authors draw from to prepare materials are similar among eMERGE institutions. It may therefore be useful to provide access to these resources in a common authoring environment. We hope to draw from the experiences of others developing software (e.g., the Librarian Infobutton Tailoring Environment, LITE[9]) to provide content for the Infobutton Manager knowledge base that creates a set of context-specific links to information resources. As an important note for designing collaborative writing applications, we will also need to address open questions about the safety, reliability, divergence from traditional authoring approaches and legal implications for decision-making.[40]

Second, our finding that many resources already have sub-sections that map to our master template motivates the need for a tool to assist with adapting existing resources. Given the challenges we encountered in interpreting content-topics for pharmacogenomics scenarios, we will also need to incorporate flexibility to tailor language to the genomic medicine scenario of focus (e.g., the option to substitute "genetic condition" with "genomic predisposition" for pharmacogenomics scenarios). We expect to encounter organizational and technical challenges in our pursuits. From an organization point of view there may be many barriers that exist such as a lack of rewards to motivate sharing, little communication about the benefits and values of sharing knowledge, and a shortage of appropriate infrastructure to support sharing practices. Collaborative projects such as eMERGE provide opportunities to identify and develop models and approaches to overcome such challenges to sharing genomic medicine knowledge. From a technical standpoint, free-text is not ideal for implementing clinical decision support. We are therefore collaborating with the OpenInfobutton development team that has released the Infobutton Responder[41] to enable healthcare organizations to index their local clinical content so that it is compliant with the HL7 infobutton standard[12, 42]. Such tools could help institutions to efficiently produce sharable genomic medicine resources in a form that can be

leveraged by infobuttons in the EHR that link to specific content topics. Exploration of open source content management systems that might be customized for these purposes is underway within the eMERGE Network.

Acknowledgments

We are grateful for valuable input from Dr. Guilherme Del Fiol (University of Utah), Dr. James Cimino (NIH Clinical Center), Dr. Roberta A. Pagon (University of Washington), and Dr. Mary Relling (St. Jude Children's Research Research Hospital). The authors would also like to thank Ms. Sarah Stallings (Vanderbilt University), Vivian Pan (Northwestern University) and the PREDICT Internal Development Team (Vanderbilt University) for their contributions.

This research was supported in part by the Columbia Training in Biomedical Informatics (NIH/NLM #T15 LM007079), the University of Maryland Program for Personalized and Genomic Medicine, NIH/NIGMS (U19GM61388; the Pharmacogenomics Research Network), NIH/NHLBI PAPI (U01HL105198), UW NEXT grant (U01HG006507), UW CSER (U01HG006507), UW CTSA (UL1TR000423), and the eMERGE network [U01HG006828 (Cincinnati Children's Hospital Medical Center/Harvard); U01HG006830 (Children's Hospital of Philadelphia); U01HG006389 (Essentia Institute of Rural Health); U01HG006382 (Geisinger Clinic and University of Maryland, Baltimore); U01HG006375 (Group Health Cooperative and the University of Washington); U01HG006379 (Mayo Clinic).); U01HG006380 (Mount Sinai School of Medicine); U01HG006388 (Northwestern University); U01HG006378 (Vanderbilt University); and U01HG006385 (Vanderbilt University serving as the Coordinating Center]. Information resources we cover are supported in part by Mayo Clinic (AskMayoExpert), Vanderbilt University Medical Center (MyDrugGenome.org), Children's Hospital of Philadelphia (MyResults.org), and Northwestern University (Northwestern Patient Handout and Northwestern Clopidogrel Fact Sheet).

References

1. Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, Manolio TA, Sanderson SC, Kannry J, Zinberg R, Basford MA *et al*: **The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future**. *Genet Med* 2013, **15**(10):761-771.
2. Shuldiner AR, Relling MV, Peterson JF, Hicks JK, Freimuth RR, Sadee W, Pereira NL, Roden DM, Johnson JA, Klein TE *et al*: **The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation**. *Clin Pharmacol Ther* 2013, **94**(2):207-210.
3. Relling MV, Klein TE: **CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network**. *Clin Pharmacol Ther* 2011, **89**(3):464-467.
4. Caudle KE, Klein TE, Hoffman JM, Muller DJ, Whirl-Carrillo M, Gong L, McDonagh EM, Sangkuhl K, Thorn CF, Agundez JA *et al*: **Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process**. *Curr Drug Metab* 2014.
5. Overby CL, Kohane I, Kannry JL, Williams MS, Starren J, Bottinger E, Gottesman O, Denny JC, Weng C, Tarczy-Hornoch P *et al*: **Opportunities for genomic clinical decision support interventions**. *Genet Med* 2013, **15**(10):817-823.
6. Tarczy-Hornoch P, Amendola L, Aronson SJ, Garraway L, Gray S, Grundmeier RW, Hindorff LA, Jarvik G, Karavite D, Lebo M *et al*: **A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record**. *Genet Med* 2013, **15**(10):824-832.
7. Peterson JF, Bowton E, Field JR, Beller M, Mitchell J, Schildcrout J, Gregg W, Johnson K, Jirjis JN, Roden DM *et al*: **Electronic health record design and implementation for pharmacogenomics: a local perspective**. *Genet Med* 2013, **15**(10):833-841.
8. Cimino JJ, Elhanan G, Zeng Q: **Supporting infobuttons with terminological knowledge**. *Proc AMIA Annu Fall Symp* 1997:528-532.
9. 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* 2012, **2012**:112-120.
10. Del Fiol G, Curtis C, Cimino JJ, Iskander A, Kalluri AS, Jing X, Hulse NC, Long J, Overby CL, Schardt C *et al*: **Disseminating context-specific access to online knowledge resources within electronic health record systems**. *Stud Health Technol Inform* 2013, **192**:672-676.

11. 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* 2008, **15**(6):752-759.
12. **Context-aware knowledge retrieval (infobutton) product brief. HL7 International Wiki Site.** [http://wiki.hl7.org/index.php?title=Product_Infobutton]
13. **GeneReviews™** [http://www.ncbi.nlm.nih.gov/books/NBK1116/]
14. Pagon RA: **GeneTests: an online genetic information resource for health care providers**. *J Med Libr Assoc* 2006, **94**(3):343-348.
15. Pagon RA, Tarczy-Hornoch P, Baskin PK, Edwards JE, Covington ML, Espeseth M, Beahler C, Bird TD, Popovich B, Nesbitt C *et al*: **GeneTests-GeneClinics: genetic testing information for a growing audience**. *Hum Mutat* 2002, **19**(5):501-509.
16. Gwinn M, Dotson WD, Khoury MJ: **PLoS currents: evidence on genomic tests - At the crossroads of translation**. *PLoS Curr* 2010, **2**.
17. **PLOS Currents Evidence on Genomic Tests** [http://currents.plos.org/genomictests]
18. Shepperd S, Farndon P, Grainge V, Oliver S, Parker M, Perera R, Bedford H, Elliman D, Kent A, Rose P: **DISCERN-Genetics: quality criteria for information on genetic testing**. *Eur J Hum Genet* 2006, **14**(11):1179-1188.
19. **DISCERN - The DISCERN Genetics Instrument** [http://www.discern-genetics.org/quality_criteria_and_references.php]
20. Charnock D, Shepperd S, Needham G, Gann R: **DISCERN: an instrument for judging the quality of written consumer health information on treatment choices**. *J Epidemiol Community Health* 1999, **53**(2):105-111.
21. Griffiths KM, Christensen H: **The quality and accessibility of Australian depression sites on the World Wide Web**. *Med J Aust* 2002, **176 Suppl**:S97-S104.
22. Godolphin W, Towle A, McKendry R: **Evaluation of the quality of patient information to support informed shared decision-making**. *Health Expect* 2001, **4**(4):235-242.
23. Gimenez-Perez G, Caixas A, Gimenez-Palop O, Gonzalez-Clemente JM, Mauricio D: **Dissemination of 'patient-oriented evidence that matters' on the Internet: the case of Type 2 diabetes treatment**. *Diabet Med* 2005, **22**(6):688-692.
24. Molassiotis A, Xu M: **Quality and safety issues of web-based information about herbal medicines in the treatment of cancer**. *Complement Ther Med* 2004, **12**(4):217-227.
25. Jefford M, Tattersall MH: **Informing and involving cancer patients in their own care**. *Lancet Oncol* 2002, **3**(10):629-637.
26. Jefford M, Gibbs A, Reading D: **Development and evaluation of an information booklet/decision-making guide for patients with colorectal cancer considering therapy in addition to surgery**. *Eur J Cancer Care (Engl)* 2005, **14**(1):16-27.
27. Sanger S, Nickel J, Huth A, Ollenschlager G: **[Well-informed on health matters--how well? The German 'Clearinghouse for Patient Information'--objective, background and methods]**. *Gesundheitswesen* 2002, **64**(7):391-397.
28. **MyResults.Org - EMERGE** [myresults.org]
29. StataCorp: **Stata Statistical Software: Release 13**. In. College Station, TX: StataCorp LP; 2013.
30. Thorn CF, Klein TE, Altman RB: **Pharmacogenomics and bioinformatics: PharmGKB**. *Pharmacogenomics* 2010, **11**(4):501-505.
31. Thorn CF, Klein TE, Altman RB: **PharmGKB: the Pharmacogenomics Knowledge Base**. *Methods Mol Biol* 2013, **1015**:311-320.
32. Hoeppner MA: **NCBI Bookshelf: books and documents in life sciences and health care**. *Nucleic Acids Res* 2013, **41**(Database issue):D1251-1260.
33. **Annotum hompage** [annotum.org]
34. Roberts RJ: **PubMed Central: The GenBank of the published literature**. *Proc Natl Acad Sci U S A* 2001, **98**(2):381-382.
35. **MyDrugGenome - PREDICT DGI** [mydruggenome.org/dgi.php]
36. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, Delaney JT, Bowton E, Brothers K, Johnson K *et al*: **Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project**. *Clin Pharmacol Ther* 2012, **92**(1):87-95.
37. **Smarter Prescriptions** [http://www.vanderbilthealth.com/main/41143 - how]

38. **Clinical Sequencing Exploratory Research (U01)** [http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-017.html]
39. **Dr. Iftikhar Kullo (Mayo Clinic): Different Responses to Statins** [http://www.youtube.com/watch?v=NM9zS3bgVJE&feature=player_embedded]
40. Archambault PM, van de Belt TH, Grajales FJ, 3rd, Faber MJ, Kuziemsky CE, Gagnon S, Bilodeau A, Rioux S, Nelen WL, Gagnon MP *et al*: **Wikis and collaborative writing applications in health care: a scoping review**. *J Med Internet Res* 2013, **15**(10):e210.
41. **Phase II - Infobutton Responder - OpenInfobutton** [http://www.openinfobutton.org/project-overview---phase-ii-infobutton-responder]
42. 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, **45**(4):726-735.