Advancing Interoperability of EHRs for Genomic Interpretation: A SMART on FHIR App for Community Oncologists

Abstract

The American Society of Clinical Oncologists (ASCO) held a Data Standards and Interoperability Summit in May 2016, under the auspices of the ASCO Health Information Technology (Health-IT) Workgroup, to identify unmet Health-IT needs and potential solutions in current clinical oncology practice. Severe deficiencies were identified in Omics and Precision Oncology and in Advanced Interoperability. To address these issues, ASCO convened two complementary workshops: the "Omics and Precision Oncology Workshop" in October 2016 and the "Advancing Interoperability Workshop" in December 2016. This article relates the recommendations of the "Advancing Interoperability Workshop," regarding a proposed software application (app) to help community oncologists interpret the flood of information generated by genomic cancer laboratories and molecular testing facilities. The proposed app will facilitate the searching of multiple authoritative knowledge bases with a single entry of genomic data. It will be designed using a the interoperable SMART on FHIR platform for electronic health records (EHRs). The app will also provide access to Clinical Decision Support tools, serve as an educational resource for oncologists and patients and provide feedback regarding usability and efficacy to the designers. Although the intention is to help community oncologists bring genomic data into clinical practice for the benefit of patients, the tool will also be useful for clinical outcomes research.

Introduction

The ASCO Data Standards and Interoperability Summit was held in May 2016, under the auspices of the ASCO Health Information Technology (Health-IT) Workgroup. It was unanimously decided that four areas of current oncology clinical practice have pressing unmet Health IT needs. These included Omics and Precision Oncology, Advanced Interoperability, The Engaged Patient, and Value-Based Oncology. To address the issues of Omics and Precision Oncology and Advanced Interoperability, two complementary workshops were convened., the "Omics and Precision Oncology Workshop" was held in October, 2016 and the "Advancing Interoperability Workshop" followed in December, 2016. The report of these dual meetings, entitled, the "Omics and Precision Oncology Workshop" proposed the development of a genomics software application to aid community oncologists in the interpretation of ever-increasing volumes of genomic data critical for treatment selection[1]. This article reports the results of the second workshop, the "Advanced Interoperability Workshop."and proposes a *SMART on FHIR App for Community Oncologists*.the

Despite the increasing availability of genomic data, medical oncologists and molecular tumor board coordinators lack defined processes for utilizing information about the genomic alterations found in recurrent or metastatic tumors. Community oncologists have expressed increasing frustration and mounting concern over the growing magnitude of genomic information they are required to review and interpret. The inadequacies of tools

available in or outside of EHRs to capture, analyze, visually present, and store data, to make effective use of this information difficult to potentially impossible to achieve in a timely manner. Four critical concerns have been identified: (1) Most genomic data obtained from the genomic laboratories and subsequently stored in the EHR is unstructured and thus not actionable for clinical decision support (CDS); (2) Genomic nomenclature is poorly standardized; (3) Genomic data results interpretation and nomenclature may be different from laboratory to laboratory (4) The majority ofg oncologists lack formal genomic training to interpret the data and therefore may require expert assistance (seldom available in smaller communities).

To address these concerns, the *SMART on FHIR App for Community Oncologists* proposes to link the patient's EHR to patient-specific genomic data from the genomic cancer laboratory and to multiple genomic knowledge bases for corroborating and confirmatory information. Initially, the app will identify two approved knowledge bases to help adjudicate conflicting interpretations and recommendations. In addition, a built in feedback function will query the user's reason for using the app, user satisfaction with the app, actions taken based on information the app provided, what treatment was administered, the value of clinical trial information given and whether the patient joined a specific trial, the ultimate outcome of the patient, and potential suggestions for improvement. Finally, the app will also serve as an educational resource for oncologists, and in the future, their patients. For future extensions of the app, ASCO or others will serve as the aggregator of knowledge bases, recognizing these knowledge bases will continue to evolve and compete for the status of "best of breed." While the intention is to help community oncologists bring genomic data into clinical practice for the benefit of patients, the tool will also be useful for clinical research**.**

Approach

As the task given to Workshop participants was to develop a set of specifications for a proposed app, the first area of discussion was which platform to use. To ensure interoperability with as many EHRs as possible, the participants selected a state-of-the-art platform for app development, SMART on FHIR. This platform runs substitutable medical apps reusable technologies (SMART)[4] on fast healthcare interoperability resources (FHIR).[5] It utilizes state-of-the-art data and interoperability standards and is dependent on Application Programming Interface (API)-enabled EHRs.[6] Health IT apps and API-enabled EHRs working together have the potential to allow oncology providers to quickly and efficiently obtain patient demographics and cancer-related information from the EHR, to capture external data such as genomic reports, and to provide links to up-to-date Knowledge Bases, such as genomic Knowledge Bases that currently are not available within existing EHRs, in order to create cancer treatment plans, summaries, and survivorship care plans.[7]

Health IT Apps have the Potential to Provide Specialty-Specific Tools

SMART on FHIR apps, which are able to run anywhere in a real plug and play modular EHR environment, may fundamentally enhance EHR usability and electronic workflows and create the FHIR and API-based information economy[8] **(Fig. 1)** by providing tools for real-time precision medicine, evidence-based and evidence-generated medicine; measurable quality improvement; real-time registry reporting; deep data analytics; and patient-generated/patient-sent data. Furthermore, it will allow value-based care (patient outcomes, adverse events, and costs) for our healthcare system and support rapid learning systems, such as ASCO's CancerLinQ.[9]

Current Genomic Workflow

In a typical scenario, when a patient with recurrent or metastatic tumor presents for treatment, a medical oncologist will order a genomic analysis of the tumor, its circulating tumor cells, or circulating tumor DNA. In turn, the genomics laboratory summarizes the results of their analysis in an unstructured narrative report (often 20 pages or more in length). The report describes a set of genes, including the variants and genomic alterations found in those genes. The variants are characterized as benign, pathogenic, as variations of unknown significance (VUS), or as actionable or not actionable. Additionally, the report suggests potential targeted therapies (that may or may not be FDA-approved) and lists relevant clinical trials based on the variants found. The report is usually scanned into the EHR in PDF format, where it persists as unstructured data. Findings reported by laboratories include three major types of gene abnormalities: single nucleotide variants (SNVs), structural variations (amplifications, deletions [CNVs]), and rearrangements (fusions, translocations). The current state of somatic next-generation-sequencing (NGS) panel reporting often does not meet the user's needs because the reports are lengthy and dense without clear actionability. The reports may also be out of date by the

time they are reviewed or may reflect the bias of specific curators or the curation efforts of a single institution/laboratory. Therefore, after reviewing the report, the oncologist or the molecular tumor board coordinator often accesses and queries PubMed[10] along with available knowledge bases (such as My Cancer Genome[11], ClinVar[12] or CiVic[13]) to collect more comprehensive and up-to-date information. Each knowledge base returns information about each disease-gene-variant combination depending on whether that Knowledge Base has previously curated/reviewed the combination **(Table I).** Every time the oncologist or molecular tumor board coordinator queries a new knowledge base they must reenter the patient's data.

Design Specifications

So based on my understanding, this is the database which arises from continued queries to CiViC and MyCancerGenome, not another data entry thing.

The app will be built in several phases, each phase delivering increasing functionality and capability. In Phase 1, the app will be constructed as a standalone minimally viable product (MVP). As the name implies, the MVP will have just enough features to gather validated learning about the product and its future development, but it will not connect to the patient's EHR. Hence, initially, the User will enter the patient's genomic information, once, using a convenient drop-down list of the various gene/genomic alteration combinations and cancer types. This version will be distributed to selected users for validation.

In Phase 2, the app will have enhanced functionality and will be linked with the patient's EHR. This version will be distributed for general use and will also be available as a Web app, independent of the EHR.

Phase 3 and beyond will accommodate advanced functionalities that will be added on an as-needed basis. From the start, the app will be built in modules to allow the addition of functionality over time.

1. Login and Authentication

To access the knowledge bases within the app and fulfill the respective licensing requirements, the User must log in and be authenticated. In Phase 1, therefore, a login will be required to use the app. The User will be required to register an email, which will then be authenticated. Once the email is authenticated, it serves as the login credential without need for a password.

In Phase 2, login and authentication will be accomplished by the standard SMART on FHIR approach (OAuth2-based), and the app will launch within the patient's chart. Information will be communicated to the app by a SMART on FHIR/OAuth data exchange between the EHR and the app.

2. Data Entry

Phase 1: The User navigates to the ASCO Genomics web site, opens the app, and enters the patient's genomic information manually, once, using a convenient drop-down list.

Phase 2: The User navigates to the ASCO Genomics website and enters the patient's name, EHR number, and institution to access the EHR. The SMART on FHIR app is launched within the EHR. The app automatically populates the fields for user name, patient name, patient age, gender, and cancer type. The User then enters the patient's genomic information, once, using a convenient drop-down list of the various gene/genomic alteration combinations and cancer types. At least 1 (preferably 2) SMART-enabled EHR will be chosen, and the SMART on FHIR app will have functionality with the EHR. Once the SMART on FHIR app is constructed, it should be usable on any SMART on FHIR-enabled EHR.

3. Cloud Database

So based on my understanding, this is the database which arises from continued queries to CiViC and MyCancerGenome, not another data entry thing.

A database **(Table II)** containing the results obtained from the Knowledge Base interactions will be created and stored on the cloud. No protected health information (PHI) will be stored in this database.

User Interface for Entering Data in the Database I think they mean "UI for constructing knowledge base queries"

To use the Knowledge Base, the app must transmit a finite set of information, specifically noted as required fields. The user interface will be produced as a web page usable in a browser or in the SMART on FHIR App. The fields for the User interface are shown in **Table III.** Some of the fields will be equipped with pulldowns where the list will be provided from a dictionary.

The gene, genomic alteration, and characterization fields are displayed in individual rows. As one row is filled, a second row appears to allow entry of a second gene/genomic alteration. The ability to delete a row is required. A button is available to send data to the aggregator.

In Phase 1, the app will also be designed for access via a web site independent of the EHR. Only the ID (unique number associated with this interaction) and date are filled in. No other fields are pre-filled, and required fields are entered manually, some via a pull-down as marked in Table III.

In Phase 2, the proposed app will be available through the EHR, using the most generalizable technology currently available, that is, the SMART on FHIR app platform. Some data may be pulled from the EHR to prepopulate the available fields and other data will be manually entered.

In the future, some of the data will be prepopulated from the EHR and lab data may be uploaded from a laboratory report, such as Foundation Medicine, when an xml version of the report is available. The xml report can be saved to the hard drive of the User's computer and an upload button will permit the User to pull the data into the appropriate fields. If the ID for a previous interaction is entered, a button will be constructed to prepopulate the data fields from the past query for the particular patient. A field to allow one to select a lab for upload can be filled by a pulldown. A button allows upload from a lab report saved to the host computer.

Pull-Downs

Since typing in long strings of text for gene names and genomic alterations is time consuming, prone to error, and could potentially use variant or gene names not supported by the Knowledge Base, the pulldown list was determined to be the best solution. As noted in Table III above, pull-downs will be used for multiple fields. When the Knowledge Base offers a customized dictionary, the contents will be provided in the specifications. When an external dictionary is accessed, the dictionary source will be provided usinfg that dictionary's the specifications. Another example is shown in **Table IV.**

In Phase 1, the pulldown list for cancer, gene, genomic alteration, and characterization will be constructed using standard terminology if possible. The contents of the list will be determined by the elements available in the Knowledge Base(s). These entries will be curated into a database external to the app located in the FHIR server and accessible as a service. This service will be accessed by the app to populate the pulldown. An interface to allow updating of the database will be maintained.

In Phase 2, the implementation guide/specifications for the API for each Knowledge Base will hopefully have a list of accepted entries for accepted data points. These entries will become the source data for the pulldowns.

Selection of the Patient

Phase 1, none. Patient name and data will be manually entered.

Phase 2, the patient's record in the EHR will be accessed in the usual fashion. When the SMART on FHIR App is called, the patient identifier will be assigned per the SMART on FHIR protocol.

Data from a Lab

Most labs provide their reports on paper or in PDF format, neither of which is machine readable, and therefore manual re-entry of data is required to obtain Clinical Decision Support. Some labs, such as Foundation, provide a structured lab report that is machine readable. These are usually in xml format. Ideally, the lab report should be directly uploaded into the app without manual data entry. However, this functionality will not exist during Phase 1 **(Fig. 2).** During Phase 3, the data will be uploaded from a lab message when available and if permitted under data usage agreements with the lab. In Phase 3, we will select a lab that provides reports in xml format, and a custom upload will be designed for that lab. The upload function will allow uploads from more than one lab, each with their own custom upload, as they become available, although only a single lab upload will be required in Phase 2 **(Fig. 3).**

4. FHIR message

The data transmitted to and returned from the server should follow FHIR format. This will maximize the possibility for other apps to interact with modules of this app. FHIR resources may exist already for transmitting much of the data. Where resources do not exist, extensions will be created.

Request

An FHIR bundle will be identified or created to transmit the patient's cancer type, gene, genomic alteration, and characterization. This message will be sent to the FHIR server, authenticated, and acted upon as described below.

FHIR Server

Under ideal circumstances, the data is transmitted to and from the interface using a standard FHIR message. However, current Knowledge Bases are not FHIR compatible, and in most cases, use a home-grown format to interact with their API. Our goal is to have the User enter the data once and receive their results initially from two Knowledge Bases, adding additional Knowledge Bases over time. To accomplish this task, the server will accept the data via an FHIR message, it will translate the data into the appropriate unique message for each API, then it will send the data with authentication and with the protocol required by each API, and receive the result from the API. The results from multiple APIs will be translated and bundled together in a single FHIR message and transmitted back to the interface.

For the Phase 1 prototype, a server will be constructed to accept a single FHIR message and then send out API-specific messages to the two initial Knowledge Bases. It will also receive the return API-specific results message from each API. The ability to add new Knowledge Bases to the service capability as they become available is critical. Therefore, the aggregating server will be extensible to permit the addition of new Knowledge Bases as APIs become available. The server will then accept the results message from each API, map that message to the return FHIR message, and send the message back to the app. Each Knowledge Base API implementation will differ as outlined below.

a. Server receives FHIR message and translates it into several API-specific messages
b. An API-specific message is created from the FHIR message for the API of each respective Knowledge Base
c. Each message is sent to the API from each respective Knowledge Base
d. The server receives the result from each API for the respective Knowledge Bases
e. Results are translated into the FHIR message

Not every request to a Knowledge Base will return an answer. If a variant or gene is submitted and fails to elicit an answer from a given Knowledge Base, the app should record that gap in the field KnowledgeBaseGap. In Phase 2, a report will be generated periodically detailing which gene/genomic alteration combinations return a null answer from a given database. This potentially could be reported to the knowledge bases to help them improve and become more comprehensive. Future functionality will permit the results to be summarized, rated, and prioritized, and decision support will be developed capable of ranking these activities in order of importance.

Expected Results

An FHIR bundle capable of transmitting the information produced by the Knowledge Base will be identified or created. This message will be received from the FHIR server. The bundle will transmit a set of information for each gene that includes information similar to that found in Table I but with two additional categories, the current classification of that variant, and a list of known variants.

a. Reported pathogenic (y/n) – this may be a Yes default for some of the databases
b. Potential agent(s) (there are MANY agents for one alteration)
c. Description of this gene alteration in this cancer (TEXT STRING?)
d. Clinical Trial for which the patient is eligible

During Phase 2, a copy of the data transmitted and received is stored in a database to allow the user to re-query the knowledge base later without re-entering the information. Future functionality will include the ability to periodically re-query the service for each variant to look for updates. If a non-trivial change occurs in any Knowledge Base, the user will be notified. Non-trivial changes will be defined by the owner of the knowledge base management system (MS) and will likely be defined by upcoming FDA guidance.

Examples of non-trivial changes include:

a. New prognostic information relating to a gene alteration
b. New information about the efficacy, or lack thereof, of currently available FDA-approved treatments
c. Newly FDA-approved treatment with specific efficacy, or lack thereof, for the gene alteration
d. Newly available clinical trial protocol that uses gene alteration as an eligibility criteria

5. Knowledge Bases

Multiple knowledge bases currently exist that curate interactions between cancers, genes, and gene anomalies and produce reports to help physicians use that information. The knowledge bases we have selected for initial app development include are CIVic (https://civic.genome.wustl.edu/#/browse/variants) and MyCancerGenome (MCG). These Knowledge Bases were selected because they are freely available and have a usable API with well-documented specifications. During Phase 1, we will identify specifications for using APIs for CIVic and MCG and code the server to send and receive data.

The steps necessary to acquiring an analysis from the Knowledge Base are the same for both phases of development. Briefly, after the patient's information is entered into the app, it is conveyed to the supported Knowledge Base and the app receives and displays the response in the EHR. Since the queries are saved, Knowledge Bases can be re-queried in the future without the need to re-enter the data.

Results Interface

The results returned by the Knowledge Bases will need to be displayed for the user. This display should at a minimum show the output of multiple Knowledge Bases. However, over time, the output should be consolidated, validated, and prioritized to help the clinician know what is the most relevant and important information for his/her patient. In Phase 1, all of the results will be displayed for each Knowledge Base without ranking or interpretation. In Phase 2, the results may be printed or copied and pasted into another document. Future functionality will accommodate PDFS that can be uploaded into the EHR as a note. The ultimate goal is to provide structured data, which will be entered into the EHR.**Future Functionality**

Over time, we envision having a database that periodically queries the aggregated Knowledge Bases for updates and automatically notifies the oncologist of important changes. Some examples of future functionality include:

a. Genomics app provides links to useful clinical decision support genomic educational material
b. Genomics app provides genomic information suitable for updating CancerLinQ and other secondary data purposes
c. Genomics app provides genomic education, genomic reporting and updates for the patient, other providers, and caregivers
d. Genomics app provides genomic data to ASCO's clinical oncology treatment plan and summary dashboard (COTPS) and the survivorship care plan (SCP) template
e. Genomics app provides extensions for Family History tool with family pedigrees, Cancer Risk information, Clinical trials and other appropriate genetic and genomic data for EHR supplementation and enhancements
f. Work with future AJCC Cancer Staging app

Other future functionality may include new prognostic information, as new knowledge and population-health analyses provide additional insights.

Discussion

The ASCO Interoperability Workshop has identified the need for an app to aid oncologists in interpreting the increasing volume of patient molecular data generated by genomic cancer laboratories and testing facilities. We believe the proposed *SMART on FHIR App for Community Oncologists* will have many important capabilities. The app will link laboratories directly to the patient's EHR, as well as to multiple authoritative knowledge bases. The use of SMART on FHIR will allow easy integration with the largest number of EHRs. By building on an interactive suite of modules, allowing for future use of any or all modules in other apps. The app will include a function for gathering user feedback on multiple parameters. It will also provide access to Decision Support Tools and thereby serve as an educational resource for oncologists and future patients. It will also set the stage for ASCO or others high quality knowledge bases, recognizing that contenders will constantly be competing and newcomers will require evaluation. While the current focus is on helping community oncologists bring genomic data into clinical practice, there was a consensus among participants that the tool will also be useful for clinical research**.** Ultimately, we anticipate that these Clinical Decision Support and SMART on FHIR apps should help ASCO and its members better integrate genomic data into clinical practice.

Figures Legends

Figure 1. FIHR and API (Apps)-Based Information Economy.

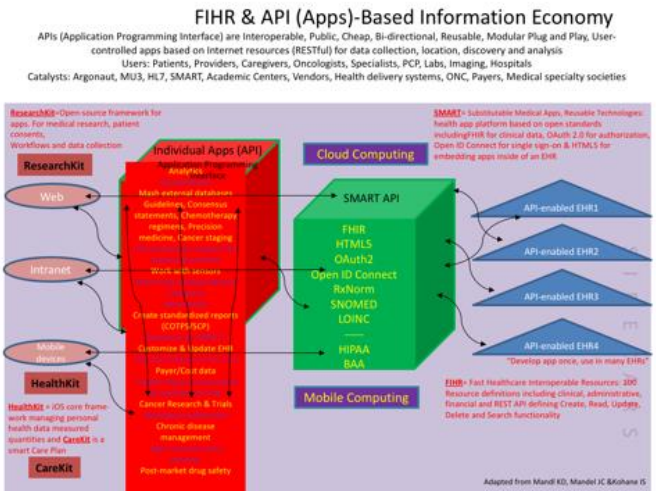


Figure 2. Phase 1 laboratory data.

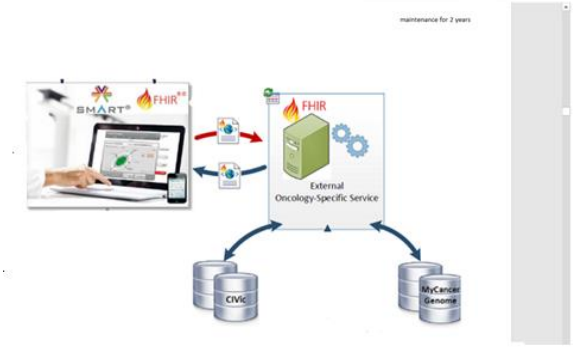
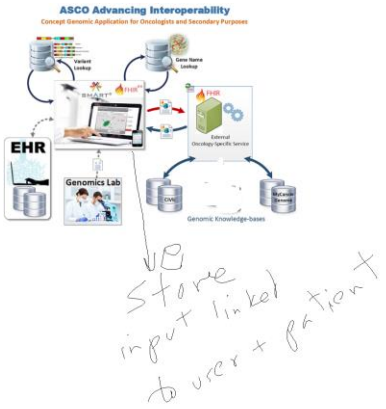


Figure 3. Phase 2 Laboratory data/



Tables

Table I. Findings Obtained from Knowledge Base for a Curated Gene Variant

"Properties" (description) of the gene in cancer
"Implications" (or suggested treatment options) specific to that variant
"Clinical Trials"
"Text" describing the variant with embedded hyperlinked references
"Date of last update"

Table II. Database for Cloud Storage

Data field	Interface	Pulldown	Dictionary	Store	Example/Explanation	Times Per Interaction	Linked
New Analysis (Yes/No)	Both	yes	Custom	yes			
Name	Both			no		1	
MRN	Both			no		1	
Gender	Both	yes	Custom	yes		1	
Cancer type	Both	yes	Custom	yes		1	
Gene	Both	yes	Derive	yes	Derive pulldown list from Knowledge Base used	Many	a
Genomic alteration	Both	yes	Derive	yes	Derive pulldown list from Knowledge Base used	Many	a
Characterization	Both	yes	Derive	yes	Derive pulldown list from Knowledge Base used	Many	a
Lab	Both	yes	Custom	yes		1	
age	Both			yes	48	1	
Date	Both			yes		1	
ID	Both			yes	Unique number associated with this interaction	1	
Institution	Both			Yes		1	
User	Both			Yes		1	
Functional status	Result			yes		Many	a
Alteration Type	Result			yes		Many	a
description	Result			yes		Many	a
Protein effect	Result			yes		Many	a
Transcript effect	Result			yes		Many	a
DEPTH	Result			yes		Many	a
Amplification Deletion	Result			yes		Many	a
Copy Number	Result			yes		Many	a
Suggested Treatment	Result			yes		Many	a
Prognostic Implications	Result			yes		Many	a
Knowledge Base	Result						
Knowledge Base Gap	Neither						

*The gene-genomic alteration plus the ID will define the linkage with one row per set.

Table III. Required Fields

Data field	Interface	Pulldown	Dictionary		Example/Explanation	Required	
New Analysis(Yes/No)	Both	yes	Custom			Default to yes	
Name	Both					no	
MRN	Both					no	
Gender	Both	yes	Custom			no	
Cancer type	Both	yes	Custom			yes	
Gene	Both	yes	Derive		Derive pulldown list from Knowledge Base used	yes	
Genomic alteration	Both	yes	Derive		Derive pulldown list from Knowledge Base used	no	
Characterization	Both	yes	Derive		Derive pulldown list from Knowledge Base used	no	
Lab	Both	yes	Custom			no	
age	Both				48	no	
Date	Both					Prefilled	
ID	Both				Unique number associated with this interaction	Yes. Will be prefilled for new and can be overwritten with an older ID if this is a re-query	
Institution	Both	No	No			No	
User	Both	No	No			Yes	

Table IV. Custom v. External Dictionary

Gender	Both	yes	Custom
Cancer type	Both	yes	Custom
Gene	Both	yes	Derive
Genomic alteration	Both	yes	Derive
Characterization	Both	yes	Derive
Lab	Both	yes	Custom