Building Partnerships for Precision Medicine

Presented by:

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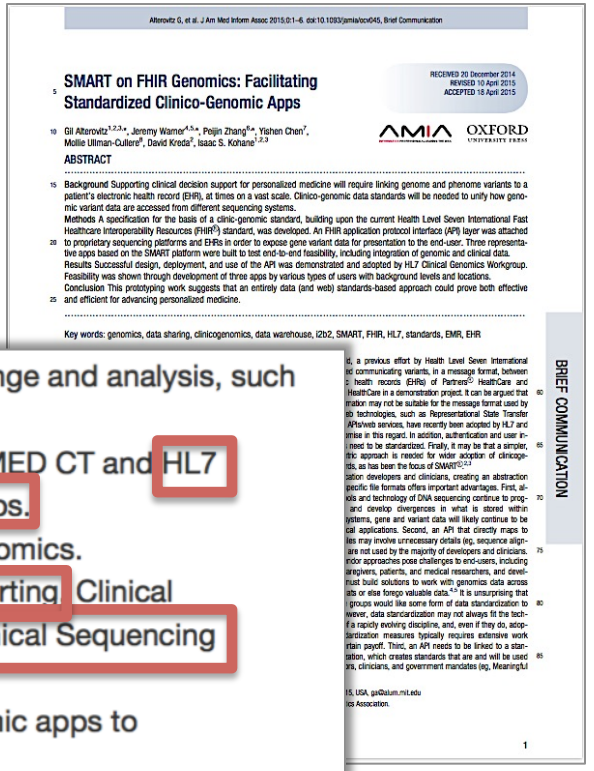
Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

The Problem

How do we enable Precision Medicine at point of care?

Precision Medicine Initiative®
Cohort Program RFA



Alterovitz G, et al. J Am Med Inform Assoc 2015;0:1–6. doi:10.1093/jamia/ocv045, Brief Communication

SMART on FHIR Genomics: Facilitating Standardized Clinico-Genomic Apps

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ABSTRACT

Background Supporting clinical decision support for personalized medicine will require linking genome and phenome variants to a patient's electronic health record (EHR), at times on a vast scale. Clinico-genomic data standards will be needed to unify how genomic variant data are accessed from different sequencing systems.
Methods A specification for the basis of a clinic-genomic standard, building upon the current Health Level Seven International Fast Healthcare Interoperability Resources (FHIR®) standard, was developed. An FHIR application protocol interface (API) layer was attached to proprietary sequencing platforms and EHRs in order to expose gene variant data for presentation to the end-user. Three representative apps based on the SMART platform were built to test end-to-end feasibility, including integration of genomic and clinical data.
Results Successful design, deployment, and use of the API was demonstrated and adopted by HL7 Clinical Genomics Workgroup. Feasibility was shown through development of three apps by various types of users with background levels and locations.
Conclusion This prototyping work suggests that an entirely data (and web) standards-based approach could prove both effective and efficient for advancing personalized medicine.

Key words: genomics, data sharing, clinicogenomics, data warehouse, i2b2, SMART, FHIR, HL7, standards, EMR, EHR

BRIEF COMMUNICATION

Describe potential utilization of current and emerging standards to facilitate data exchange and analysis, such as:

- Standards for capture and representation of family health history such as SNOMED CT and HL7 Version 3 Implementation Guide: Family History/Pedigree for familial relationships.
- HL7 DIGITizE Actions Collaborative draft LOINC specification for pharmacogenomics.
- HL7 Clinical Genomics WG standards including CDA R2 Clinical Genetics Reporting, Clinical Genomics Pedigree Model, HL7 Genetic Testing Results Message (V2), and Clinical Sequencing Domain Analysis Model (DAM).
- SMART on FHIR Genomics standards to support development of clinico-genomic apps to communicate clinical genomics data between EHR systems.
- Open ID Connect, OAuth and UMA for individual authorization and authentication
- More complete authorization standards (e.g., IHE XUA, IUA, etc.) to ensure authorization standards are compatible across disparate networks.
- Global Alliance for Genomics and Health (GA4GH) standards to address computable consent for

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

More Than You Think

- 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.

HL7 V2 Example from Institute of Medicine (IOM)

- 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

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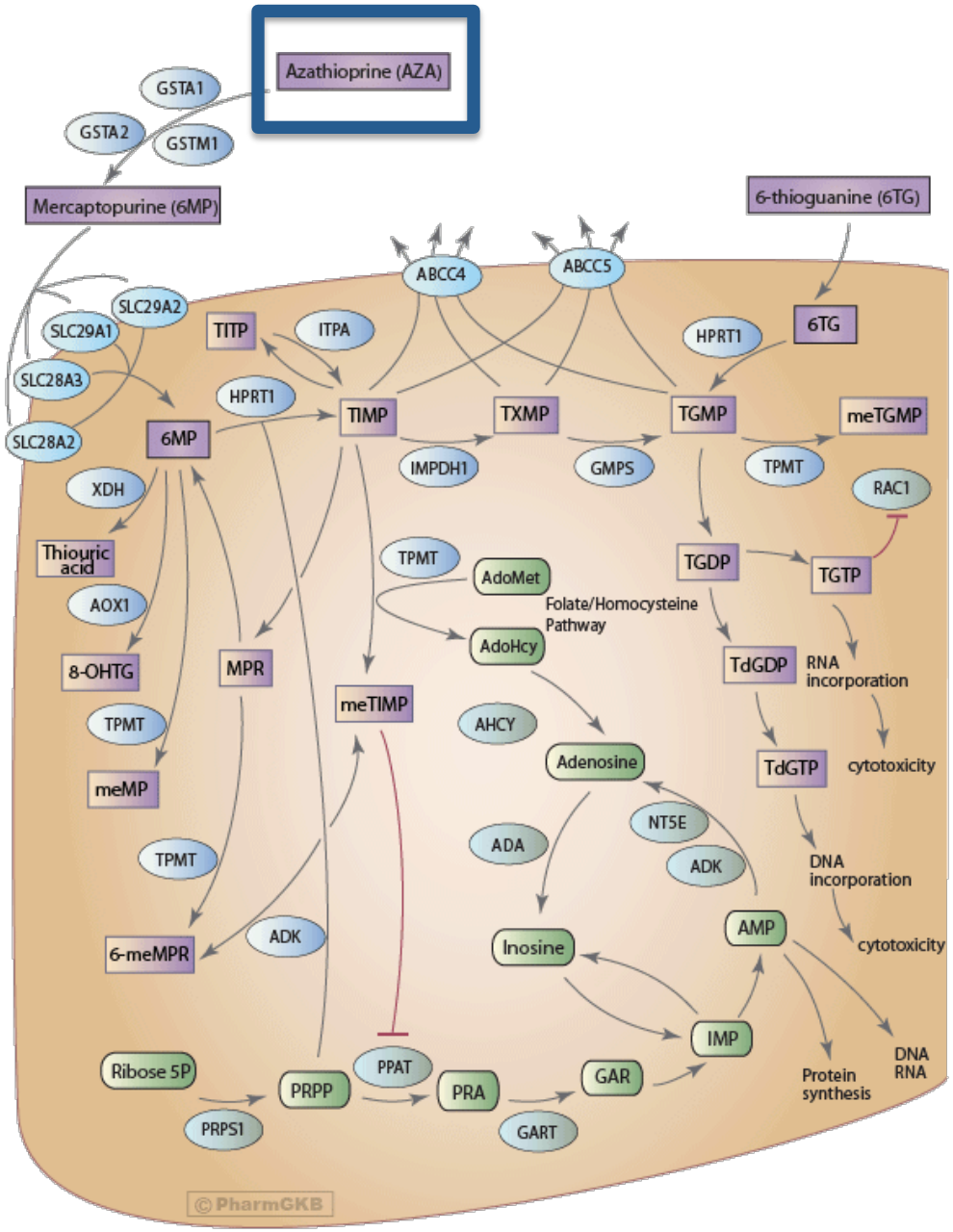
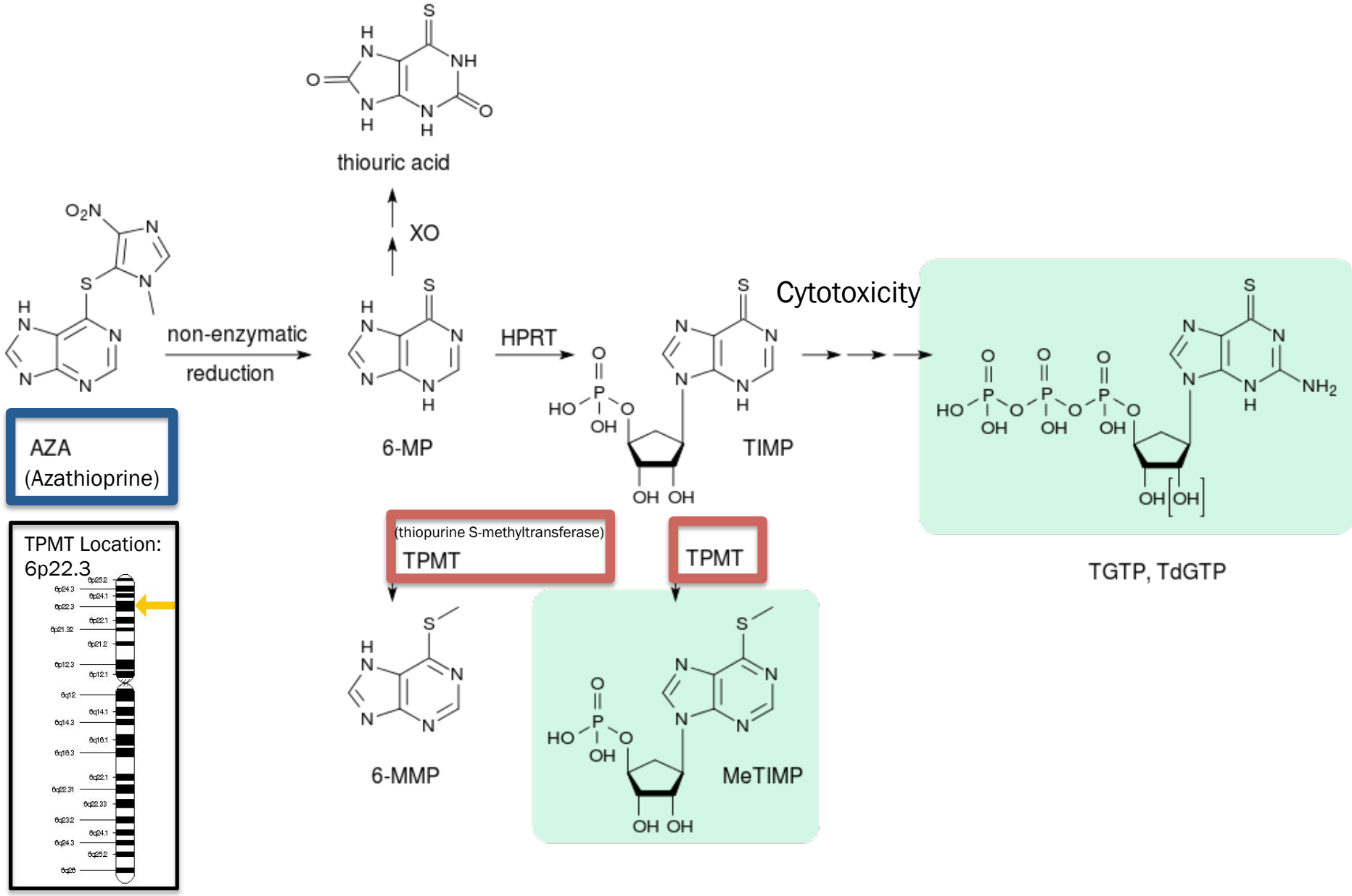

Azathioprine (AZA)
GSTA1
GSTA2
GSTM1
Mercaptopurine (6MP)
6-thioguanine (6TG)
ABCC4
ABCC5
SLC29A2
SLC29A1
SLC28A3
SLC28A2
TITP
ITPA
HPRT1
6TG
6MP
TIMP
TXMP
TGMP
meTGMP
IMPDH1
GMPS
TPMT
XDH
RAC1
Thiouric acid
AOX1
8-OHTG
TPMT
AdoMet
Folate/Homocysteine Pathway
AdoHcy
TGDP
TGTP
TdGDP
RNA incorporation
MPR
meTIMP
AHCY
Adenosine
TdGTP
cytotoxicity
meMP
TPMT
NT5E
ADA
ADK
DNA incorporation
cytotoxicity
6-meMPR
ADK
Inosine
AMP
IMP
Ribose 5P
PRPP
PPAT
PRA
GAR
Protein synthesis
DNA RNA
PRPS1
GART
© PharmGKB


thiouric acid
XO
non-enzymatic
reduction
HPRT
Cytotoxicity
AZA
(Azathioprine)
6-MP
TIMP
(thiopurine S-methyltransferase)
TPMT
TPMT
TGTP, TdGTP
TPMT Location:
6p22.3
6-MMP
MeTIMP

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:

LOINC CD	Component	Long Common Name
79713-4	TPMT gene product metabolic activity interpretation	TPMT gene product metabolic activity interpretation in Blood or Tissue Qualitative by CPIC

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]

Answer List*

	Seq #	Answer	AnswerID
	1	Ultrarapid metabolizer	LA10315-2
	2	Rapid metabolizer	LA25390-8
	3	Normal metabolizer	LA25391-6
	4	Intermediate metabolizer	LA10317-8
	5	Poor metabolizer	LA9657-3

*based on the CPIC Delphi Survey

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

OBX|1|CWE|79713-4^ TPMT gene product metabolic activity interpretation ^LN||LA10317-8^Intermediate metabolizer^LN-ANS…

V3

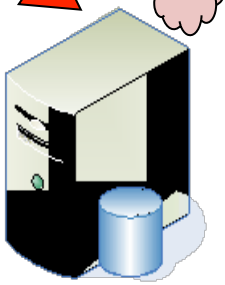
Hughes RiskApps: Less work + CDS=Higher Quality

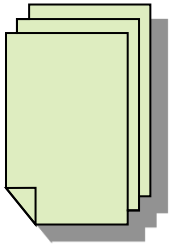
More Than You Think

Patient enters data into Tablet PC

Risk Engine WebService

HL7 V3 ➔ FHIR Genomics





Patient educational materials

Reviews Intuitive Report & suggested management

Genetic Testing

Courtesy: Dr. Kevin Hughes, MGH

Hughes RiskApps™

Patient Lifestyle Question

English | French | Spanish | Portuguese

Cancer Risk Assessment

hughesriskApps™

How many alcoholic beverages do you consume weekly?

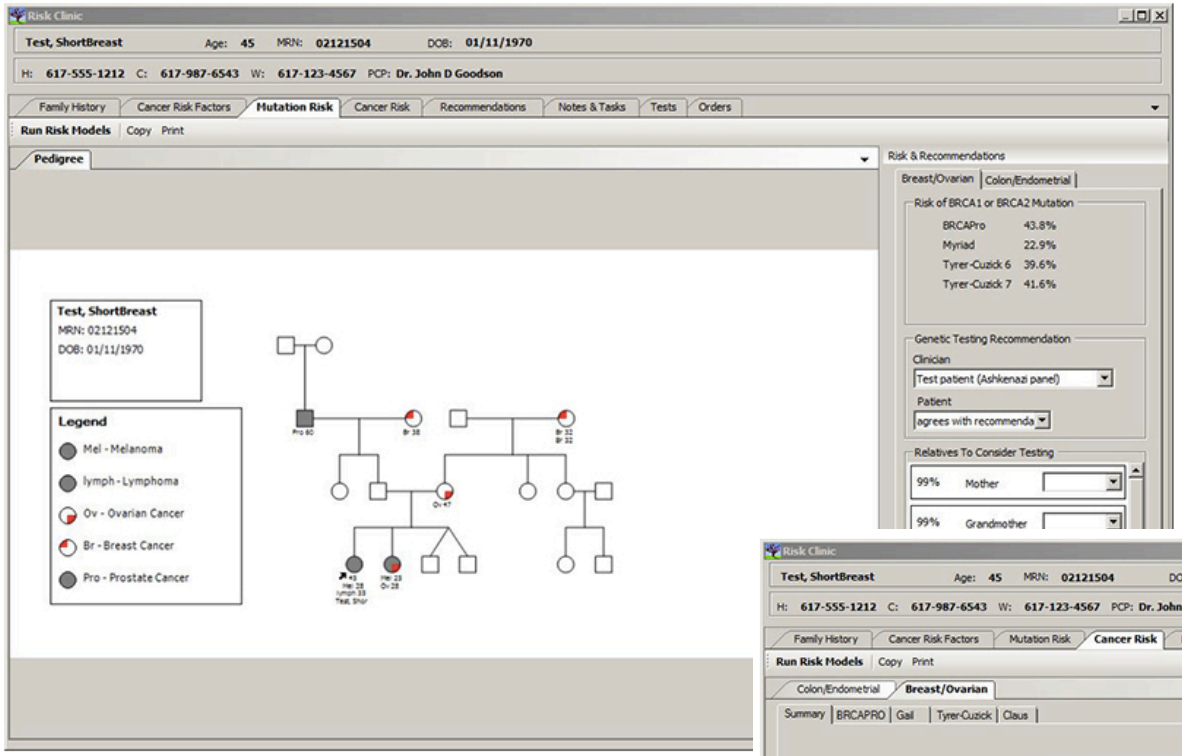
5 - 9 drinks per week

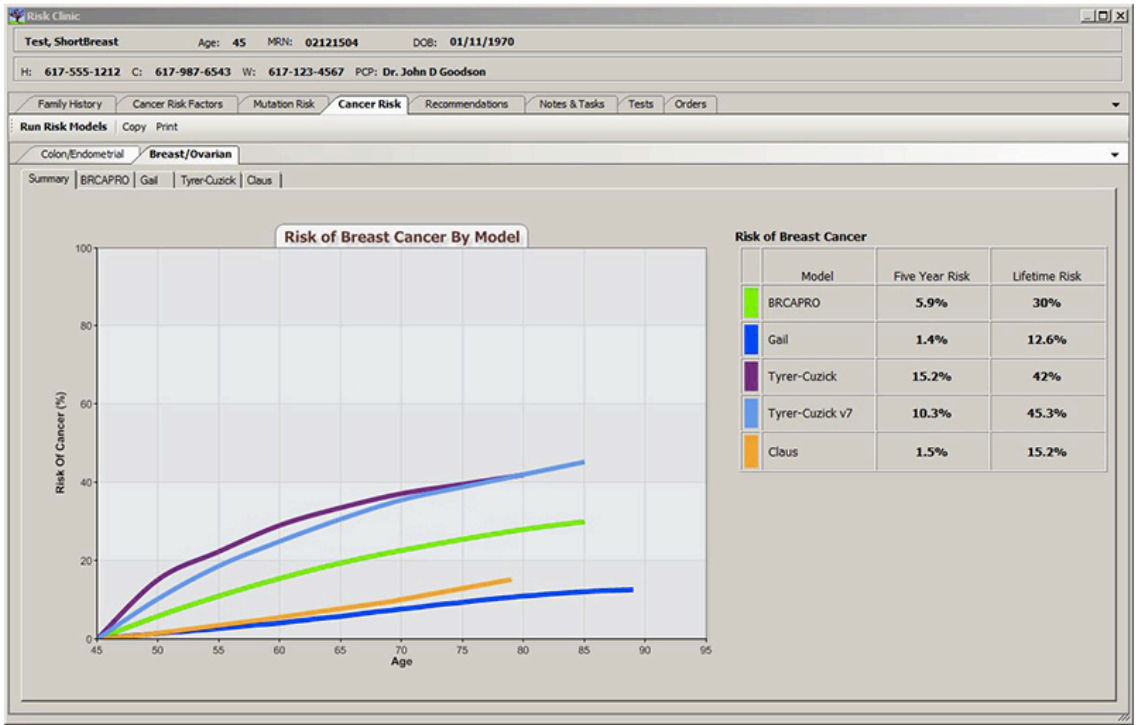
None	5 - 9 drinks per week
Less than 1 drink a week	10 - 19 drinks per week
1 - 4 drinks per week	More than 19 drinks per week

Clear

Pedigree/Breast Cancer Risk

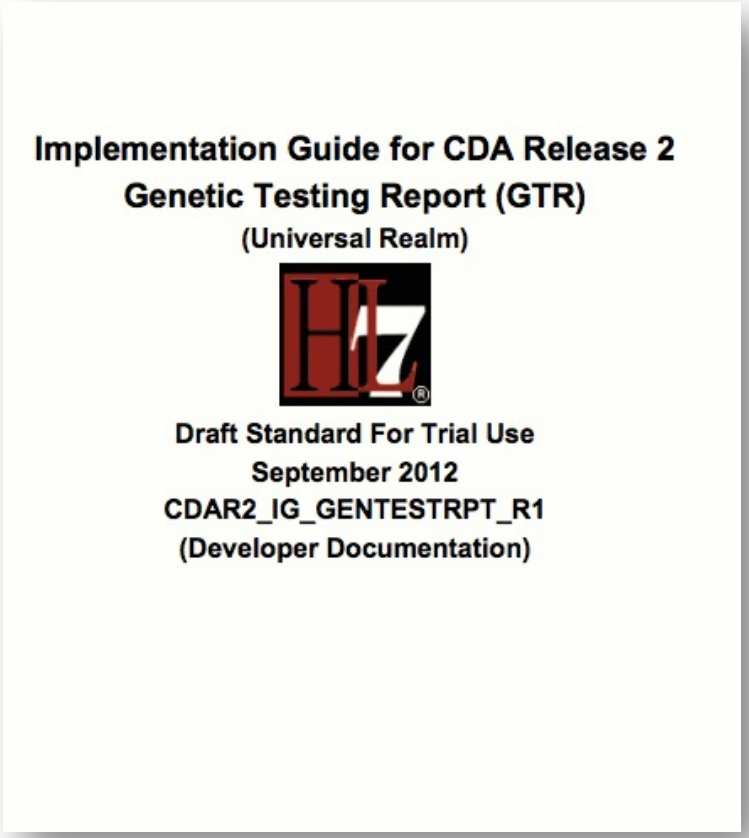
More Than You Think





Clinical Document Architecture (CDA)

Genetic Test Report



GTR - Design Principles

More Than You Think

- 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 GeneticVariation 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

[ClinicalDocument: templateId 2.16.840.1.113883.10.20.20]

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

SMART/FHIR Genomics

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

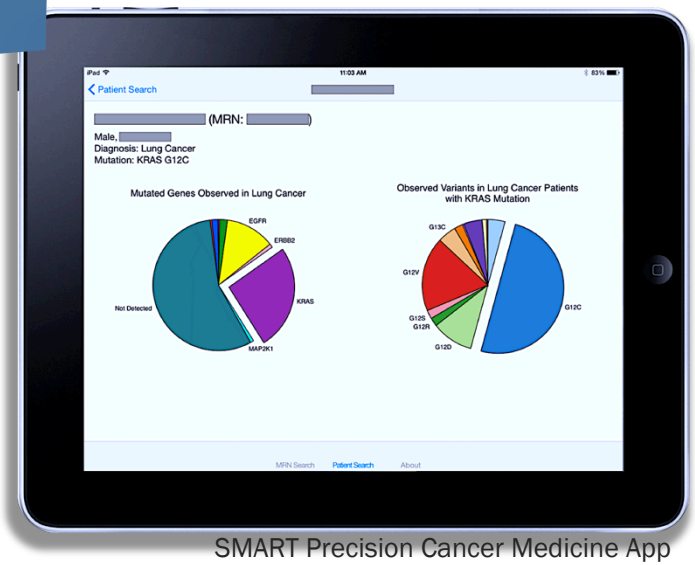
More Than You Think

1 Order Genetics Labs

EMR System

3 Present & Contextualize Genetics Labs Results

SMART on FHIR Clinico-Genomics Apps



SMART Precision Cancer Medicine App
(Warner, et al, JAMIA, 2016)

Diagnostic Order App

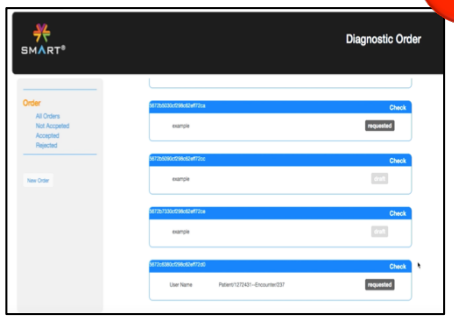
Diagnostic Reporter App

FHIR Data
Order
Demographics
Sequence
...

FHIR Data
Report
Sequence
...

Sequencing Lab

2 Return Genetics Labs Results



1

Diagnostic Order App

Order

SMART on FHIR Genomics LAB

SMART Services

HL7 FHIR Genomics

GA4GH

Clinical data

SMART on FHIR EMR

SMART Services

HL7 FHIR Genomics

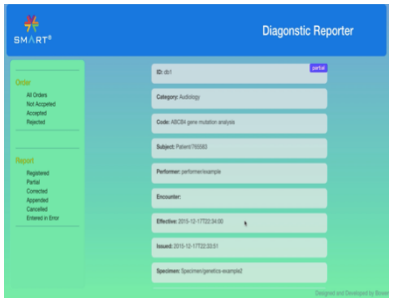
EMR

2

Order Response

Genomic data

Diagnostic Reporter App



Source: Gil Alterovitz, SMART-on-FHIR Genomics

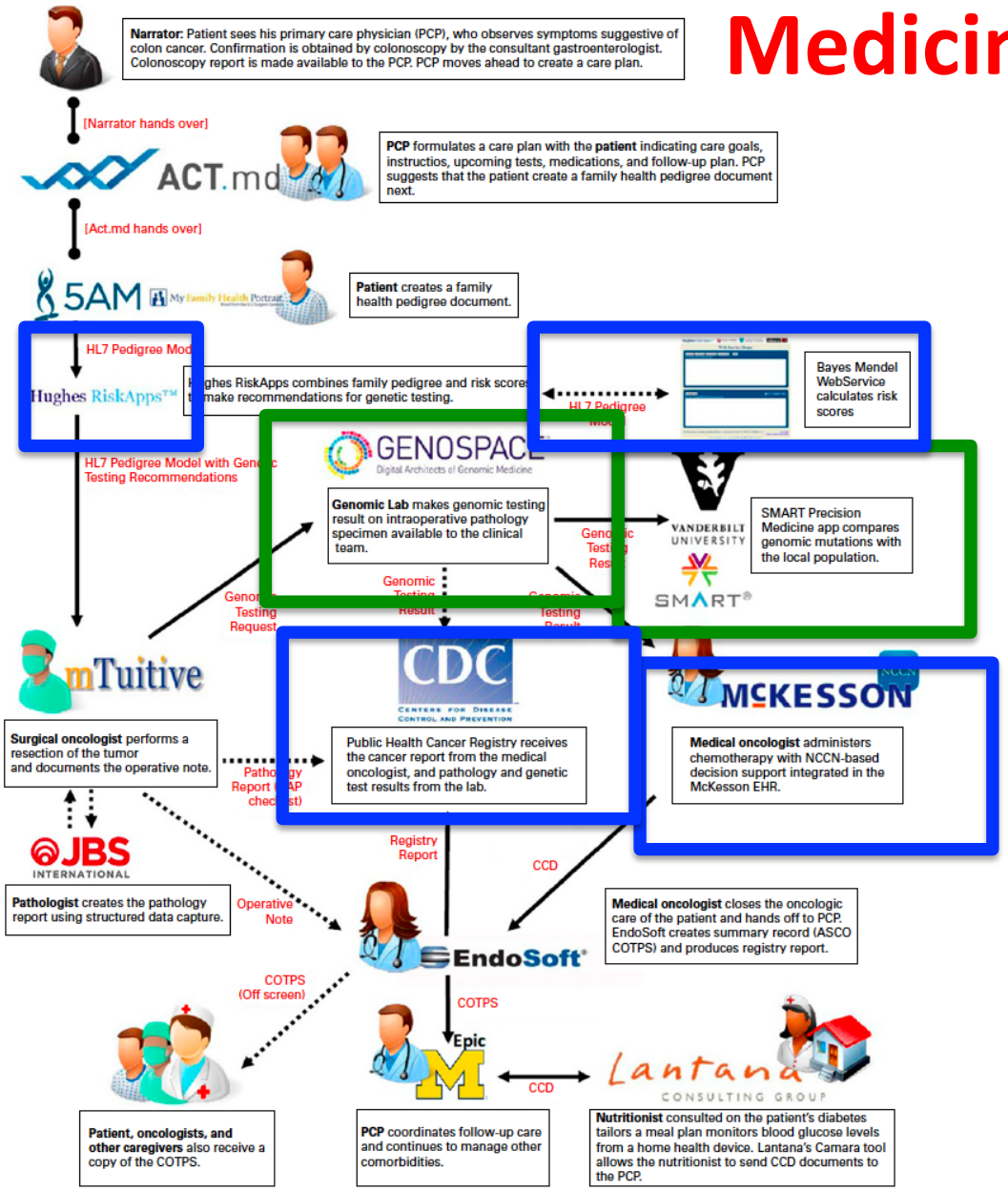
CG Data

3

PCM App (at Point of Care)

SMART on FHIR Genomics API Server + Sandbox

SMART on FHIR Pilots for Precision Medicine in Cancer



Org. support SMART/FHIR

Org. pilots of SMART/FHIR

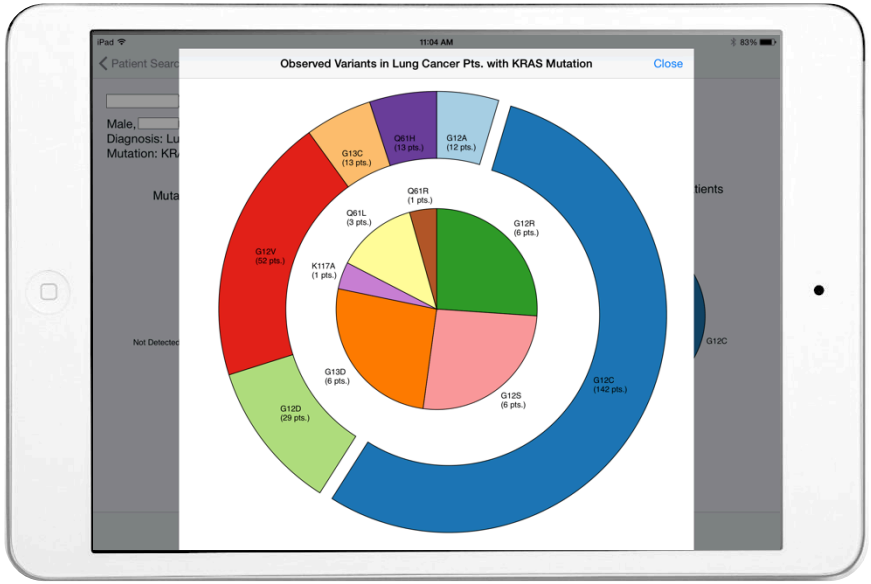
Krauss JC, et al. Data Sharing to Support the Cancer Journey in the Digital Era. Journal of oncology practice. 2016.

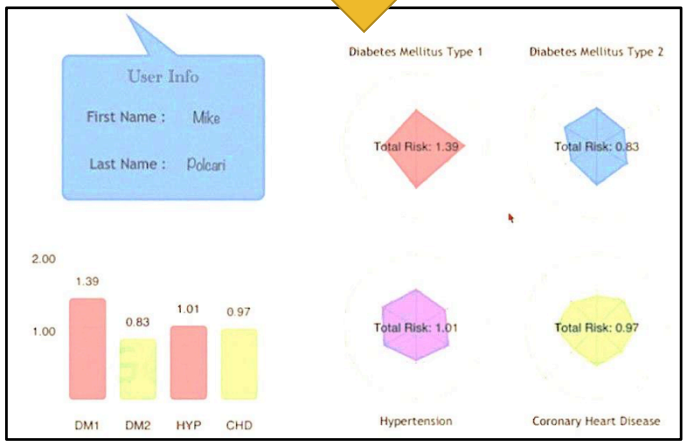
DB (Diabetes Bear) EMR App

Alterovitz & Yang

Precision Cancer Medicine (PCM) App

Warner & Alterovitz



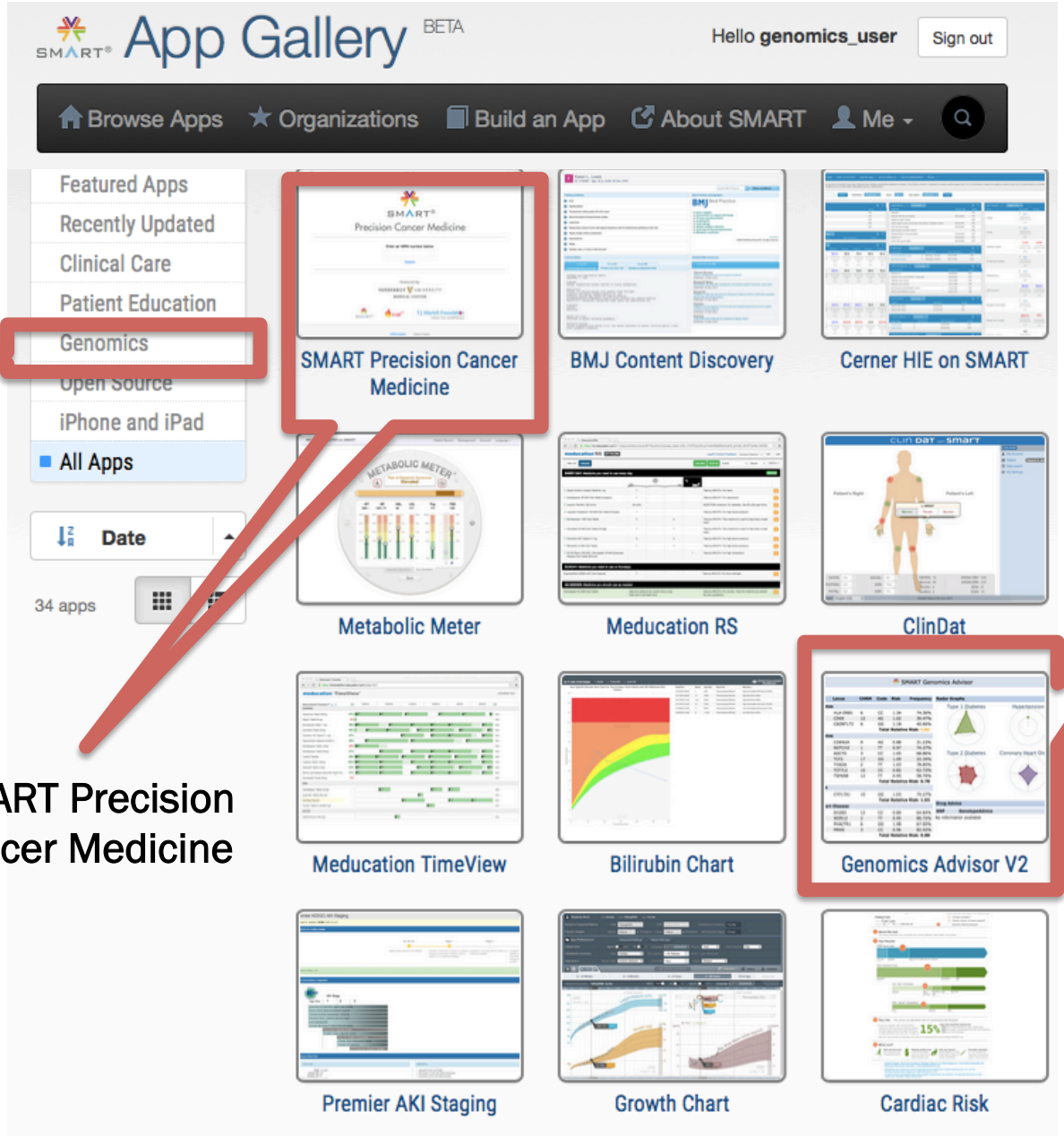


Genomics Advisor App

Alterovitz & Zhang

Alterovitz G, et al. SMAR[illegible]
Genomics: facilitating standardized clinico-genomic apps. JAMIA. 2015;22(6):1173-8.

https://gallery.smarthealthit.org



Genomics Category

SMART Precision Cancer Medicine

Genomics Advisor V2

SMART App Gallery BETA

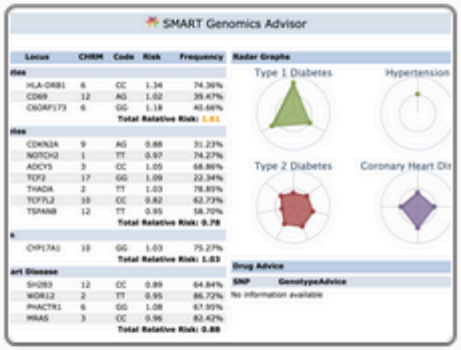
Hello **genomics_user** Sign out

Browse Apps | Organizations | Build an App | About SMART | Me

You are here: Home / Genomics Advisor V2

Genomics Advisor V2

https://gallery.smarthealthit.org



Author	diabetes-monograph
Website	--
Last Update	Friday, February 19, 2016
Tags	Asthma & Allergies, Cardiovascular, Diabetes, Diagnosis, Genomics

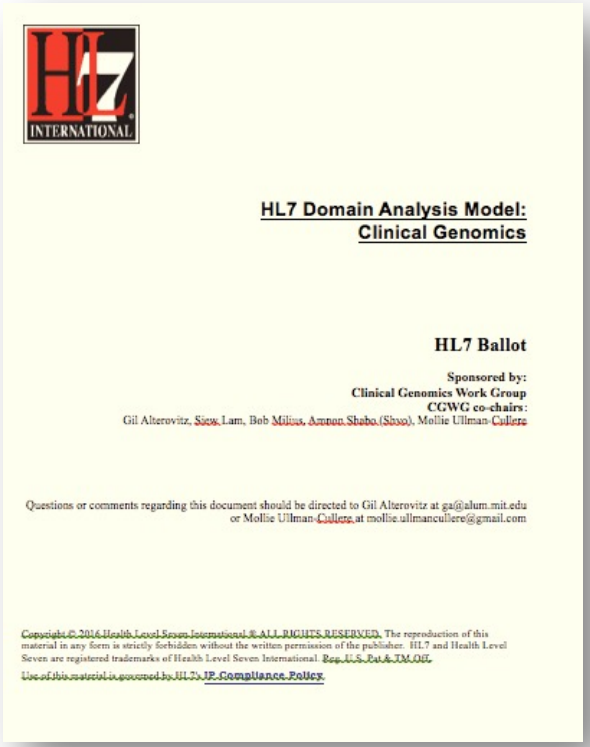
Try It

App Description

Diabetes and related diseases risk analysis.

Related Apps

Other apps by diabetes-monograph



HL7 INTERNATIONAL

HL7 Domain Analysis Model:
Clinical Genomics

HL7 Ballot

Sponsored by:
Clinical Genomics Work Group
CGWG co-chairs:
Gil Alterovitz, Siew Lam, Bob Milius, Ammon Shabo (Shvo), Mollie Ullman-Cullere

Questions or comments regarding this document should be directed to Gil Alterovitz at ga@alum.mit.edu or Mollie Ullman-Cullere at mollie.ullmancullere@gmail.com

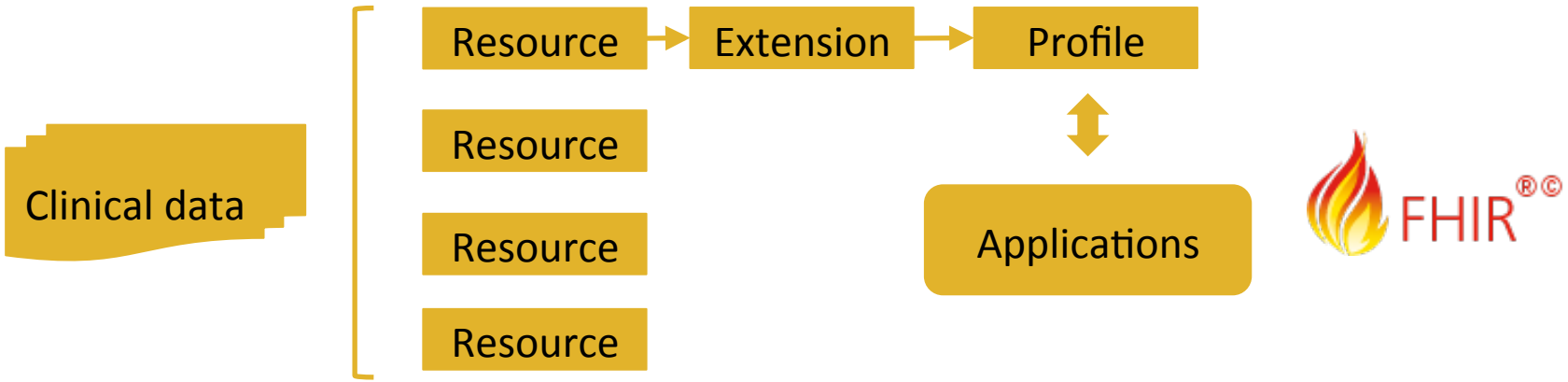
Domain Analysis Model (DAM) for Clinical Genomics, Use Cases:

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

...

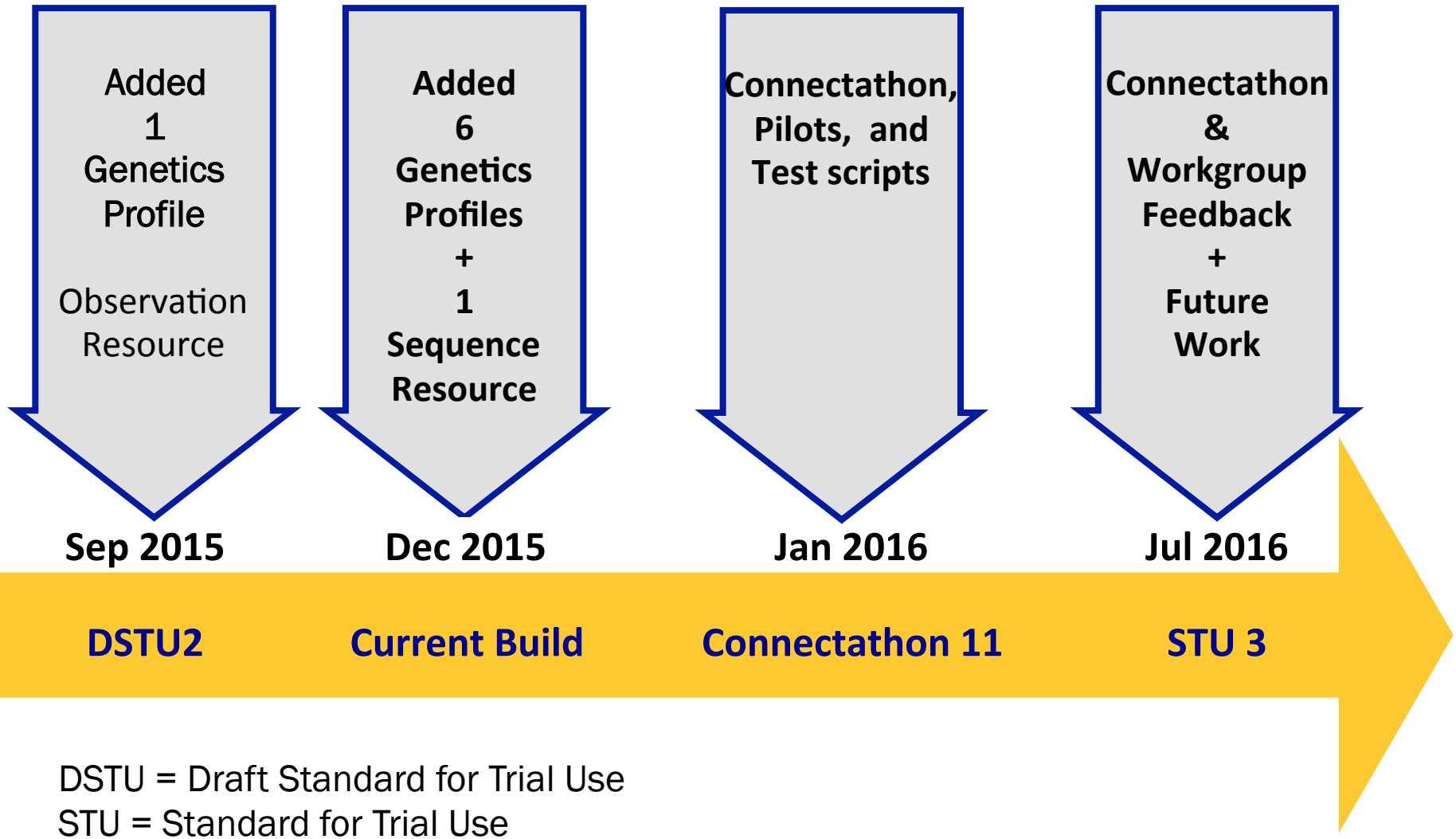
Alterovitz, et al., Domain Analysis Model: Clinical Genomics, 2016.

Fast Healthcare Interoperability Resources

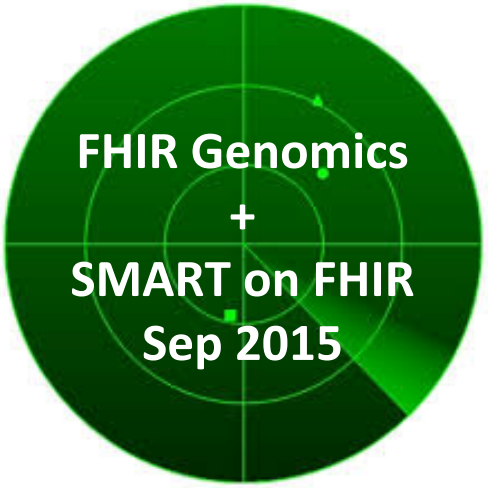


Concise, easily understood specifications
Well-defined data model and API
Easy to implement
Modern (RESTFul API, JSON, Oauth)
Extensibile

FHIR Genomics Time Line



DSTU = Draft Standard for Trial Use
STU = Standard for Trial Use



FHIR®

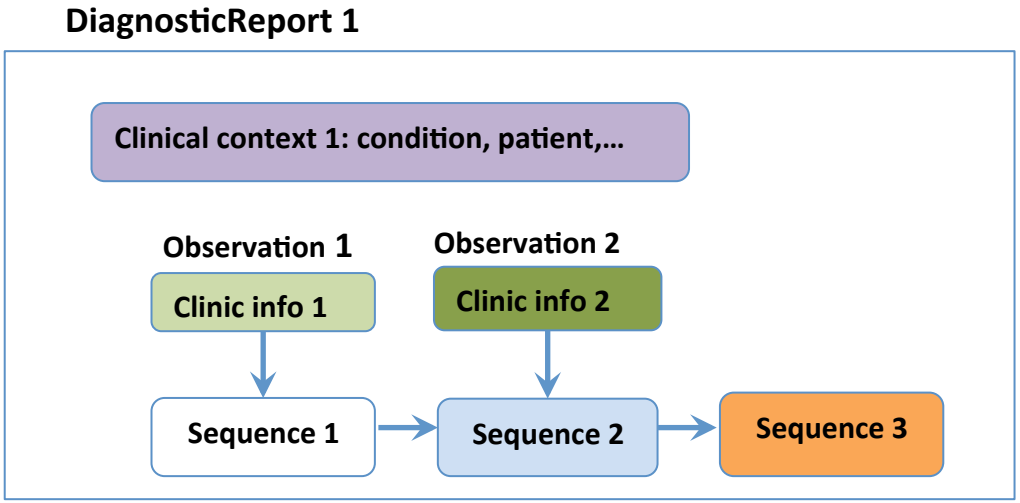
SMART®

Recommendation	Actions to Advance
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 **SMART on FHIR Genomics**[1]	*Apply accelerators (e.g., S&I Initiative, pilot project, policy guidance) to existing standards by ONC*

Recommendation	Actions to Advance
2016 PMI S&I: Additional ONC investment in pilots of **FHIR for PMI** research/individual data donation use case	*Apply accelerators (e.g., S&I Initiative, pilot project, policy guidance) to existing standards by ONC*

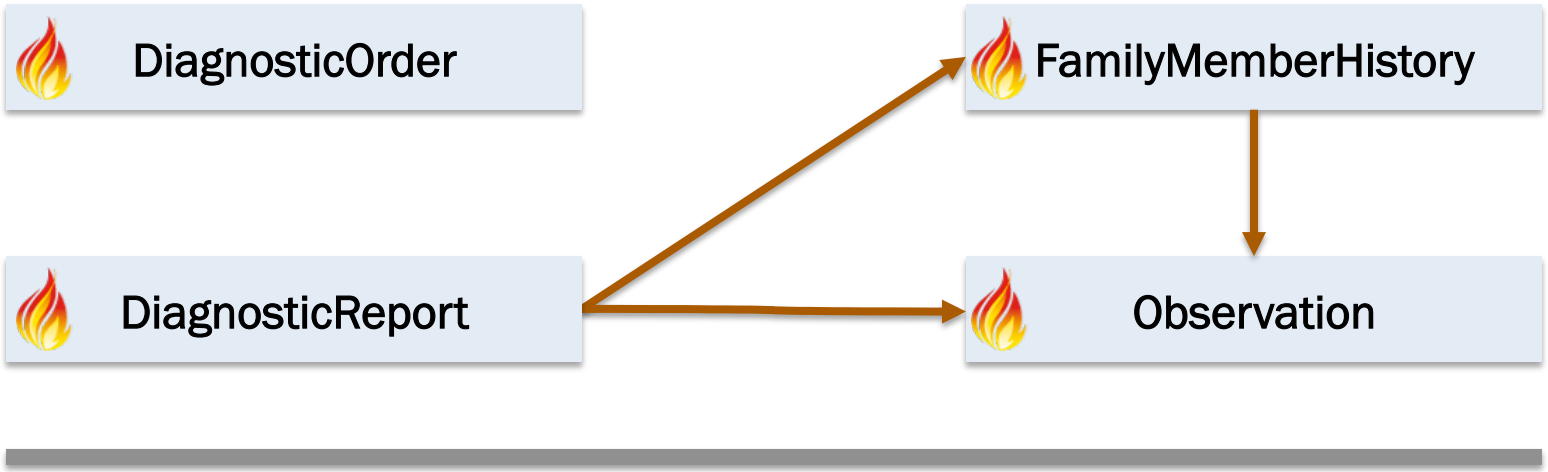
[1] Alterovitz G, et al. SMART on FHIR Genomics: facilitating standardized clinico-genomic apps. JAMIA. 2015;22(6):1173-8.

Integrated into Clinical Data Model and Workflow

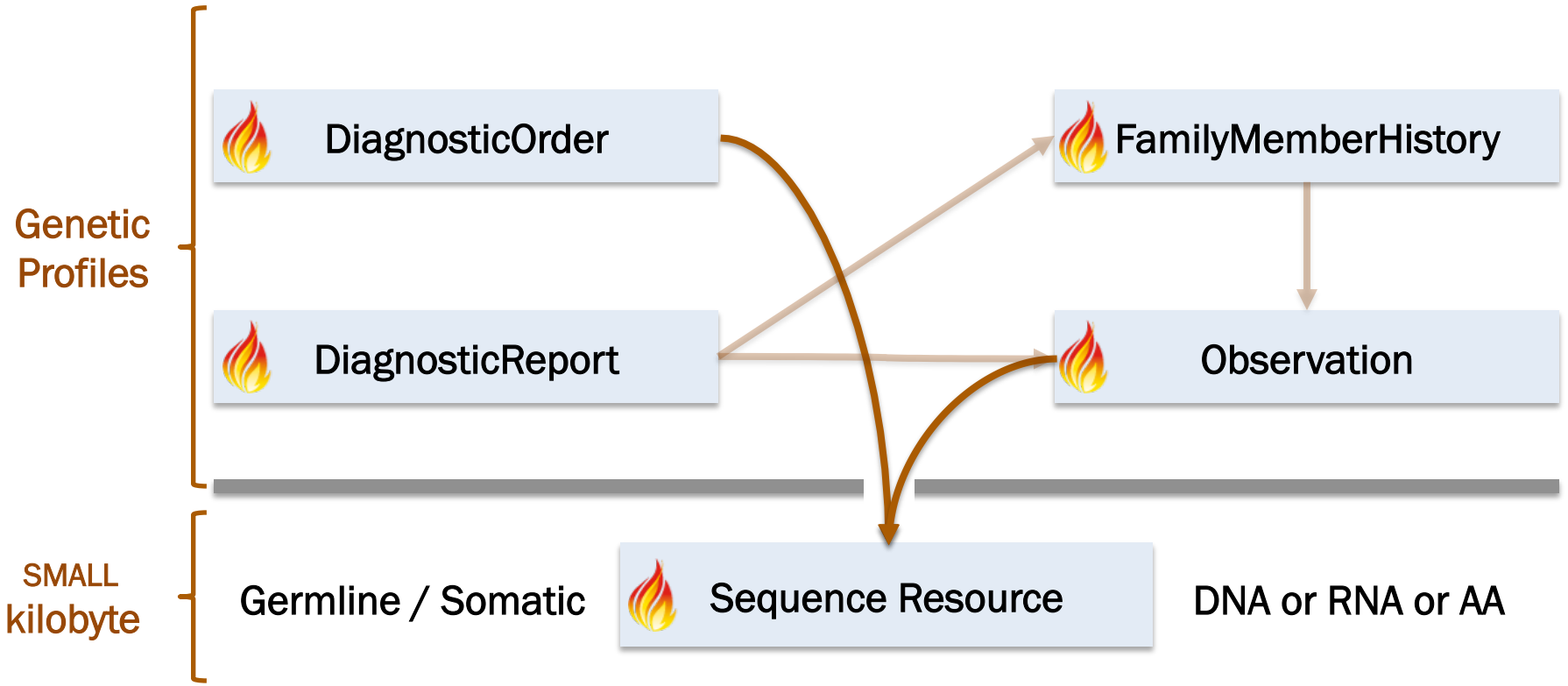


Genetics Test: Lab (Code) Only

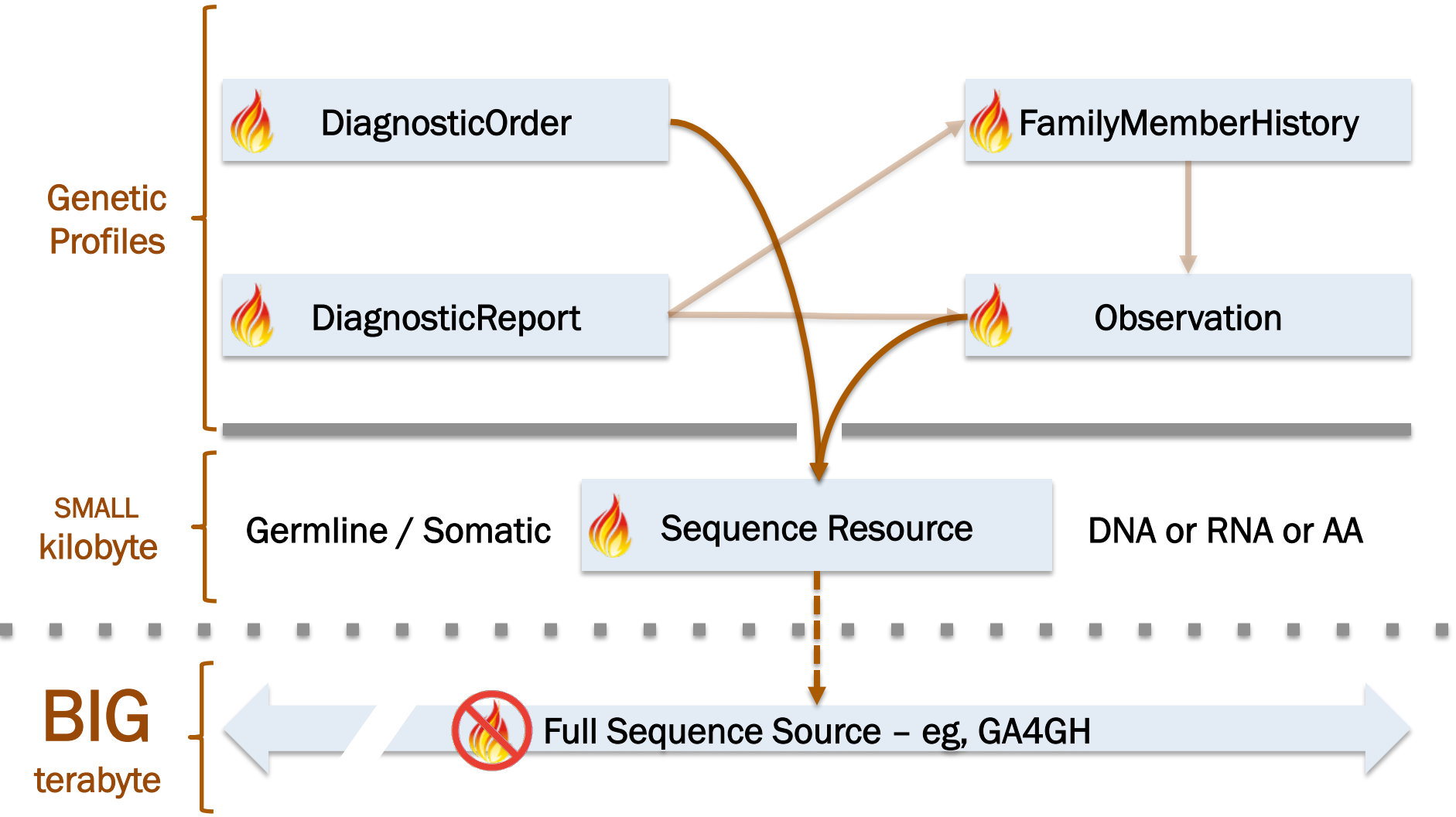
Genetic Profiles Introduce Links

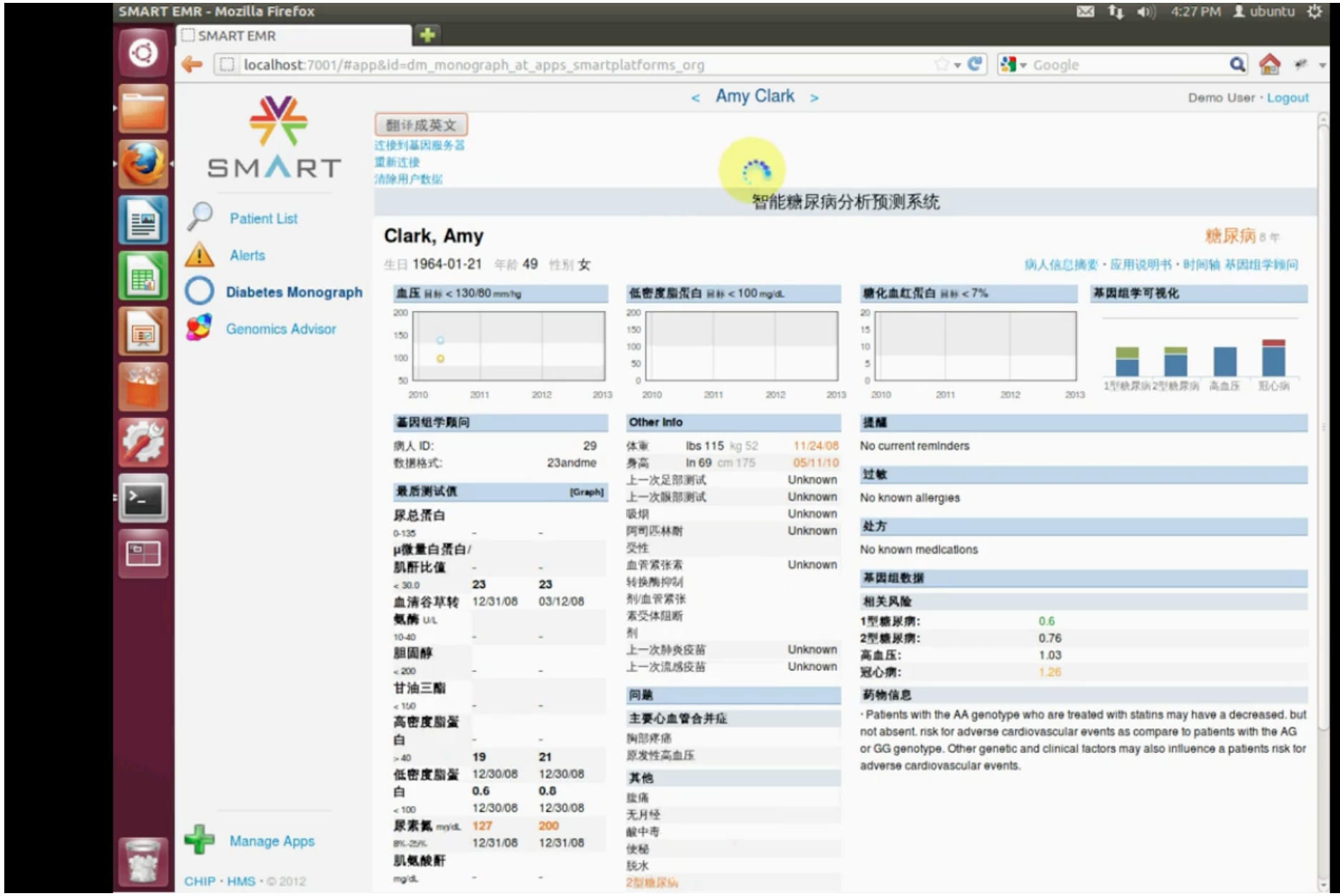


Genetics Test: Lab (Code) + Sequence Data



Genetics Test: Lab (Code) + Sequence Data + External




SMART EMR - Mozilla Firefox
4:27 PM
ubuntu
SMART EMR
localhost:7001/#app&id=dm_monograph_at_apps_smartplatforms_org
Google
< Amy Clark >
Demo User · Logout
SMART
翻译成英文
连接到基因服务器
重新连接
清除用户数据
智能糖尿病分析预测系统
Patient List
Alerts
Diabetes Monograph
Genomics Advisor
Manage Apps
CHIP · HMS · © 2012
Clark, Amy
糖尿病 8 年
生日 1964-01-21 年龄 49 性别 女
病人信息摘要 · 应用说明书 · 时间轴 基因组学顾问
血压 目标 < 130/80 mm/hg
低密度脂蛋白 目标 < 100 mg/dL
糖化血红蛋白 目标 < 7%
基因组学可视化
1型糖尿病 2型糖尿病 高血压 冠心病
基因组学顾问
病人 ID: 29
数据格式: 23andme
最后测试值 [Graph]
尿总蛋白 0-135 - -
μ微量白蛋白/肌酐比值 < 30.0 23 23
血清谷草转氨酶 U/L 10-40 12/31/08 03/12/08
胆固醇 < 200 - -
甘油三酯 < 150 - -
高密度脂蛋白 > 40 19 21
低密度脂蛋白 < 100 12/30/08 12/30/08
白 0.6 0.8
12/30/08 12/30/08
尿素氮 mg/dL 8%-25% 127 200
12/31/08 12/31/08
肌氨酸酐 mg/dL - -
Other Info
体重 lbs 115 kg 52 11/24/08
身高 In 69 cm 175 05/11/10
上一次足部测试 Unknown
上一次腹部测试 Unknown
吸烟 Unknown
阿司匹林耐受性 Unknown
血管紧张素转换酶抑制剂/血管紧张素受体阻断剂 Unknown
上一次肺炎疫苗 Unknown
上一次流感疫苗 Unknown
问题
主要心血管合并症
胸部疼痛
原发性高血压
其他
腹痛
无月经
酸中毒
使秘
脱水
2型糖尿病
提醒
No current reminders
过敏
No known allergies
处方
No known medications
基因组数据
相关风险
1型糖尿病: 0.6
2型糖尿病: 0.76
高血压: 1.03
冠心病: 1.26
药物信息
· Patients with the AA genotype who are treated with statins may have a decreased, but not absent, risk for adverse cardiovascular events as compare to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patients risk for adverse cardiovascular events.

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/GeneInsight/Medseq
- Hefei Institute of Technology in China
- Google (BCH/HMS)
- DNA Nexus/PrecisionFDA
- TBResist

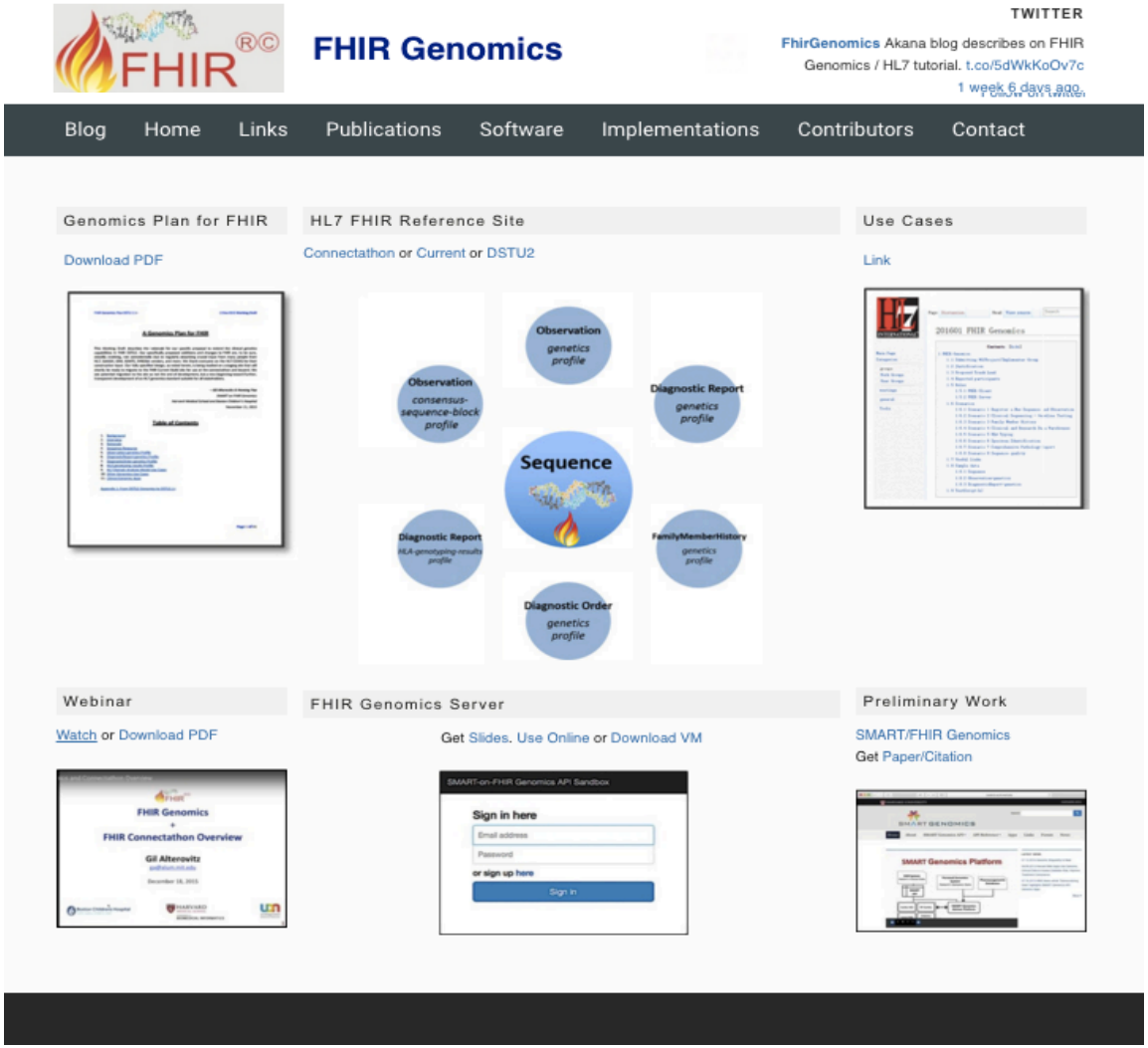
Global Alliance federated queries SMART on FHIR Genomics server:

- 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

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.

Fhirgenomics.org



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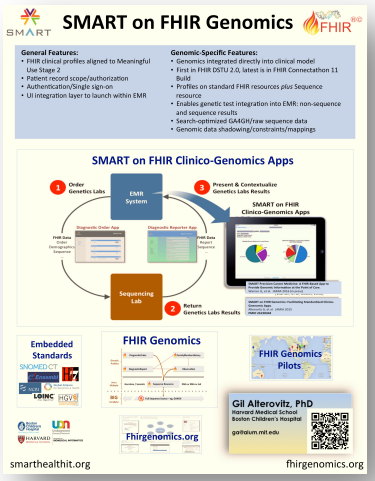
LinkedIn Contact:

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...