Prototype of a Standards-Based EHR and Genetic Test Reporting Tool Coupled with HL7-Compliant Infobuttons

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Abstract

Integration of genetic information is becoming increasingly important in clinical practice. However, genetic information is often ambiguous and difficult to understand, and clinicians have reported low-self-efficacy in integrating genetics into their care routine. The Health Level Seven (HL7) Infobutton standard helps to integrate online knowledge resources within Electronic Health Records (EHRs) and is required for EHR certification in the US. We implemented a prototype of a standards-based genetic reporting application coupled with infobuttons leveraging the Infobutton and Fast Healthcare Interoperability Resources (FHIR) Standards. Infobutton capabilities were provided by OpenInfobutton, an open source package compliant with the HL7 Infobutton Standard. The resulting prototype demonstrates how standards-based reporting of genetic results, coupled with curated knowledge resources, can provide dynamic access to clinical knowledge on demand at the point of care. The proposed functionality can be enabled within any EHR system that has been certified through the US Meaningful Use program.

Introduction

Access to genetic information in medical practice is becoming increasingly prevalent[1]. Since the end of the Human Genome Project in 2003, over 1000 genetic tests have become available[2], allowing clinicians to more easily obtain an individual's genetic information[3]. Methods in informatics are permitting these vast amounts of data to be integrated into clinically relevant systems[4]. Once discovered and translated into clinical practice, biomarkers in the genome, such as an existing gene or variant, can provide clinical help in diagnoses, predictive medicine, and drug treatment (i.e. pharmacogenomics)[5]. Pharmacogenomics research, as one example, has been found in some cases to reduce healthcare cost[6] and improve patient care[7]. Pharmacogenomics knowledge is rapidly increasing, but the assimilation of this and other kinds of genetic information into clinical practice has been slow[8].

In medical practice, questions that clinicians pose often remain unanswered due to lack of time to search available knowledge resources and lack of self-efficacy in choosing and searching multiple potentially relevant resources[9]. Unanswered questions associated with knowledge gaps can lead to errors and lower quality care[10]. Clinically actionable genetic information, in particular, can be difficult to obtain. Genetic knowledge resources are especially needed because clinicians report poor knowledge in genetics and low self-efficacy integrating genetics into their decision-making process[8]. Therefore, care providers may benefit from access to clinically actionable recommendations to guide them in the integration of genetics into routine patient care decisions. Several online resources exist to provide healthcare professionals and patients genetic information, such as ClinVar, Genetic Testing Resources (GTR), and GeneReviews[11,12]. However, these resources were designed to serve multiple purposes and audiences, with clinically actionable genetic information being dispersed within and across resources[8].

The ClinGen (Clinical Genome Resource) project aims to enable "an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research"[13]. ClinGen seeks to produce open resources by means of community collaboration to continuously improve understanding of genetic variation in a standardized fashion[14]. However, even with genetic standards, genetic information needs to be easily accessible within a clinical setting. Therefore, the ClinGen Electronic Health Record Working Group (EHR WG) was tasked to integrate available genomic resources (including ClinGen resources) into electronic health record (EHR) systems via clinical decision support (CDS) tools such as "infobuttons"[15,16]. Based on the context of the interaction between a clinician and the EHR, infobuttons anticipate clinicians' information needs and provide automated links to relevant resources. Infobuttons are typically placed on the EHR screen next to data such as problems, medications, and laboratory tests[17]. A recent systematic review has reported the effect of infobuttons on clinicians, particularly on increased search efficiency, decision enhancement, and learning[17]. Infobuttons can be implemented in a standards-based fashion

through the Health Level Seven (HL7) Infobutton Standard, which is required for EHR certification in the US Meaningful Use Program[18]. In a previous study, Heale et al. enabled infobutton access to several genetic information resources through OpenInfobutton, an open source, HL7-compliant software suite designed to help healthcare organizations enable infobuttons within their EHR systems[19]. In the present study, we aimed to implement HL7-compliant infobuttons within a prototype EHR coupled with a standards-based genetic reporting application to demonstrate how this kind of CDS tool could be used to help provide clinicians with seamless access to genetic knowledge resources.

Methods

To accomplish the goals of this study, we leveraged an information display of a multi-gene sequencing panel report that was designed and evaluated in a previous study[20]. We developed a user interface to represent a prototypical EHR coupled with the multi-gene sequencing panel report and incorporated infobutton features to help clinicians understand other genetic-related information, such as diseases and medications (i.e., pharmacogenomics). The prototype was developed in three steps: (1) configuration of access to genetic resources within OpenInfobutton; (2) development of the prototype EHR user interface with the gene sequencing panel reports coupled with infobutton functionality; and (3) population of the panel prototype with data from sample laboratory tests and the EHR prototype with mock patient data, respectively. The patient data were represented using HL7 Fast Healthcare Interoperability Resources (FHIR). Infobutton functionality, compliant with the HL7 Infobutton Standard, was implemented with OpenInfobutton. Brief summaries of the multi-gene sequencing panel report, the HL7 Infobutton Standard, OpenInfobutton, and FHIR are provided below.

Multi-gene sequencing panel report design. In a study done by Cutting et al., a multi-gene sequencing panel report was iteratively designed and evaluated through clinician feedback on suitable genetic reporting[20]. The report, known as Genomic Medicine Assistant (GMA), featured the clinically significant gene and variant names discovered in the panel with infobuttons next to those names. The report also featured the clinical significance of the findings, recommended actions, and other relevant features. Clinicians in the study rated the usability of the GMA and the results were favorable.

HL7 Infobutton Standard. EHR certification under the US "Meaningful Use" program requires the implementation of infobutton functionality compliant with the HL7 Context-Aware Knowledge Retrieval ("Infobutton") Standard[21]. The infobutton standard defines a means to integrate EHR systems with health knowledge resources[22]. Infobuttons utilize the context of the EHR to anticipate clinicians' and patients' information needs; select relevant Web resources; and automatically retrieve relevant information from the selected resources to address those needs. The Infobutton Standard allows EHRs to capture and send context in a standard context information model according to four dimensions: the patient (e.g., age, gender, conditions), the infobutton user (e.g., clinician, patient), the care setting (e.g., inpatient, outpatient), and the EHR task (e.g., order entry, medication list review, laboratory test result review, problem list entry)[19]. In addition, the standard allows capturing one or more concepts that the user might be interested in, such as a specific medication, gene, or laboratory test.

OpenInfobutton (www.OpenInfobutton.org). Infobutton functionality can be implemented through a Web service called an "infobutton manager", which serves as a broker between EHR systems and multiple knowledge resources. All configuration of infobutton behavior is done within the infobutton manager's knowledge base. OpenInfobutton is an HL7 compliant, open source software suite that includes an infobutton manager and a Web-based infobutton configuration application called *LITE* (Librarian Infobutton Tailoring Environment). LITE allows knowledge resource experts, such as medical librarians, to collaboratively configure access to knowledge resources within the infobutton manager's knowledge base[23,24]. Knowledge resource configuration is stored in XML files called knowledge resource *profiles,* which include the resource's base URL, the contexts in which the resource is relevant, and the search parameters and terminologies that the resource's Web service application program interface (API) supports. For resources that are not HL7-compliant, the resource profile also includes mappings between search parameters in the resource's API and the HL7 Infobutton Standard. Once a resource profile is configured in LITE, it can be made available for download to all institutions using OpenInfobutton via LITE's resource profile store.

FHIR (www.hl7.org/fhir/). HL7 FHIR is an emerging standard that is rapidly gaining attention and adoption by the health IT industry and health care organizations[25]. The basic building block of FHIR is a *resource*, which consists of a set of data attributes that are defined based on FHIR data types and bound to standard terminologies whenever applicable[26]. A few examples of FHIR resources include *Patient*, *Condition*, and *Observation* [27]. FHIR profiles are available to define the semantic structure of resources for specific use cases through constraints and extensions[28].

Configuration of ClinGen and other genetic resources in OpenInfobutton
A set of clinically useful genetic resources was chosen by consensus among ClinGen EHR WG members. Also with input from the ClinGen EHR WG, resource profiles were selected and fine-tuned from those initially developed by Heale et al[19]. In addition, new profiles were created in LITE for APIs that became available after the work done by Heale et al. All knowledge resource profiles were validated using LITE's testing tool.

Development of a prototype EHR with gene sequencing panel reports coupled with infobuttons
The goal of our infobutton-enabled prototypical EHR was to demonstrate how genetic knowledge resources can be integrated within EHR systems to help clinicians' meet their genetic information needs. The prototype user interface was developed in Javascript, HTML, and CSS. Using the same approach, gene sequencing panel reports based on the design by Cutting et al[20] were included in the prototype EHR. Infobutton "i" icons were placed next to each clinical data element in both the EHR and embedded panel reports. Infobutton icons contained hyperlinks with HL7-compliant OpenInfobutton requests.

Population of the prototypes with data from sample laboratory tests and FHIR compliant JSON files
The gene panel prototype was populated with data from three case vignettes developed by Cutting et al.[20] and sample laboratory test reports from Integrated Genetics[29]. To demonstrate the use of the FHIR standard, data in the EHR prototype were represented according to FHIR resources. Example FHIR resources were selected from two openly available FHIR servers: HAPI (hapifhir.io) and Health Services Platform Consortium (HSPC) Sandbox (sandbox.hspconsortium.org)[30]. Using these sample resources as guidelines, FHIR compliant JSON files with FHIR resources were created for three sample patients. These FHIR compliant JSON files were utilized to populate the prototype EHR.

Results

Configuration of ClinGen and other genetic resources in OpenInfobutton
Eight genetic knowledge resources selected by members of the ClinGen EHR Work Group were configured for EHR integration using LITE (Table 1). Although only one (PharmGKB) out of the eight genetic knowledge resources was compliant with the HL7 Infobutton Standard, we were able to successfully connect with all eight resources. Profiles were created for each resource by setting the base URLs, EHR contexts, support for standard terminologies, and mappings between resource-proprietary parameters and the HL7 Infobutton Standard (for resources that were not HL7-compliant). The infobutton user was selected as "Provider" for each resource.

Table 1. Summary of the knowledge resources connected through the HL7 Infobutton Standard via LITE.

Infobutton Resource	Information Available	EHR Context
ClinGen Allele Registry	Identifiers for genetic variants	Genetic Lab Review/Entry
ClinGen Curated Summaries	Gene-drug interactions and genetically caused diseases	Problem List Review/Entry
ClinVar	Clinical significance of known genetic variants	Genetic Lab Review/Entry
CPIC	Clinical guidelines on genetic testing and treatment related to pharmacogenomics	Medication List Review/Entry
GeneReviews	Genetic disease knowledge management	Problem List Review/Entry
Genetics Home Reference	Consumer health information	Genetic Lab Review/Entry
Genetic Practice Guidelines	Genetic disease guidelines	Problem and Medication List Review/Entry
Genetic Testing Registry	Genetic tests and laboratories	Problem List Review/Entry
PharmGKB	Curated pharmacogenomics knowledge base	Medication List Review/Entry

Development of a prototype EHR with gene sequencing panel reports coupled with infobuttons
The EHR prototype is available at http://lite.bmi.utah.edu/ClinGenDemo/Interface_Project/main.html. Four sections were created in the prototype EHR user interface (Figure 1): *Patient Profile*, *Problems*, *Medications*, and *Results*. The

Patient Profile tab contains patient demographics, allergies, future appointments, and a history of past appointments. These data were populated from the following FHIR resources respectively: *Patient, AllergyIntolerance, Appointment,* and *Encounter*. The *Problems, Medications,* and *Results* tabs were populated by *Condition, MedicationStatement,* and *Observation* FHIR resources respectively. The *Problems* and *Medications* tabs are formatted as lists of buttons that, when clicked, present relevant metadata (e.g., onset date, "last updated", prescription date). The *Results* tab is also presented as a list of buttons that, when clicked, show other genetic information such as the clinical significance and a single nucleotide polymorphisms (SNP) identifier (if available), as well as a link to the referenced multi-gene sequencing panel report (Figure 2). Each panel report contains infobuttons next to the gene and variant names. Infobuttons were also integrated into the EHR next to the conditions, medications, and genes/variants. A dropdown list on the top right of the EHR prototype contains the patient names. When a name is selected, the information from the corresponding patient's JSON file is extracted and presented via the EHR interface.
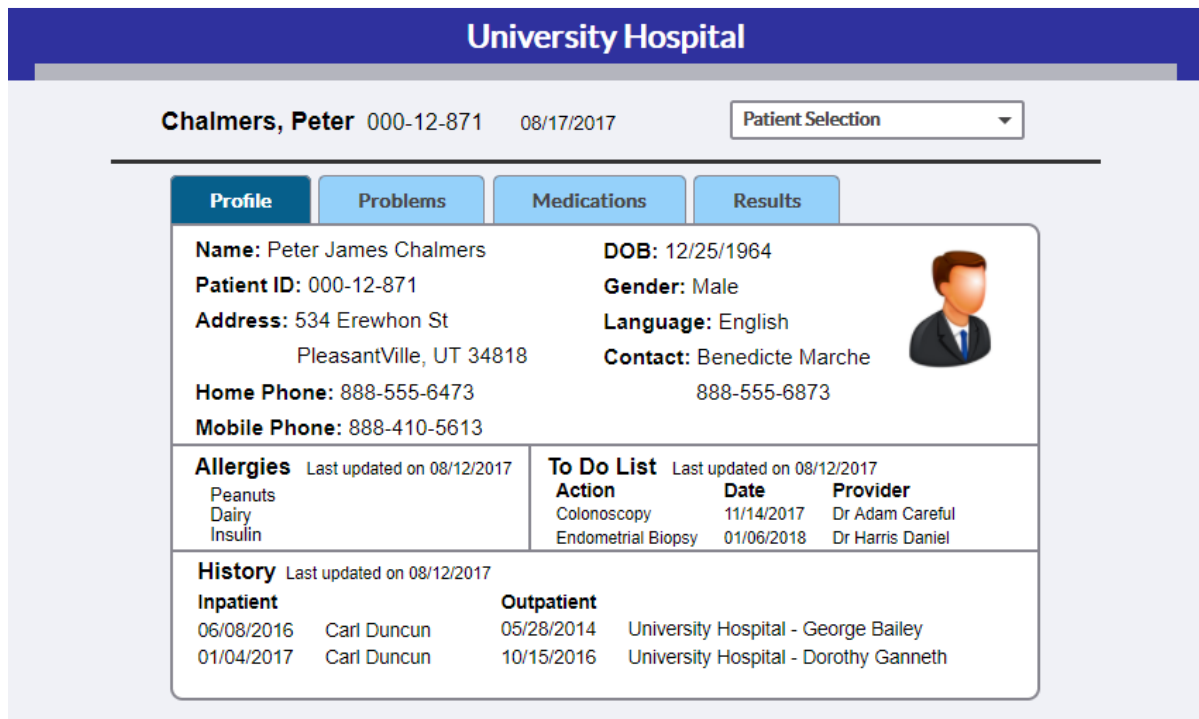

Figure 1. Main screen of the EHR prototype showing the *Profile, Problems, Medications,* and *Results* tabs which can be accessed by clicking on the respective tab headings.

Figure 2. An example of genetic laboratory results as shown in the *Results* tab. A clinician can click on individual results to view the Clinical Significance, SNP, and a link to the full laboratory report from which each result is retrieved. The infobutton "i" icons can be clicked to send HL7-compiant requests to OpenInfobutton to retrieve information on the clinical interpretation of each result.

Infobutton links included a URL-based request to OpenInfobutton including seven parameters, four of which represent the context of the EHR (Table 2). Figures 3 and 4 show examples of the user interface returned by OpenInfobutton after an infobutton is clicked.

Table 2. List of parameters included in the HL7-compliant infobutton request sent by the prototype EHR to OpenInfobutton.

| Infobutton Request URL Segment	Use	Example values
http://service.oib.utah.edu:8080/infobutton-service/infoRequest	Base URL of the knowledge resource	---
representedOrganization.id.root	Domain name of requesting organization	ClinicalGenome.org
taskContext.c.c	Context of EHR task	PROBLISREV, MLREV, GENEREV, VARREV
mainSearchCriteria.v.c	Search term code	LOINC, or SNOMED-CT codes
mainSearchCriteria.v.cs	Search term code system	Code system identifier
mainSearchCriteria.v.dn	Search term	Display name
informationRecipient.languageCode.c	Language	English, Spanish
performer	Role of person wanting results	PROV (provider)
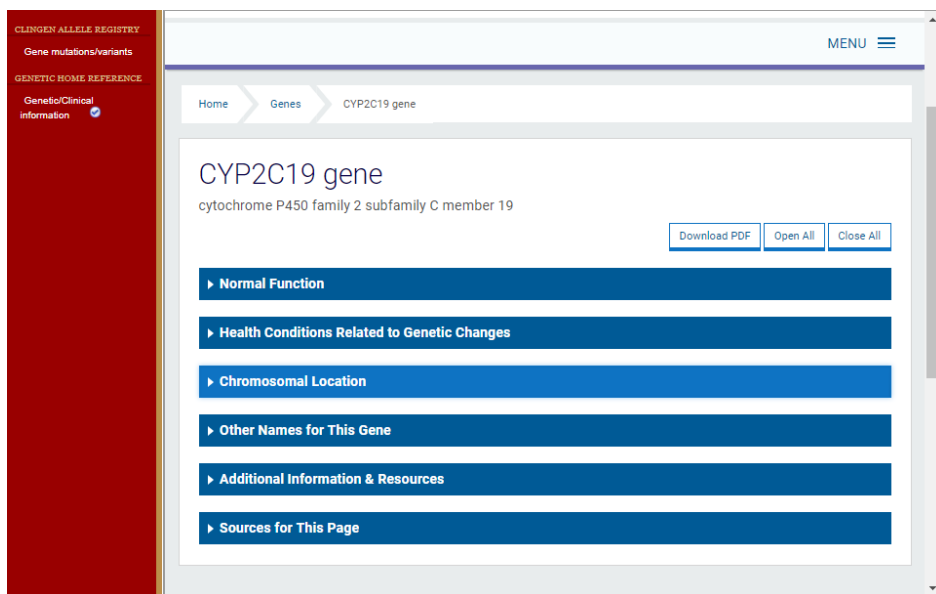
Figure 3. User interface returned from OpenInfobutton in response to a request for information on the gene "HNF1A" when a provider is reviewing the patient's lab result list. This example shows a resource that could be used for both clinicians and patients.

Figure 4. User interface returned from OpenInfobutton in response to a request for information on the variant "c.681G>A" when a provider is reviewing the patient's lab result list. This shows an example of a clinician resource known as "ClinVar."

Population of the EHR prototype with data from sample laboratory tests and FHIR compliant JSON files
The gene panel prototypes were populated with information about the variant results of the test, the clinical significance, a brief interpretation summary, clinical recommendations, and information about the test itself (Figure 5). References sited within the test are also provided, allowing clinicians to check the sources.

Figure 5. Multi-gene paneling report, which can be accessed from the *Results* tab. The infobutton links request provider reference information related to genes or variants in the context of genetic test results review.

A *Bundle* FHIR resource, which holds an embedded list of other FHIR resources, was created for three sample patients, each containing all the resources necessary to populate the EHR prototype (see table 3 for all resources implemented). Table 4 displays the genetic FHIR extensions required to bind each genetic data type, allowing for additional genetic information to be supported outside of the *Observation* resource. Standard terminologies were used within each FHIR resource as follows: SNOMED-CT for problem list items, medications, and allergies; HGNC for gene names; and LOINC for laboratory tests. The resources for each patient were validated as FHIR compliant by uploading them to the HAPI server, which passes all data through a FHIR-JSON validator before storing to the backend[30].

Table 3. Links to example JSON FHIR resources.

FHIR Resource	Example JSON URL
Patient	http://fhirtest.uhn.ca/baseDstu3/Patient/cf-1499797715321/_history/1?_format=json
AllergyIntolerance	http://fhirtest.uhn.ca/baseDstu3/AllergyIntolerance/cf-1500043653189/_history/1?_format=json
Appointment	http://fhirtest.uhn.ca/baseDstu3/Appointment/cf-1500043688254/_history/1?_format=json
Encounter	http://fhirtest.uhn.ca/baseDstu3/Encounter/cf-1500043817379/_history/1?_format=json
Condition	http://fhirtest.uhn.ca/baseDstu3/Condition/cf-1500043739116/_history/1?_format=json
MedicationStatement	http://fhirtest.uhn.ca/baseDstu3/MedicationStatement/cf-1503330877335/_history/1?_format=json
Observation	http://fhirtest.uhn.ca/baseDstu3/Observation/cf-1500043993905/_history/1?_format=json

Table 4. FHIR Extension references for genetic data types.

Genetic Resource Type	Extension URL
Gene	http://hl7.org/fhir/StructureDefinition/observation-geneticsGene
DNA Sequence Variant Name	http://hl7.org/fhir/StructureDefinition/observation-geneticsDNASequenceVariantName
Allelic state (Zygosity)	https://www.hl7.org/fhir/extension-observation-geneticsallelicstate.html
Amino Acid Change Name	http://hl7.org/fhir/extension-observation-geneticsaminoacidchangename.html
DNA Variant Id (SNP)	http://hl7.org/fhir/StructureDefinition/observation-geneticsDNAVariantId

Discussion

Clinical Significance

We have developed a prototype EHR with a multi-gene sequencing panel report to test and demonstrate the feasibility of infobuttons to provide clinicians with access to relevant genetic knowledge resources at the point of care. This project demonstrated that several knowledge resources could be integrated with a prototypical EHR through a standards-based approach. It also shows how genetic data and infobutton capabilities can be integrated into an EHR user interface. Health care organizations can follow similar steps to implement this functionality within their EHRs in real health care settings.

We were able to configure eight genetic knowledge resources using LITE, with no need for programming or changes to the underlying OpenInfobutton software. Our experience supports the findings by a usability study conducted by Jing et al., which found that medical librarians were able to configure resource profiles in LITE without any formal training[31]. URL-based, HL7-compliant infobutton requests were also easy to implement into the prototype EHR. Similar experiences have been reported in interviews with implementers of the HL7 Infobutton Standard[18]. Meaningful Use certified EHRs must be able to connect to knowledge resources using the HL7 Infobutton Standard[18]. Therefore, the functionality demonstrated in our prototype EHR can also be implemented within any certified EHR that is configured to use OpenInfobutton. Detailed documentation on how to deploy and use OpenInfobutton is available at http://www.openinfobutton.org/documentation. Three deployment alternatives are available: (1) access a cloud-based

instance, such as the one hosted at the University of Utah (not production-level, available only for development and demonstration purposes); (2) download and install a virtual machine that includes all the OpenInfobutton software; and (3) pull the source code from OpenInfobutton's GitHub repository and build it within the target deployment environment.

A usability issue to consider when implementing infobuttons in an EHR system is how the infobutton interface is presented to the user. The prototype in this study is coded in such a way to have the interface appear in a new window. However, the infobutton interface can be presented in any way the EHR system developer sees fit, whether in a new window or as a "popup" in the same window. An advantage of showing the interface through a "popup" window is to minimize workflow interruptions. However, showing the interface in a new window allows for multiple infobutton interfaces to be open at once. EHR system implementers will need to consider which option best suits their system when integrating infobuttons.

Challenges and Limitations

The vast majority of genetic knowledge resources were not designed for use by clinicians at the point of care and are not yet compliant with the HL7 Infobutton Standard. Therefore, most of the resources required manual mapping of the resources' API parameters to the Infobutton standard. Those mappings were stored within the resources' profiles in the infobutton manager and are available for use by any healthcare organization that uses OpenInfobutton.

We faced several interoperability challenges related to the lack of support for standard terminologies in the genetics domain. Knowledge resource APIs and EHR systems do not support gene standard terminologies, such as HGNC.[19] To address this limitation, we created infobutton requests only with gene names. A similar problem was faced with allele variants. Representing genetic panel reports within FHIR requires the use of a standard terminology to uniquely identify the different kinds of panels. EHR Meaningful Use criteria requires adoption of LOINC to encode laboratory test panels and results. However, LOINC does not currently provide a comprehensive set of concepts for the growing number of available the genetic sequencing panels. Therefore, in the *Observation* resources created, a general LOINC code, corresponding with the term "Genetic analysis report", was used for the terminology code in the *Observation* resources.

Genetic labs still provide their reports primarily in unstructured, PDF format, which imposes a challenge to infobutton integration since discrete genetic results are required for auto-generated infobutton requests[32]. The sample laboratory reports leveraged to populate the prototype multi-gene sequencing panels were all in PDF format, thus the data had to be loaded into the prototype EHR manually. Similar difficulties will be found in clinical practice until structured, standards-compliant genomic testing reports are more widely implemented.

Future Work

Future studies include investigating the usefulness of infobutton responses to clinical genomics inquiries in clinical practice. Ongoing efforts are focusing on continuously expanding, updating and improving OpenInfobutton resource profiles for clinical genomics. Future plans also include deploying access to clinical genomics resources via infobuttons in patient care settings. As mentioned previously, several options are available to facilitate deployment of OpenInfobutton at different healthcare organizations.

Conclusion

There is a critical need to provide clinicians with efficient access to clinically actionable genetic information at the point of care. We developed a prototype that demonstrates an approach to help address this need using standards-based functionality that is required for EHR certification in the Meaningful Use program.

Acknowledgements

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