SMART-on-FHIR Genomics: Enabling Precision Medicine by Bridging Clinical and Genomic Information

Presented by:

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Today’s Presentation

The Problem: How to enable Precision Medicine at point of care.

Clinical Genomic Apps for EMRs
Precision Cancer Medicine

SMART on FHIR/FHIR/GA4GH
Precision Medicine
SMART on FHIR 2.1+
Use Cases
SORRY, SON... THERE'S NO APP FOR THAT
DB (Diabetes Bear) EMR App  
*Alterovitz & Yang*

Precision Cancer Medicine (PCM) App  
*Warner & Alterovitz*

Genomics Advisor App  
*Alterovitz & Zhang*
**Problem**

EMR apps only include clinical information, but genomics can add complementary information about risk of disease, drug susceptibility, and related conditions.

**Solution**

Create a module that can be integrated into disease-specific apps.

**Features**

Present relative risks of diseases based on patient's genotype.
SMART on FHIR

- **SMART Clinical server**
  - Get /Patient
  - Get /Medication
  - Get /Observation
  - Clinical data

- **SMART Genomic server**
  - Get /Sequence
  - Get /DiagnosticReport?profile=genetics
  - Genetic data

- **Google Genomics (Ga4gh)**
  - Call variantSet, readGroupSet
  - Reads, Variant info

- **Genomics Advisor**
  - Get /callSet
  - ...
Genomics Advisor Integrated with Ga4gh and 1KGP

SMART Genomics Advisor

Type 1 Diabetes

<table>
<thead>
<tr>
<th>SNP</th>
<th>Locus</th>
<th>CHRM</th>
<th>Code</th>
<th>Risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3129934</td>
<td>HLA-DRB1</td>
<td>6</td>
<td>CC</td>
<td>1.34</td>
<td>74.36%</td>
</tr>
<tr>
<td>rs4763879</td>
<td>CD69</td>
<td>12</td>
<td>AG</td>
<td>1.02</td>
<td>39.47%</td>
</tr>
<tr>
<td>rs9388489</td>
<td>C6orf173</td>
<td>6</td>
<td>GG</td>
<td>1.18</td>
<td>40.66%</td>
</tr>
</tbody>
</table>

Total Relative Risk: **1.61**

Type 2 Diabetes

<table>
<thead>
<tr>
<th>SNP</th>
<th>Locus</th>
<th>CHRM</th>
<th>Code</th>
<th>Risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2383208</td>
<td>CDKN2A</td>
<td>9</td>
<td>AG</td>
<td>0.88</td>
<td>31.23%</td>
</tr>
<tr>
<td>rs2793831</td>
<td>NOTCH2</td>
<td>1</td>
<td>TT</td>
<td>0.97</td>
<td>74.27%</td>
</tr>
<tr>
<td>rs2877716</td>
<td>ADCY5</td>
<td>3</td>
<td>CC</td>
<td>1.05</td>
<td>68.66%</td>
</tr>
<tr>
<td>rs4430796</td>
<td>TCF2</td>
<td>17</td>
<td>GG</td>
<td>1.09</td>
<td>22.34%</td>
</tr>
<tr>
<td>rs7578597</td>
<td>THADA</td>
<td>2</td>
<td>TT</td>
<td>1.03</td>
<td>78.85%</td>
</tr>
<tr>
<td>rs7903146</td>
<td>TCF7L2</td>
<td>10</td>
<td>CC</td>
<td>0.82</td>
<td>62.73%</td>
</tr>
<tr>
<td>rs7961581</td>
<td>TSPAN8</td>
<td>12</td>
<td>TT</td>
<td>0.95</td>
<td>58.70%</td>
</tr>
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</table>

Total Relative Risk: **0.78**

Hypertension

<table>
<thead>
<tr>
<th>SNP</th>
<th>Locus</th>
<th>CHRM</th>
<th>Code</th>
<th>Risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12413409</td>
<td>CYP17A1</td>
<td>10</td>
<td>GG</td>
<td>1.03</td>
<td>75.27%</td>
</tr>
</tbody>
</table>

Total Relative Risk: **1.03**

Coronary Heart Disease

<table>
<thead>
<tr>
<th>SNP</th>
<th>Locus</th>
<th>CHRM</th>
<th>Code</th>
<th>Risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3184504</td>
<td>SH2B3</td>
<td>12</td>
<td>CC</td>
<td>0.89</td>
<td>64.84%</td>
</tr>
<tr>
<td>rs6725887</td>
<td>WDR12</td>
<td>2</td>
<td>TT</td>
<td>0.95</td>
<td>86.72%</td>
</tr>
<tr>
<td>rs7739181</td>
<td>PHACTR1</td>
<td>6</td>
<td>GG</td>
<td>1.08</td>
<td>67.95%</td>
</tr>
<tr>
<td>rs9818870</td>
<td>MRAS</td>
<td>3</td>
<td>CC</td>
<td>0.96</td>
<td>82.42%</td>
</tr>
</tbody>
</table>

Total Relative Risk: **0.89**
Precision Cancer Medicine (PCM)

Problem

Many rare somatic mutations need to be taken into account for cancer prognostics.

Solution

iPad app for clinicians to compare patient variations with those of population on site.

Features

View variants of patient and population

Planned

Bayesian updates on stats

In-app comparison of patient-based prognostics for different drugs

Clinical Informatics webinar series. Nov. 05, 2015
Target: Developers, Clinicians/patients as end-users.
Use: Access and search patient clinical, genomic records, and genomics datasets/repositories.

Clinical Informatics webinar series. Nov. 05, 2015
Target: Clinicians, Hospital IT Professionals
Use: Standard for access and search of patient clinical and genomic records
Target: Genomic researchers, others. Use: Standard to share genomic data for research/development.
- Genomics integrated directly into clinical model.
- Genomics as a profile on top of Observation resource
- Sequence and non-sequence based genomic tests
- Genomics adopted in FHIR DSTU 2.0
- Uses current standards
- FHIR Profiles
- Alignment (e.g. MU 2.0)
- Patient record scope/authentication
- Single sign-on layer
- UI Integration Layer (Launch within EHR)
- Integrates GA4GH and FHIR Genomics
- Provides genomic data shadowing/constraints/mappings
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Actions to Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHIR could be included as an emerging standard(^4), 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>(^1)</td>
<td><strong>Apply accelerators (e.g., S&amp;I Initiative, pilot project, policy guidance) to existing standards by ONC</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Actions to Advance</th>
</tr>
</thead>
<tbody>
<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><strong>Apply accelerators (e.g., S&amp;I Initiative, pilot project, policy guidance) to existing standards by ONC</strong></td>
</tr>
</tbody>
</table>
Preparing For Precision Medicine

Omics Data

High-dimensional
Different format
Different ways to interpret
New data in the future

Representation
Storage
Analysis
?

Clinical Informatics webinar series. Nov. 05, 2015
SMART on FHIR Genomics and GA4GH

Standard Genetics Profile:
AssessedCondition, familyMemberHistory

DiagnosticOrder-genetics:
Subject, orderer
Items

Observation-genetics:
Subject, performer, device, specimen, ...

Genetics and sequence pointer

Clinical data
Genetics data
Clinical data
Genetics data
SMART on FHIR Genomics and GA4GH

**Genetic Profile:** Assessed Condition
Family Member History

- Diagnostic Report
  - result
- result
- result

**Observation:** clinic info, knowledge-based analysis, variant

**Sequence**
- Variant info in ga4gh
  - (coordinate, name, id)
- Other info not in ga4gh
  - (species, source, etc)
- Read info

**Atomic result**

**SMART on FHIR Genomics**

Ga4gh variant info
Ga4gh read group

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Integrated into Clinical Data Model and Workflow

DiagnosticReport 1

Clinical context 1: condition, patient,...

Observation 1
  Clinic info 1
  Sequence 1

Observation 2
  Clinic info 2
  Sequence 2

Observation 3
  Clinic info 3
  Sequence 3
Sequence Resource

Single variant and key elements or a sequence

Cross references to GA4GH

Extensible to future omics
GA4GH full sequence links

GA4GH API:
https://www.googleapis.com/genomics/v1beta2
http://grch37.rest.ensembl.org/ga4gh, etc.

CallSet
1 sample

Variant call
- genotype determination for 1 variant

Read group
- collections of reads produced by a sequencer

Search Reads:
- Read group set ID, start, end

Clinical Informatics webinar series. Nov. 05, 2015
### Observation Resource

#### Examples for component.code

<table>
<thead>
<tr>
<th>LOINC Code</th>
<th>LOINC Element Name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>51963-7</td>
<td>Medication Assessed</td>
<td>A coded medication accessed in a pharmacogenic test (recommend RxNorm).</td>
</tr>
<tr>
<td>51967-8</td>
<td>Genetic disease assessed</td>
<td>A coded disease which is associated with the region of DNA covered by the genetic test (recommend SNOMED).</td>
</tr>
<tr>
<td>53037-8</td>
<td>Genetic Disease Sequence Variation Interpretation</td>
<td>Interpretation of the pathogenicity of the DNA Sequence Variation in the context of the assessed genetic disease.</td>
</tr>
<tr>
<td>53040-2</td>
<td>Drug Metabolism Sequence Variation Interpretation</td>
<td>Predicted phenotype for drug efficacy. A sequence variation interpretation value known to allow (responsive) or prevent (resistant) the drug to perform.</td>
</tr>
<tr>
<td>51961-1</td>
<td>Drug Efficacy Sequence Variation Interpretation</td>
<td>Predicted phenotype for ability of drug to bind to intended site in order to deliver intended effect. A Sequence Variation interpretation value known to allow (responsive) or prevent (resistant) the drug to perform.</td>
</tr>
</tbody>
</table>
Example for Observation resource - Somatic mutation

Generated Narrative with Details

id: ob-genetics-1

contained:

status: final

code: Genetic analysis master panel (Details: {LOINC code '55233-1' = 'Genetic analysis master panel - Blood or Tissue by Molecular genetics method', given as 'Genetic analysis master panel'}

subject: Molecular Lab Patient ID: HOSP-23456

issued: 2013-3-11 10:28:00

performer: Molecular Diagnostic Laboratory

value: Sequence/example

interpretation: positive (Details: {http://hl7.org/fhir/v2/0078 code 'POS' = 'Positive'}

specimen: Molecular Specimen ID: MLD45-Z4-1234

Clinical Informatics webinar series. Nov. 05, 2015
Example for Sequence resource - EGFR mutation

Generated Narrative with Details

id: example


Variations

<table>
<thead>
<tr>
<th>Type</th>
<th>VariationHGVS</th>
<th>VariationType</th>
<th>ReferenceSeq</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>c.1443T&gt;G (Details: {<a href="http://www.hgvs.org/mutnomen">http://www.hgvs.org/mutnomen</a> code 'NM_005228.3' = 'NM_005228.3', given as 'c.1443T&gt;G'})</td>
<td>Substitution (Details: {<a href="http://hl7.org/fhir/LOINC-48019-4-answerlist">http://hl7.org/fhir/LOINC-48019-4-answerlist</a> code 'LA6690-7' = 'Substitution'})</td>
<td>ENSESTT000000085772.1 (Details: {<a href="http://www.ensembl.org">http://www.ensembl.org</a> code 'ENSESTT000000085772.1' = 'ENSESTT000000085772.1})</td>
</tr>
</tbody>
</table>

Coordinates

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Start</th>
<th>End</th>
<th>GenomeBuild</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (Details: {[not stated] code '7' = '7})</td>
<td>55227976</td>
<td>55227977</td>
<td>GRCh37 (Details)</td>
</tr>
</tbody>
</table>

gene: EGFR (Details: {http://www.genenames.org code '3236' = '3236', given as 'EGFR'})

region: Exon 21 (Details)

species: Homo sapiens (Details: {SNOMED CT code '337915000' = '337915000'})

source: Somatic (Details: {http://hl7.org/fhir/LOINC-48002-0-answerlist code 'LA6684-0' = 'Somatic'})

Ga4ghs

<table>
<thead>
<tr>
<th>Repository</th>
<th>VariantId</th>
<th>ReadGroupSetId</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="https://www.googleapis.com/genomics/v1beta2">https://www.googleapis.com/genomics/v1beta2</a></td>
<td>AAAA</td>
<td>BBBB</td>
</tr>
</tbody>
</table>
Domain Analysis Model (DAM) Use Cases, Release 2

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
Specimen Identification

Explore antibacterial drug resistance over time (non-patient DNA)

Get references to all DNA sequences of tuberculosis bacteria (SNOMED code: 56717001) from given patient:

GET /Observation?
value-reference.species=http://snomed.info/sct|56717001&
subject=123
Search results:
.Bundle
  .entry
    .resource
      .Observation
        .id value="o1"/
        .subject
          .reference value="123"/
        .valueReference
          .reference value="s1"/
      .valueReference
    .Observation
  .resource
    .Sequence
      .id value="s1"/
      .species
        .coding
          .system value="http://snomed.info/sct"/
          .code value="56717007"/
          .display value="tuberculosis bacteria"/
      .display value="tuberculosis bacteria"/
    .Sequence

### Genetic test Report for Peter James Chalmers (MRN: 12345)

<table>
<thead>
<tr>
<th>Gene</th>
<th>DNA Variation</th>
<th>Status</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td></td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>185delAG</td>
<td>Positive</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>

**Method:** BRACAnalysis CDx Offered by Myriad Genetic Laboratories, Inc

**Issued:** 2015-05-26T15:30:10+01:00

**Family Member History:** Mother

<table>
<thead>
<tr>
<th>Gene</th>
<th>DNA Variation</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>185delAG</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Method:** BRACAnalysis CDx Offered by Myriad Genetic Laboratories, Inc
<Observation>
  <status value="final"/>
  <code>
    <coding>
      <system value="http://loinc.org"/>
      <code value="55233-1"/>
      <display value="Genetic analysis master panel"/>
    </coding>
  </code>
  <subject>
    <reference value="Patient/example"/>
    <display value="Peter James Chalmers(MRN: 12345)"/>
  </subject>
  <issued value="2015-05-26T15:30:10+01:00"/>
  <method>
    <coding>
      <code value="GTR000521311.1"/>
      <display value="BRACAnalysis CDx Offered by Myriad Genetic Laboratories, Inc"/>
    </coding>
  </method>
</Observation>
Family History – Genetics – Search Results

Genetic test Report for Peter James Chalmers (MRN: 12345)

Genetic test Report for the mother of Peter James Chalmers (MRN: 12345)

Clinical Informatics webinar series. Nov. 05, 2015
Desiderata For Improved Clinical-Genomics Apps

FHIR for clinical ‘omics

Concise & consistency over diverse data resources

Focus on relevance to clinical-genomic apps

Leverages GA4GH research models for translation
FHIR Genomics Connectathon

- January Orlando
- FHIR Genomics use cases
- Experts meet with teams beforehand or available in-person/video conferencing/skype at event.
- Develop apps and put completed ones in gallery
Ver. 2.1 Staging URLs

Sequence Resource
http://genomics-advisor.smartplatforms.org:4000/sequence.html

Standard Profile for Genetics

Standard Profile for Family Member History Genetics
http://genomics-advisor.smartplatforms.org:4000/family-member-history-genetics.html
Other Links

FHIR Clinical Genomics (DSTU 2)
http://hl7.org/fhir/observation-genetics-cg-prf-1a.html

GA4GH Clinical Working Group
https://genomicsandhealth.org/working-groups/clinical-working-group

JAMIA Paper on SMART Genomics/FHIR DSTU 2.0
http://jamia.oxfordjournals.org/content/early/2015/07/21/jamia.ocv045.long

SMART Genomics (direct link)
http://projects.iq.harvard.edu/smartgenomics/home

SMART Platform
http://smarthealthit.org/
People

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

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

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