Building Partnerships for Precision Medicine

Presented by:

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Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.
The Problem

How do we enable Precision Medicine at point of care?
SMART on FHIR Genomics standards to support development of clinico-genomic apps to communicate clinical genomics data between EHR systems.
HL7 Standards: V2, V3, CDA, FHIR

- V2- lots of implementations
- V3- nice models, few implementations
- CDA- document (V3-based, Reference Information Model)
- FHIR- lots of excitement, emerging standard, standard for trial use.
People metabolize drugs at different rates based on genes (e.g. TPMT for Azathioprine, an immunosuppressant given to prevent transplant rejection)

By determining TPMT activity, amount of drug given for particular patient can be optimized to reduce toxicity

IOM guide stated how to communicate such results via HL7 v2 Observation (and gave pointers for how to do it in FHIR as well)
DIGITizE: Displaying and Integrating Genetic Information Through the EHR

Establishing Connectivity and Pharmacogenomic Clinical Decision Support Rules to Protect Patients Carrying HLA-B*57:01 and TPMT Variants

An Implementation Guide

12/1/2015
Displaying and Integrating Genetic Information Through the EHR Action Collaborative (DIGITizE AC)

Version 1.0

DIGITizE AC Participants

Sandy Aronson, Partners HealthCare (co-chair)
J.D. Nolen, Cerner (co-chair)
Mark Adams, Good Start Genetics
Gil Alterovitz, Harvard Medical School
Brian Anderson, athenahealth
Jane Atkinson, NIDCR
Larry Babb, Partners HealthCare
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Gillian Bell, Mission Health
Adam Berger, FDA
Chris Chute, Johns Hopkins University
Chris Coffin, Invitae
Mauricio De Castro, U.S. Air Force
Carol Edgington, McKesson
Laurel Estabrooks, Soft Computer Corporation
Robert Freimuth, Mayo Clinic
Geoff Ginsburg, Duke University
Jennifer Hall, University of Minnesota
Stephanie Hallam, Good Start Genetics
AZA (Azathioprine)

TPMT Location: 6p22.3

Cytotoxicity

TGTP, TdGTP
**TPMT Gene Product Metabolic Activity Interpretation**

A new LOINC observation code, 79713-4: TPMT gene product metabolic activity interpretation, has been created precisely to support the requirement for the azathioprine use case. The details of the LOINC code follow:

<table>
<thead>
<tr>
<th>LOINC CD</th>
<th>Component</th>
<th>Long Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>79713-4</td>
<td>TPMT gene product metabolic activity interpretation</td>
<td>TPMT gene product metabolic activity interpretation in Blood or Tissue Qualitative by CPIC</td>
</tr>
</tbody>
</table>

**Part Definition/Description(s)**

The TPMT gene product metabolic activity interpretation is determined by the reporting lab and returned with the structured test results. It indicates the lab's interpretation of the phenotype that meets the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for reporting TPMT gene product metabolic activity (phenotype), regardless of whether the lab assay's method was genetic or enzymatic. This specific interpretation would be considered a separate observation made by the lab in addition to the primary reported results (e.g., genotype or measured activity level) and it could be included with other assay-specific observations, which would ideally support the interpretation value. [https://cpicpgx.org/resources.html](https://cpicpgx.org/resources.html)

**Answer List**

<table>
<thead>
<tr>
<th>Seq #</th>
<th>Answer</th>
<th>AnswerID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ultrarapid metabolizer</td>
<td>LA10315-2</td>
</tr>
<tr>
<td>2</td>
<td>Rapid metabolizer</td>
<td>LA25390-8</td>
</tr>
<tr>
<td>3</td>
<td>Normal metabolizer</td>
<td>LA25391-6</td>
</tr>
<tr>
<td>4</td>
<td>Intermediate metabolizer</td>
<td>LA10317-8</td>
</tr>
<tr>
<td>5</td>
<td>Poor metabolizer</td>
<td>LA9657-3</td>
</tr>
</tbody>
</table>

*based on the CPIC Delphi Survey

For an Intermediate metabolizer TPMT gene product metabolic activity interpretation observation...

```
OBX|ICW|79713-4^ TPMT gene product metabolic activity interpretation ^LN
8^Intermediate metabolizer^LN-ANS
```

**LA10317-8**
Hughes RiskApps: Less work + CDS = Higher Quality

Patient enters data into Tablet PC

Risk Engine WebService

HL7 V3 Þ FHIR Genomics

Reviews Intuitive Report & suggested management

Genetic Testing

Patient educational materials

Courtesy: Dr. Kevin Hughes, MGH

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Patient Lifestyle Question

Cancer Risk Assessment

How many alcoholic beverages do you consume weekly?

- 5 - 9 drinks per week
- None
- Less than 1 drink a week
- 1 - 4 drinks per week
- 5 - 9 drinks per week
- 10 - 19 drinks per week
- More than 19 drinks per week

Clear
Pedigree/Breast Cancer Risk
Clinical Document Architecture (CDA)
GeneLC Test Report

Implementation Guide for CDA Release 2
Genetic Testing Report (GTR)
(Universal Realm)

Draft Standard For Trial Use
September 2012
CDAR2_IG_GENTESTRPT_R1
(Developer Documentation)
GTR - Design Principles

- Follow existing report formats commonly used in healthcare & research
- Emphasize interpretations & recommendations
- Provide general background information on tests performed
- Reference HL7 Clinical Genomics instances (e.g., v3 or v2 Genetic Variation and Pedigree) as the place holders of full-blown raw genomic data and fully-structured family history data
- Utilize patterns of ‘genotype-phenotype’ associations in the HL7 v3 Clinical Genomics Domain
  - Implement them as ‘clinical genomic statement’ entry-level templates (see next slide), enabling meaningful use of the data

Courtesy: Amnon Shabo
Genetic Testing Report

The GeneticTestingReport is a document template and thus serves as the root template for the GTR Implementation Guide. Its organization is described in the Approach section of this document. The sub-sections residing here constitute the backbone of the GTR. Most of them share a common structure represented by the Test Details Section which serves as a blueprint for most of the test-oriented sections like genetic variation or gene expression sections.

1. SHALL contain exactly one [1..1] code/@code="51969-4" Genetic analysis summary report (CodeSystem: 2.16.840.1.113883.6.1 LOINC) (CONF-GTR-1)

2. SHALL contain exactly one [1..1] title (CONF-GTR-7)
   • Default title is "Genetic Testing Report"

3. SHALL contain exactly one [1..1] component, such that
   a. Contains exactly one [1..1] Summary Section (templateId: 2.16.840.1.113883.10.20.20.1.1)

4. MAY contain zero or one [0..1] component, such that
   a. Contains exactly one [1..1] Genetic Variations Section (templateId: 2.16.840.1.113883.10.20.20.1.2)

5. MAY contain zero or one [0..1] component, such that
   a. Contains exactly one [1..1] Cytogenetics Section (templateId: 2.16.840.1.113883.10.20.20.1.4)

6. MAY contain zero or one [0..1] component, such that
   a. Contains exactly one [1..1] Gene Expression Section (templateId: 2.16.840.1.113883.10.20.20.1.3)

7. MAY contain zero or one [0..1] component, such that
   a. Contains exactly one [1..1] Other Testing Section (templateId: 2.16.840.1.113883.10.20.20.1.6)

8. MAY contain zero or one [0..1] component, such that
   a. Contains exactly one [1..1] Test Information Section (templateId: 2.16.840.1.113883.10.20.20.1.9)

9. Sections and subsections SHALL have a title and the title SHALL NOT be empty.

10. All sections MAY occur in any order except for the SummarySection which SHALL appear first and TestInformationSection which SHOULD appear last. Note that a TestInformationSection can appear in each of the specific test sections.

Courtesy: Amnon Shabo
General Features:

- FHIR clinical profiles aligned to MU2
- Patient record scope/authorization
- Authentication/Single-Sign on
- UI integration layer to launch within EMR
Genomic-Specific Features:

- Genomics integrated directly into clinical model
- First in FHIR DSTU 2.0, latest is tested FHIR Connectathon 11 Build
- Profiles on standard FHIR resources *plus* new resource (Sequence)
- Enables EMR to obtain genetic results: both non-sequence and sequence-based.
- Search-optimized GA4GH/raw sequence data
- Genomic data shadowing/constraints/mappings
SMART on FHIR Genomics: Clinico-Genomic Apps

1. Order Genetics Labs
   - EMR System
   - Diagnostic Order App
   - Diagnostic Reporter App
   - Sequencing Lab

2. Return Genetics Labs Results
   - FHIR Data Order
   - Demographics
   - Sequence

3. Present & Contextualize Genetics Labs Results
   - SMART on FHIR Clinico-Genomics Apps
   - SMART Precision Cancer Medicine App
     (Warner, et al, JAMIA, 2016)
SMART on FHIR Genomics LAB
- SMART Services
  - HL7 FHIR Genomics
  - GA4GH

Diagnostic Order App

Clinical data

SMART on FHIR EMR
- SMART Services
  - HL7 FHIR Genomics
  - EMR

Genomic data

Diagnostic Reporter App

CG Data

PCM App (at Point of Care)
https://gallery.smarthealthit.org
Genomics Advisor V2

Author: diabetes-monograph

Website: --

Last Update: Friday, February 19, 2016

Tags: Asthma & Allergies, Cardiovascular, Diabetes, Diagnosis, Genomics

App Description

Diabetes and related diseases risk analysis.

Related Apps

Other apps by diabetes-monograph

https://gallery.smarthealthit.org
Domain Analysis Model (DAM) for Clinical Genomics, Use Cases:

1. Specimen Identification
2. Clinical Sequencing (Germline)
3. Cancer Profiling (Somatic)
4. CDS (Family History and Drug Dosage Calculator)
5. Public Health Reporting
6. Clinical and Research Data Warehouses

...
Fast Healthcare Interoperability Resources

Clinical data

- Resource
- Extension
- Profile

Applications

Concise, easily understood specifications
Well-defined data model and API
Easy to implement
Modern (RESTful API, JSON, OAuth)
Extensible
FHIR Genomics Time Line

- **Sep 2015**: Added 1 Genetics Profile for Observation Resource
- **Dec 2015**: Added 6 Genetics Profiles + 1 Sequence Resource
- **Jan 2016**: Connectathon, Pilots, and Test scripts
- **Jul 2016**: Connectathon & Workgroup Feedback + Future Work

**STU3**

DSTU = Draft Standard for Trial Use
STU = Standard for Trial Use
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Actions to Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHIR could be included as an emerging standard, especially for transport of data. Argonaut may provide opportunities to advance. Sample uses of FHIR: authorization; genetics, family health history, build on current work on <strong>SMART on FHIR Genomics</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Apply accelerators (e.g., S&amp;I Initiative, pilot project, policy guidance) to existing standards by ONC</td>
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<tr>
<td>2016 PMI S&amp;I: Additional ONC investment in pilots of <strong>FHIR for PMI</strong> research/individual data donation use case</td>
<td>Apply accelerators (e.g., S&amp;I Initiative, pilot project, policy guidance) to existing standards by ONC</td>
</tr>
</tbody>
</table>

DiagnosticReport 1

Clinical context 1: condition, patient, ...

Observation 1
- Clinic info 1
- Sequence 1

Observation 2
- Clinic info 2
- Sequence 2

Sequence 3

Integrated into Clinical Data Model and Workflow
Genetics Test: Lab (Code) Only

DiagnosticOrder

FamilyMemberHistory

DiagnosticReport

Observation

Genetic Profiles
Introduce Links

Links

Observation
Genetics Test: Lab (Code) + Sequence Data

Genetic Profiles

- DiagnosticOrder
- DiagnosticReport
- FamilyMemberHistory
- Observation
- Germline / Somatic
- Sequence Resource

SMALL kilobyte

Data Resource

DNA or RNA or AA
Genetics Test: Lab (Code) + Sequence Data + External

Genetic Profiles

- DiagnosticOrder
- FamilyMemberHistory
- DiagnosticReport
- Observation

SMALL kilobyte

Germline / Somatic: Sequence Resource

BIG terabyte

Full Sequence Source – eg, GA4GH

DNA or RNA or AA
Actively working on pilots

National and International:
- MGH/Hughes RiskApps
- Cerner
- Intermountain
- GRIN (BCH/HMS, CHOP, Univ. of Cincinnati)
- Vanderbilt University
- National Marrow Donor Program / BeTheMatch
- Precision Link
- Genospace
- Allscripts/Nant Health
- Partners/GenelInsight/Medseq
- Hefei Institute of Technology in China
- Google (BCH/HMS)
- DNA Nexus/PrecisionFDA
- TBResist

Global Alliance federated queries SMART on FHIR Genomics server:
- Stratified Medicine Scotland Innovation Centre
- UCSC
- Royal Melbourne Hospital & Biogrid Australia
- Beijing Institute of Genetics, Chinese Academy of Science
- EMC R&D
- Wellcome Trust Centre for Human Genetics
- Harvard/MIT
- Aridhia Informatics
- Australia- Health Intersections
Building Partnerships for Precision Medicine:

FHIR Genomics Pilots

1. Pharmacogenomic clinic: Precision Link
   - Precision Link is the first the exclusively Pharmacogenomic clinic in the world. It already has around 40 providers actively using it.

2. Precision Medicine for global health: TBResist
   - This effort combines clinico-genomic data from over 20 countries for diagnostics and therapeutics for drug resistant tuberculosis - to enable targeted patient approaches. Consortium also was founded by Dale Nordenberg (former CIO of CDC).

3. Precision Medicine Cloud Computing: DNA Nexus/PrecisionFDA
   - DNA Nexus set up the precisionFDA portal (for testing genetic tests submitted to FDA) and working on setting up FHIR Genomics server/apps on their platform.
Gil Alterovitz

ga@alum.mit.edu

LinkedIn Contact:

Follow at: @fhirgenomics

Handout:
Acknowledgments

HL7
IOM
eMERGE
GA4GH
IGNITE
IEEE

SMART on FHIR
  Ken Mandl, Isaac Kohane, David Kreda, Rachel Ramoni, Josh Mandel...

SMART on FHIR Genomics
  Yao Hemming, Tom Chen, Peijin Zhang...