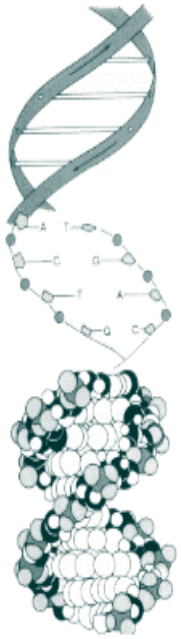
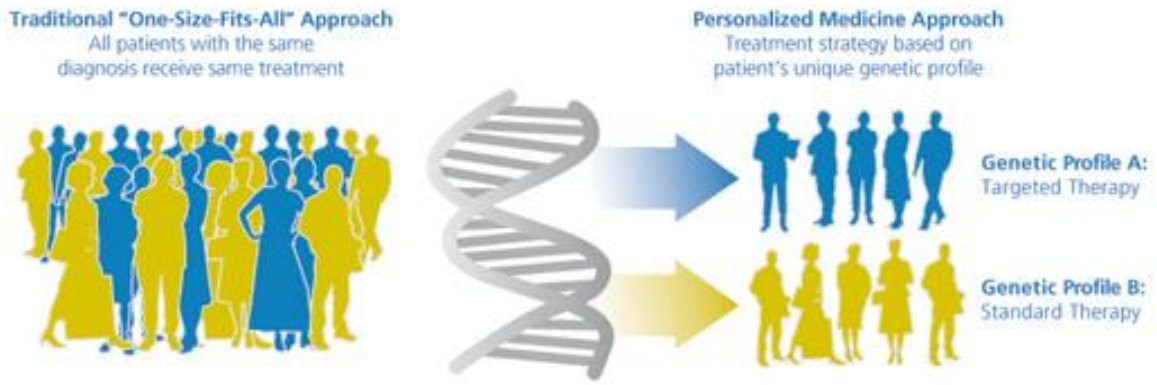


Integrating Genomic, Imaging, and Clinical Data for Precision Medicine

Shawn Murphy MD, Ph.D.
Partners Healthcare and Harvard Medical School
October 4th, 2017

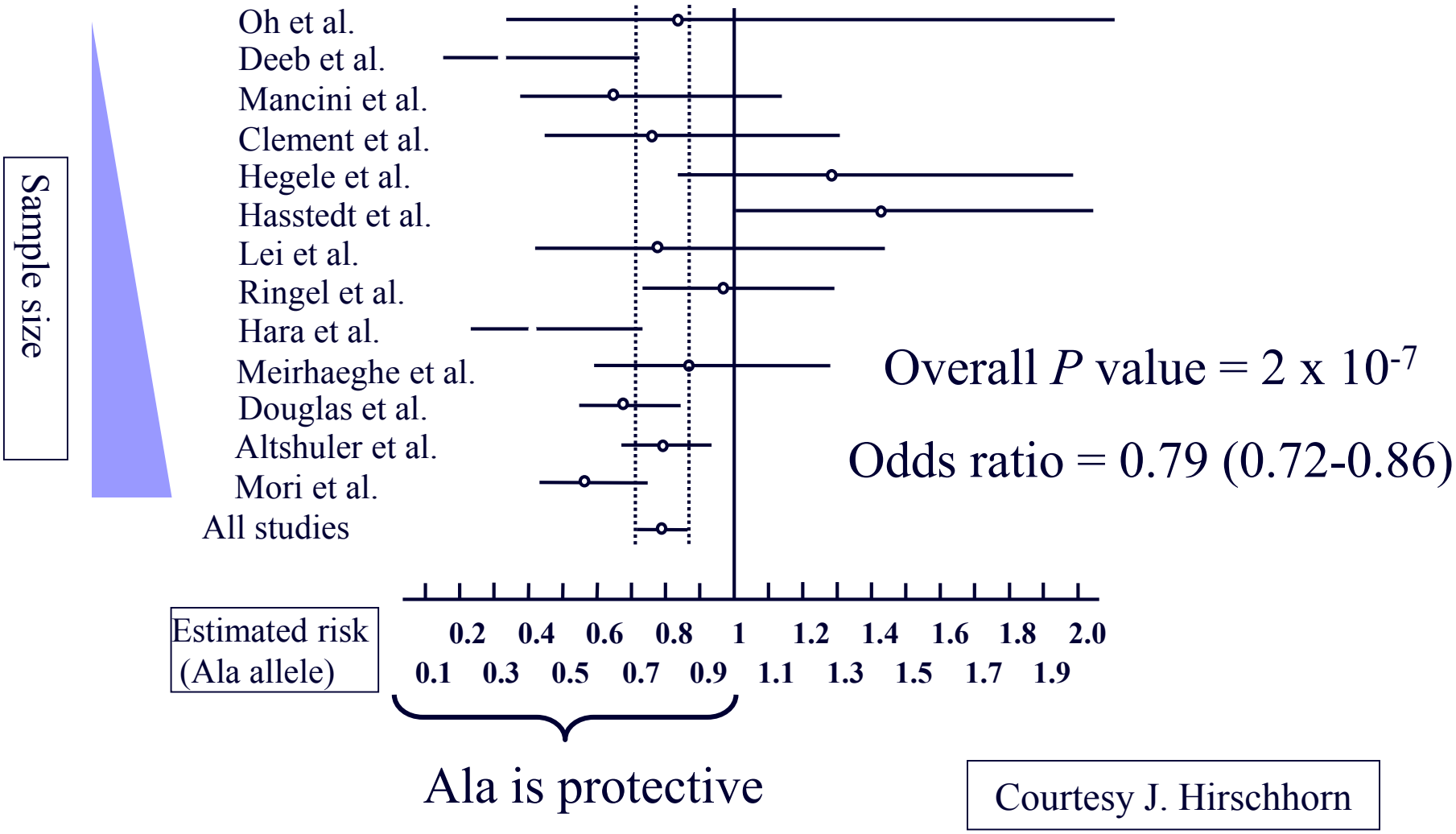
Personalized Medicine and Genomic technology are critical to managing populations



- Managing a population involves improving health outcomes of the group as a whole by identifying, monitoring and addressing health needs of individuals through:
  - Subpopulation stratification
  - Targeted, evidence-based treatment protocols
  - Predictive analytics

Source: Personalized Medicine Coalition and innovation.org ; Oliver Wyman

Example: PPARγ Pro12Ala and Diabetes



Courtesy J. Hirschhorn

High Throughput Methods for supporting Translational Research

- Set of patients is selected from medical record data in a high throughput fashion
- Investigators explore phenotypes of these patients using i2b2 tools and a translational team developed to work specifically with medical record data
- Distributed networks cross institutional boundaries for phenotype selection, public health, and hypothesis testing
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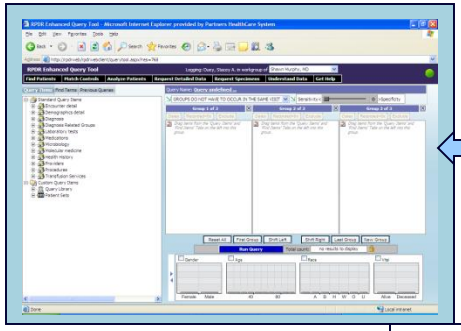
Research Patient Data Registry exists at Partners Healthcare to find patient cohorts for clinical research

1) Queries for aggregate patient numbers

- Warehouse of in & outpatient clinical data
- 6.7 million Partners Healthcare patients
- 2.5 billion diagnoses, medications, procedures, laboratories, & physical findings coupled to demographic & visit data
- Authorized use by faculty status
- Clinicians can construct complex queries
- Queries cannot identify individuals, internally can produce identifiers for (2)

Query construction in web tool



De-identified Data Warehouse

Z731984X
Z74902XX
...
..

Encrypted identifiers

2) Returns identified patient data

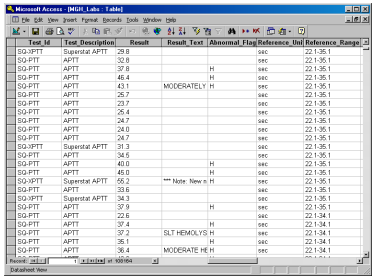
- Start with list of specific patients, usually from (1)
- Authorized use by IRB Protocol
- Returns contact and PCP information, demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology, reports (discharge, LMR, operative, radiology, pathology, cardiology, pulmonary, endoscopy), and images into a Microsoft Access database and text files.

0000004
2185793
...
...

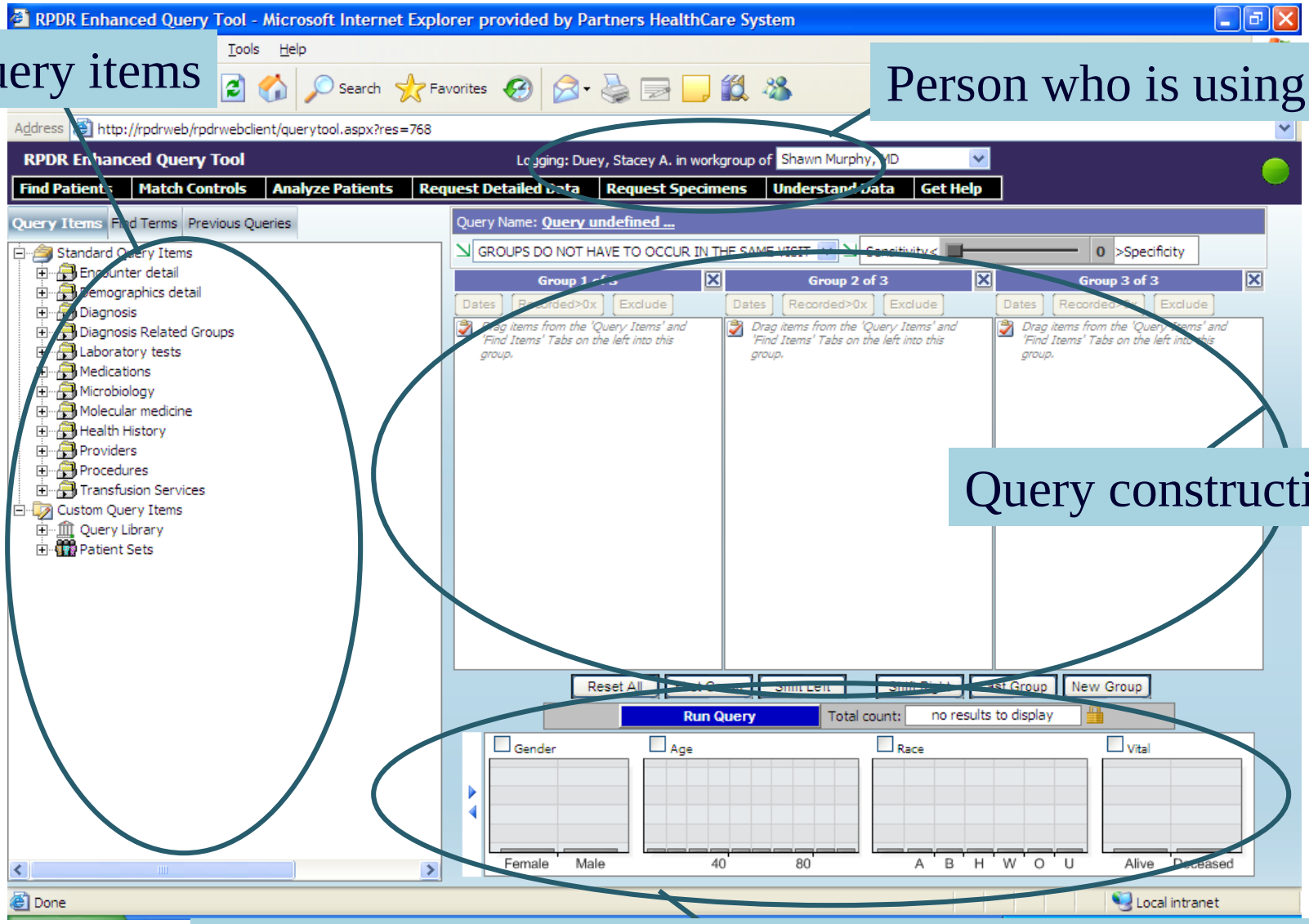
OR

0000004
2185793
...
...

Real identifiers



FINDING PATIENTS

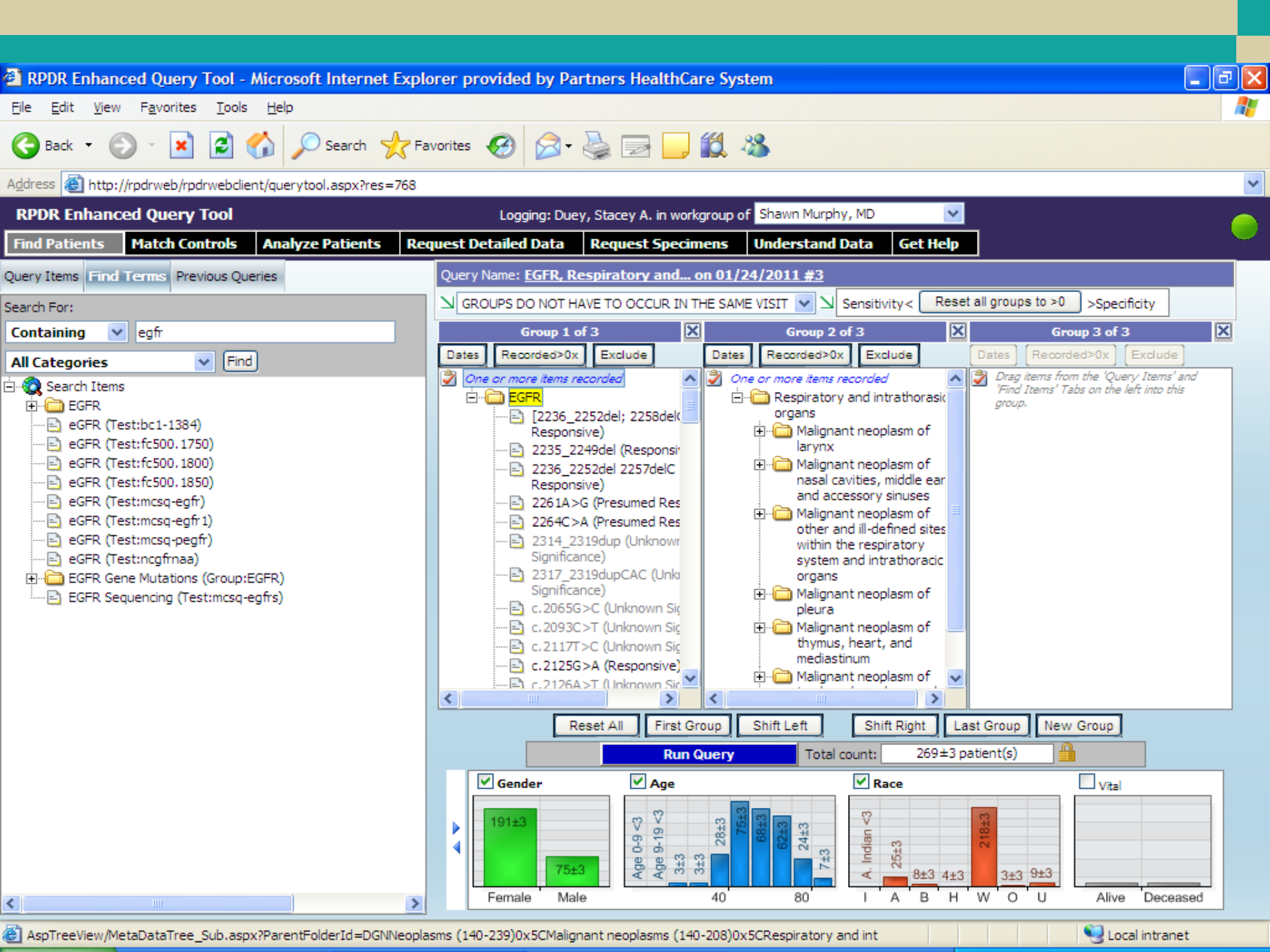


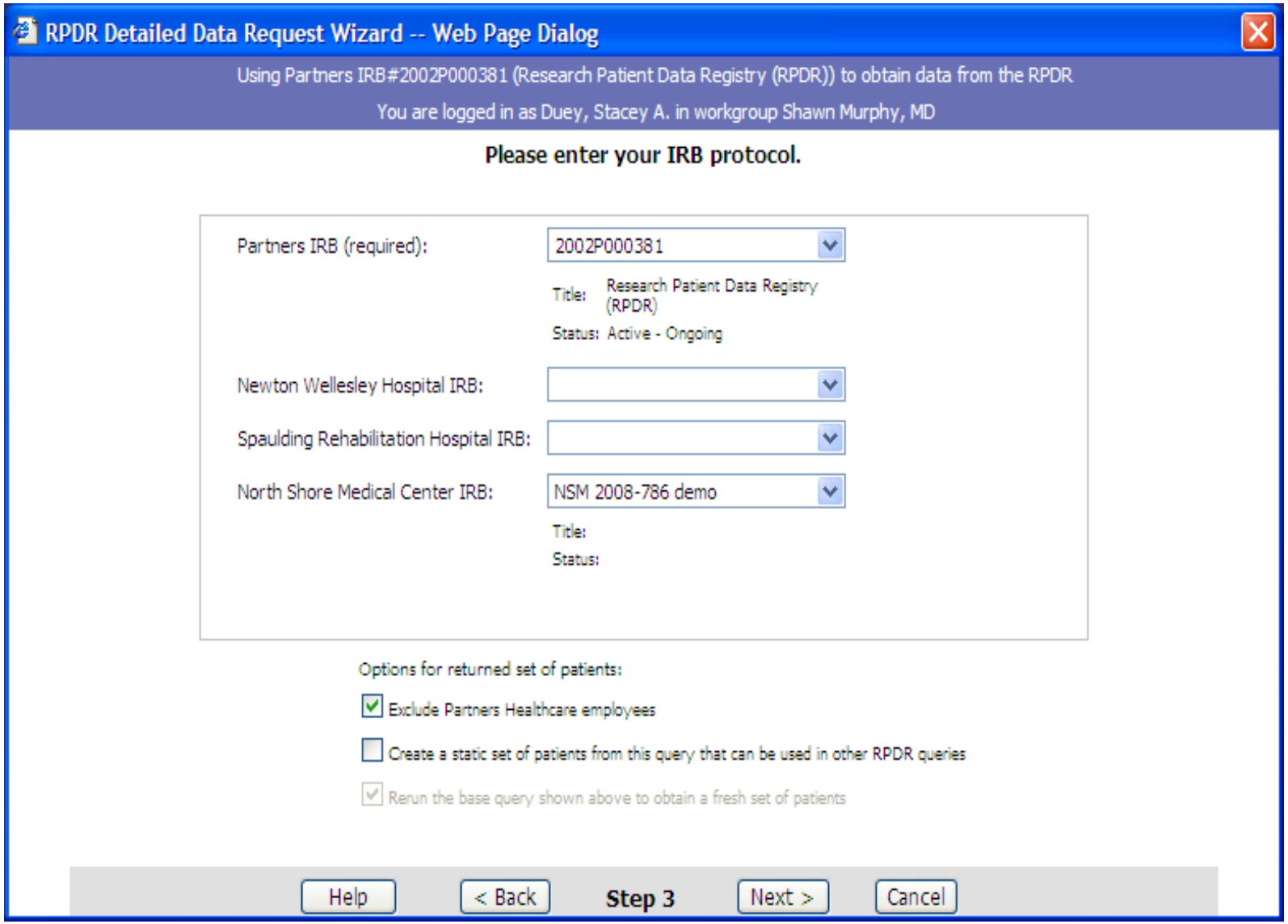
Query items

Person who is using tool

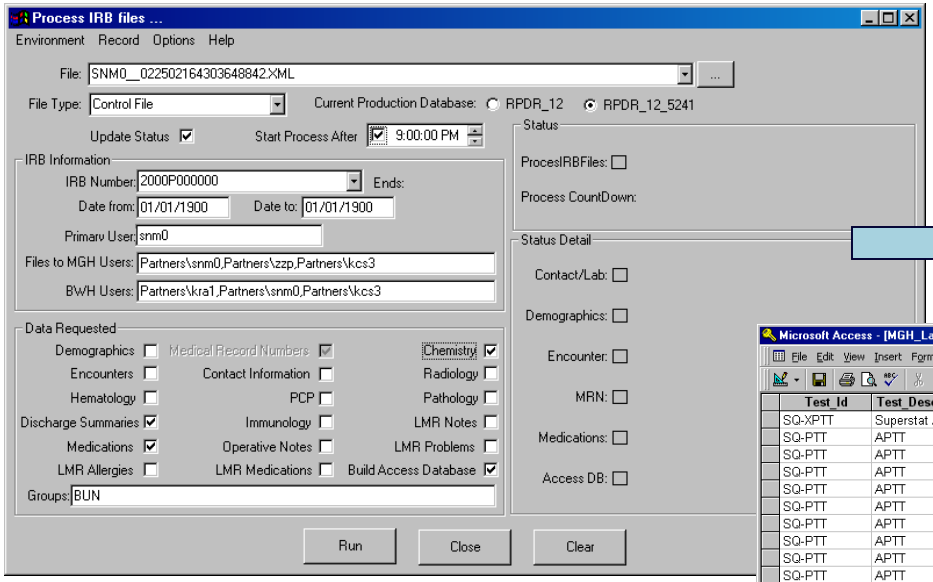
Query construction

Results - broken down by number distinct of patients

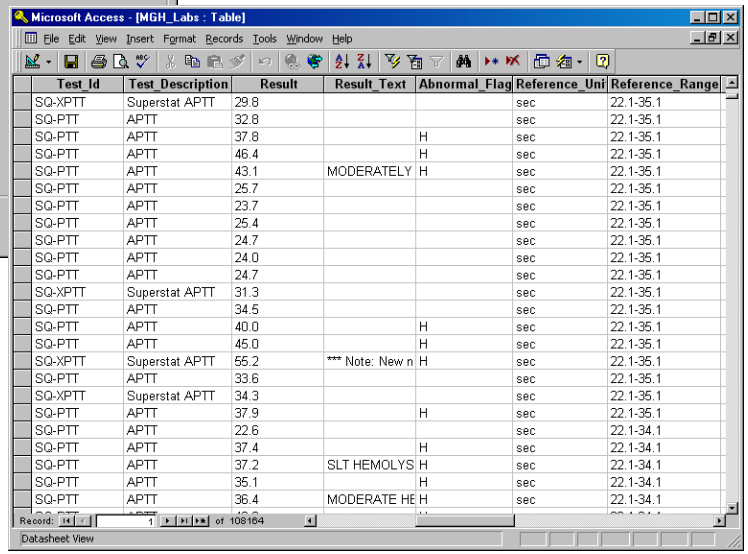

RPDR Enhanced Query Tool - Microsoft Internet Explorer provided by Partners HealthCare System
File Edit View Favorites Tools Help
Back Search Favorites
Address http://rpdrweb/rpdrwebclient/querytool.aspx?res=768
RPDR Enhanced Query Tool
Logging: Duey, Stacey A. in workgroup of Shawn Murphy, MD
Find Patients
Match Controls
Analyze Patients
Request Detailed Data
Request Specimens
Understand Data
Get Help
Query Items
Find Terms
Previous Queries
Search For:
Containing
egfr
All Categories
Find
Search Items
EGFR
eGFR (Test:bc1-1384)
eGFR (Test:fc500.1750)
eGFR (Test:fc500.1800)
eGFR (Test:fc500.1850)
eGFR (Test:mcsq-egfr)
eGFR (Test:mcsq-egfr1)
eGFR (Test:mcsq-pegfr)
eGFR (Test:ncgfrnaa)
EGFR Gene Mutations (Group:EGFR)
EGFR Sequencing (Test:mcsq-egfrs)
Query Name: EGFR, Respiratory and... on 01/24/2011 #3
GROUPS DO NOT HAVE TO OCCUR IN THE SAME VISIT
Sensitivity<
Reset all groups to >0
>Specificity
Group 1 of 3
Group 2 of 3
Group 3 of 3
Dates
Recorded>0x
Exclude
One or more items recorded
EGFR
[2236_2252del; 2258delC Responsive)
2235_2249del (Responsi
2236_2252del 2257delC Responsive)
2261A>G (Presumed Res
2264C>A (Presumed Res
2314_2319dup (Unknown Significance)
2317_2319dupCAC (Unk Significance)
c.2065G>C (Unknown Sig
c.2093C>T (Unknown Sig
c.2117T>C (Unknown Sig
c.2125G>A (Responsive)
Respiratory and intrathoracic organs
Malignant neoplasm of larynx
Malignant neoplasm of nasal cavities, middle ear and accessory sinuses
Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
Malignant neoplasm of pleura
Malignant neoplasm of thymus, heart, and mediastinum
Drag items from the 'Query Items' and 'Find Items' Tabs on the left into this group.
Reset All
First Group
Shift Left
Shift Right
Last Group
New Group
Run Query
Total count:
269±3 patient(s)
Gender
Age
Race
Vital
191±3
75±3
Female
Male
Age 0-9 <3
Age 9-19 <3
3±3
3±3
28±3
75±3
68±3
62±3
24±3
7±3
40
80
A. Indian <3
25±3
8±3
4±3
218±3
3±3
9±3
I
A
B
H
W
O
U
Alive
Deceased
AspTreeView/MetaDataTree_Sub.aspx?ParentFolderId=DGNNeoplasms (140-239)0x5CMalignant neoplasms (140-208)0x5CRespiratory and int
Local intranet


RPDR Detailed Data Request Wizard -- Web Page Dialog
Using Partners IRB#2002P000381 (Research Patient Data Registry (RPDR)) to obtain data from the RPDR
You are logged in as Duey, Stacey A. in workgroup Shawn Murphy, MD
Please enter your IRB protocol.
Partners IRB (required):
2002P000381
Title: Research Patient Data Registry (RPDR)
Status: Active - Ongoing
Newton Wellesley Hospital IRB:
Spaulding Rehabilitation Hospital IRB:
North Shore Medical Center IRB:
NSM 2008-786 demo
Title:
Status:
Options for returned set of patients:
Exclude Partners Healthcare employees
Create a static set of patients from this query that can be used in other RPDR queries
Rerun the base query shown above to obtain a fresh set of patients
Help
< Back
Step 3
Next >
Cancel

Detailed data is gathered



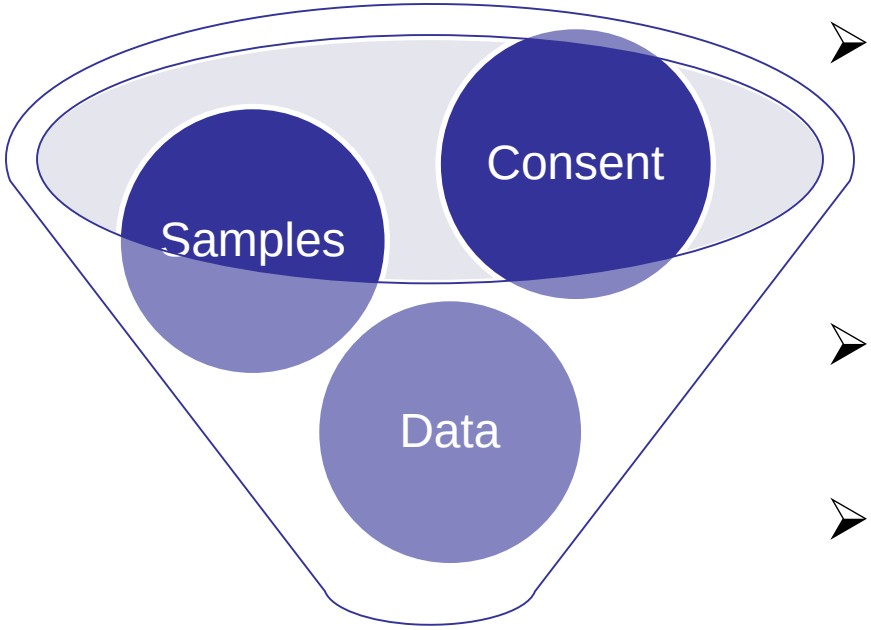
Output files placed in special directory



Data is gathered from RPDR and other Partners sources

Files include Personal Database

The Partners Biobank



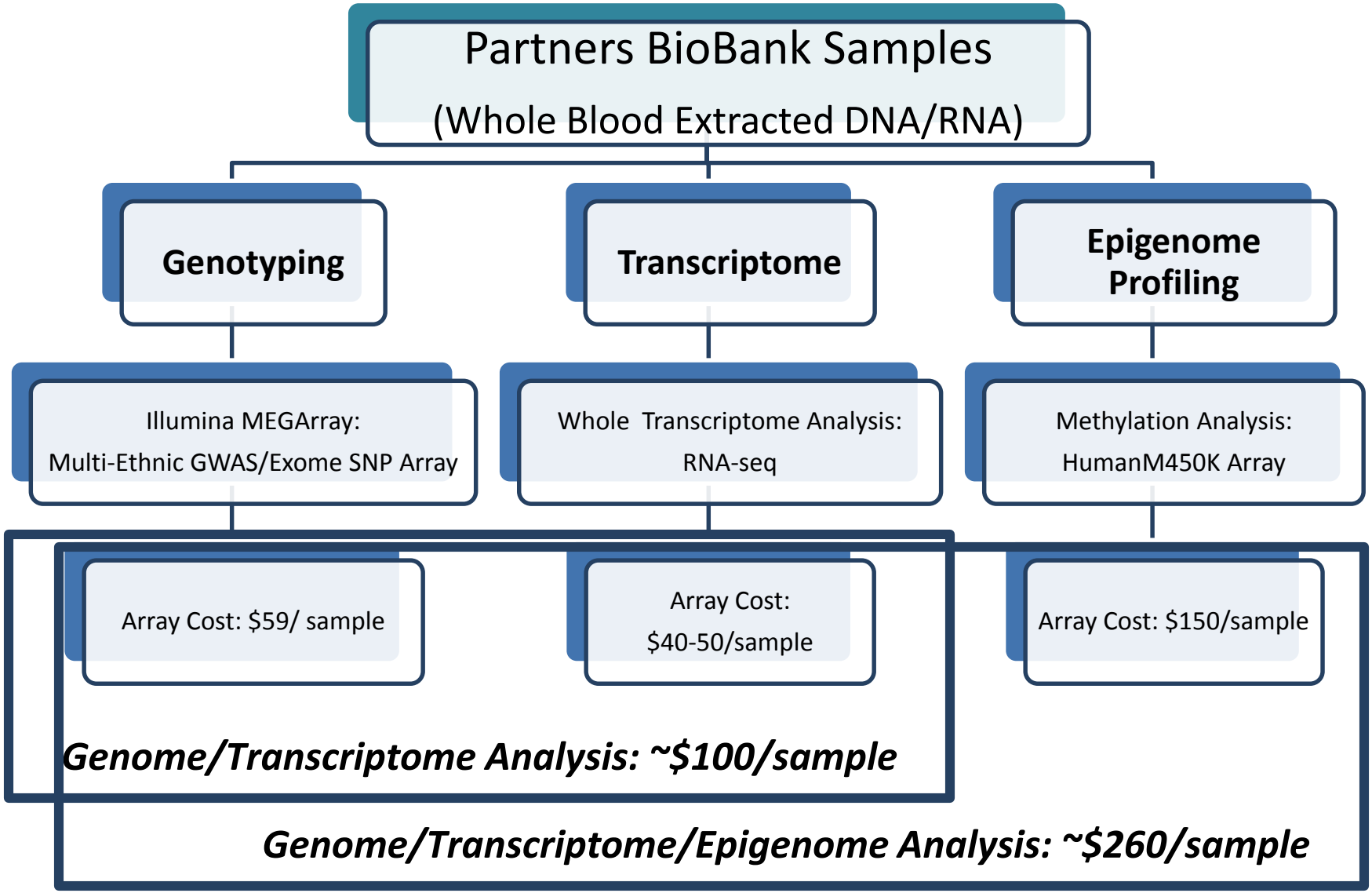
Research Discoveries

- The Partners Biobank provides samples (plasma, serum, and DNA) collected from consented patients.
- 64,000 patients have consented to date
- Samples are available for distribution to Partners investigators* to help identify novel Personalized Medicine opportunities that reduce cost and provide better care

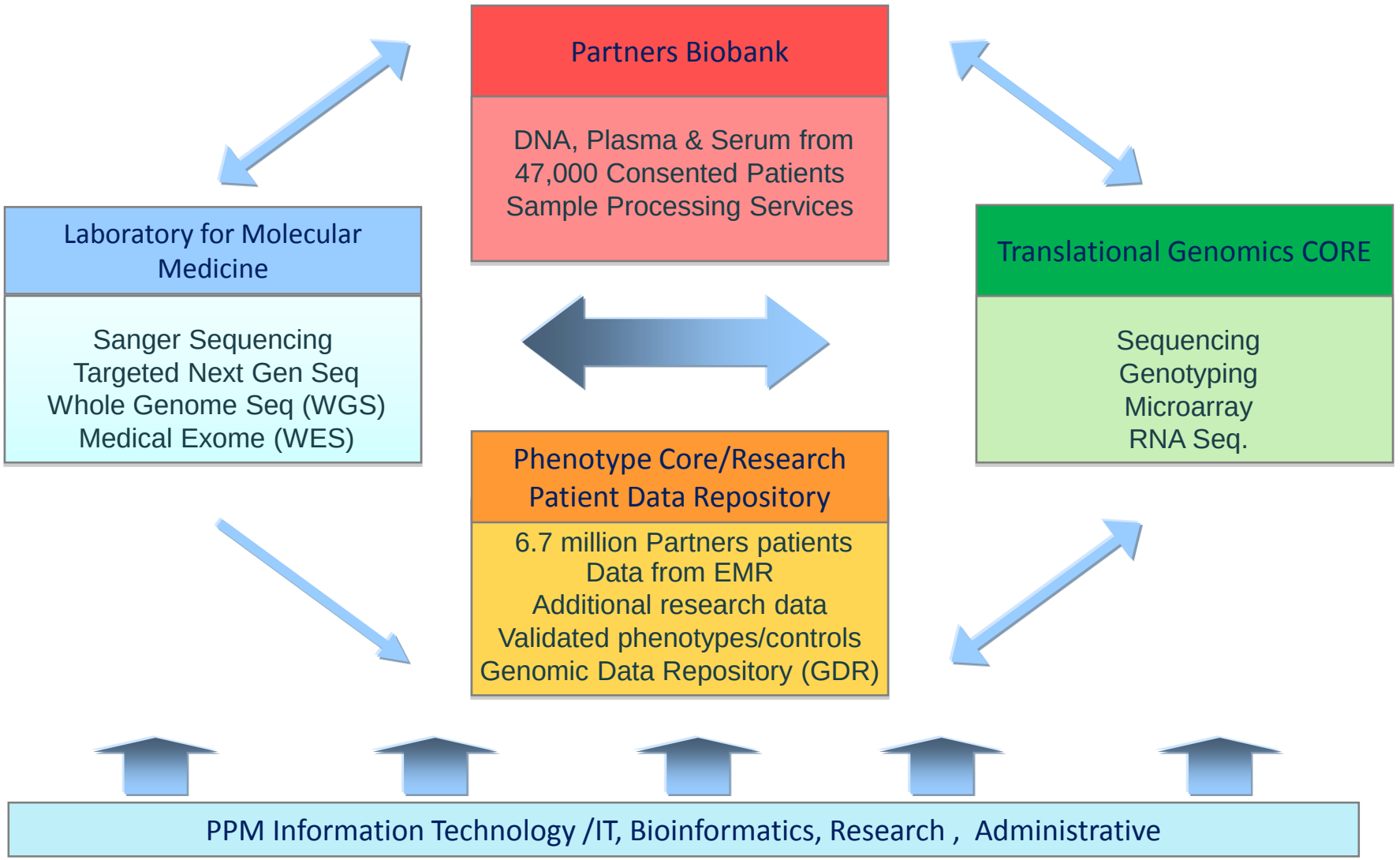
**with required approval from the Partners Institutional Review Board (IRB).*

Improved Clinical Care for All Patients

Biobank Integrative Genomics Strategy



Partners Personalized Medicine Components



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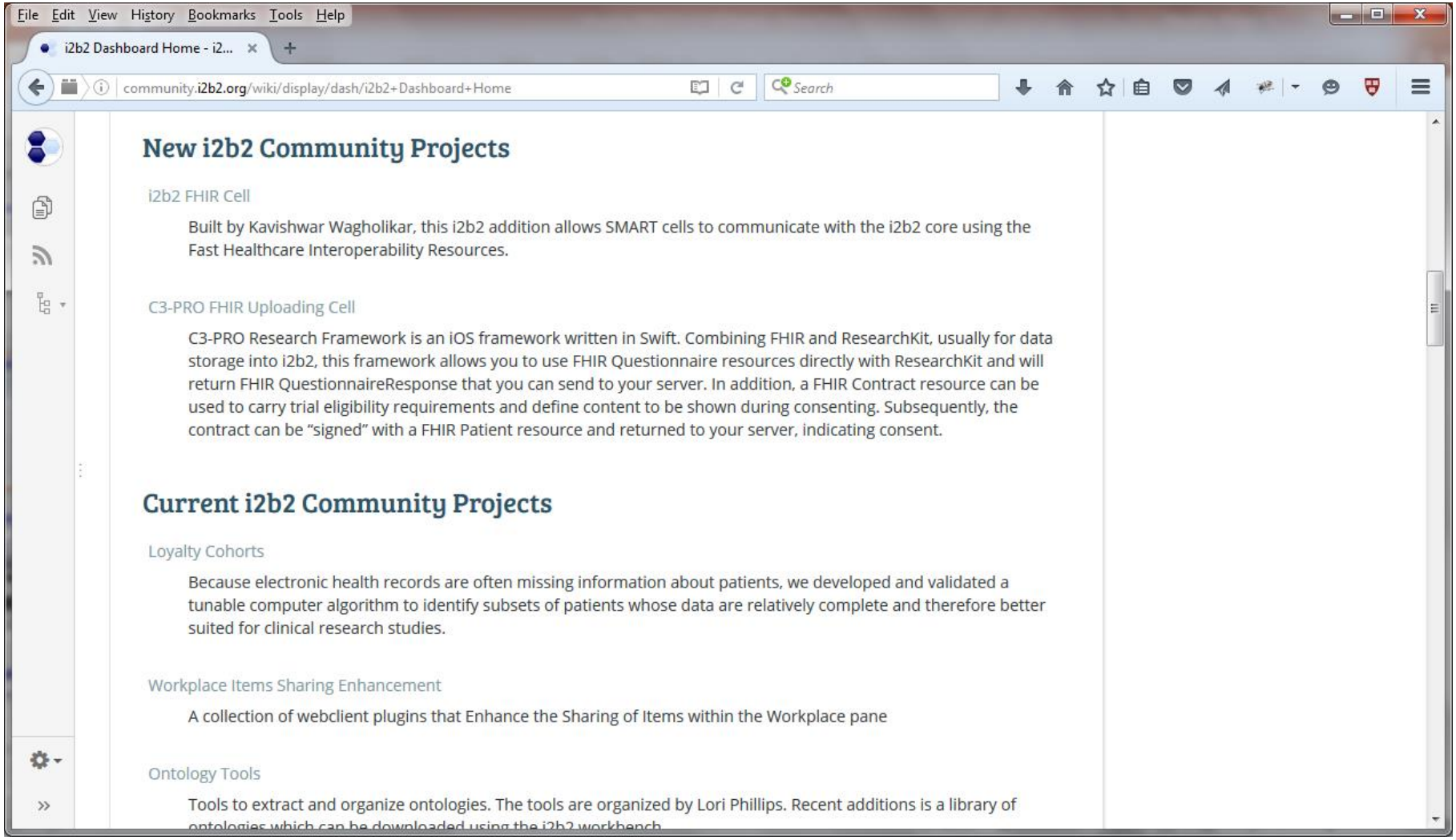
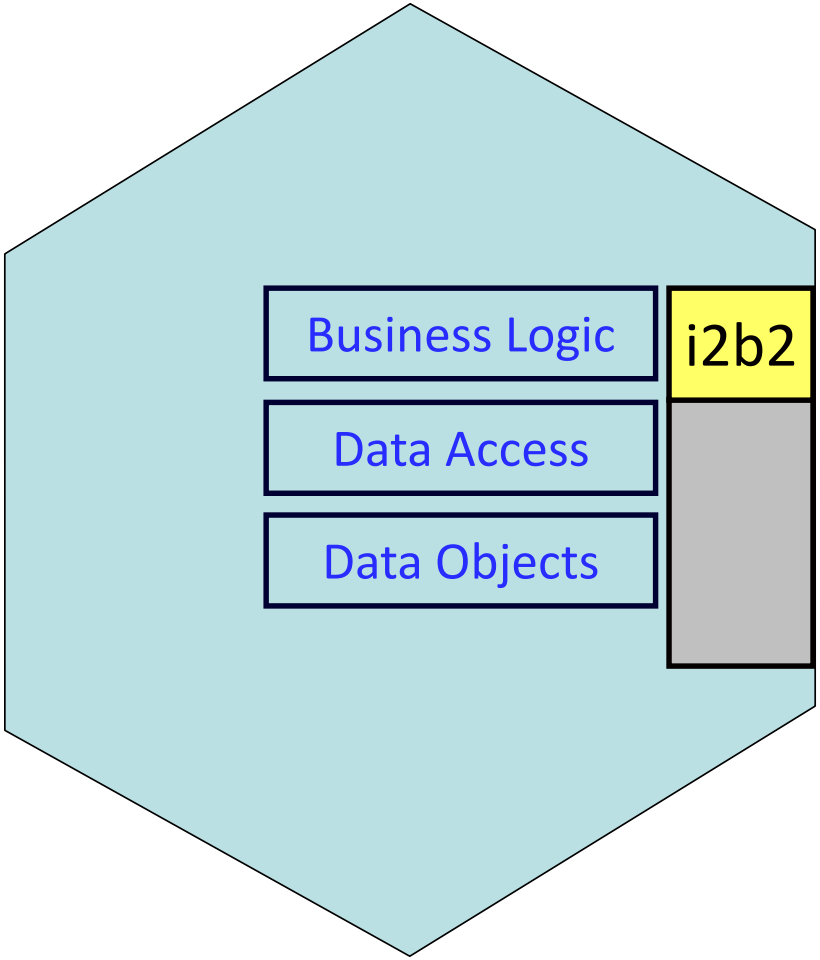
RPDR Evolved into international “Informatics for Integrating Biology and the Bedside (i2b2)” sponsored by the National Institutes of Health, what is it?

- Software for explicitly organizing and transforming person-oriented clinical data to a way that is optimized for clinical genomics research
  - Allows integration of clinical data, trials data, and genotypic data
- A portable and extensible application framework
  - Software is built in a modular pattern that allows additions without disturbing core parts
  - Available as open source at https://www.i2b2.org

I2b2 Community Software Modules contributed as “Cells”



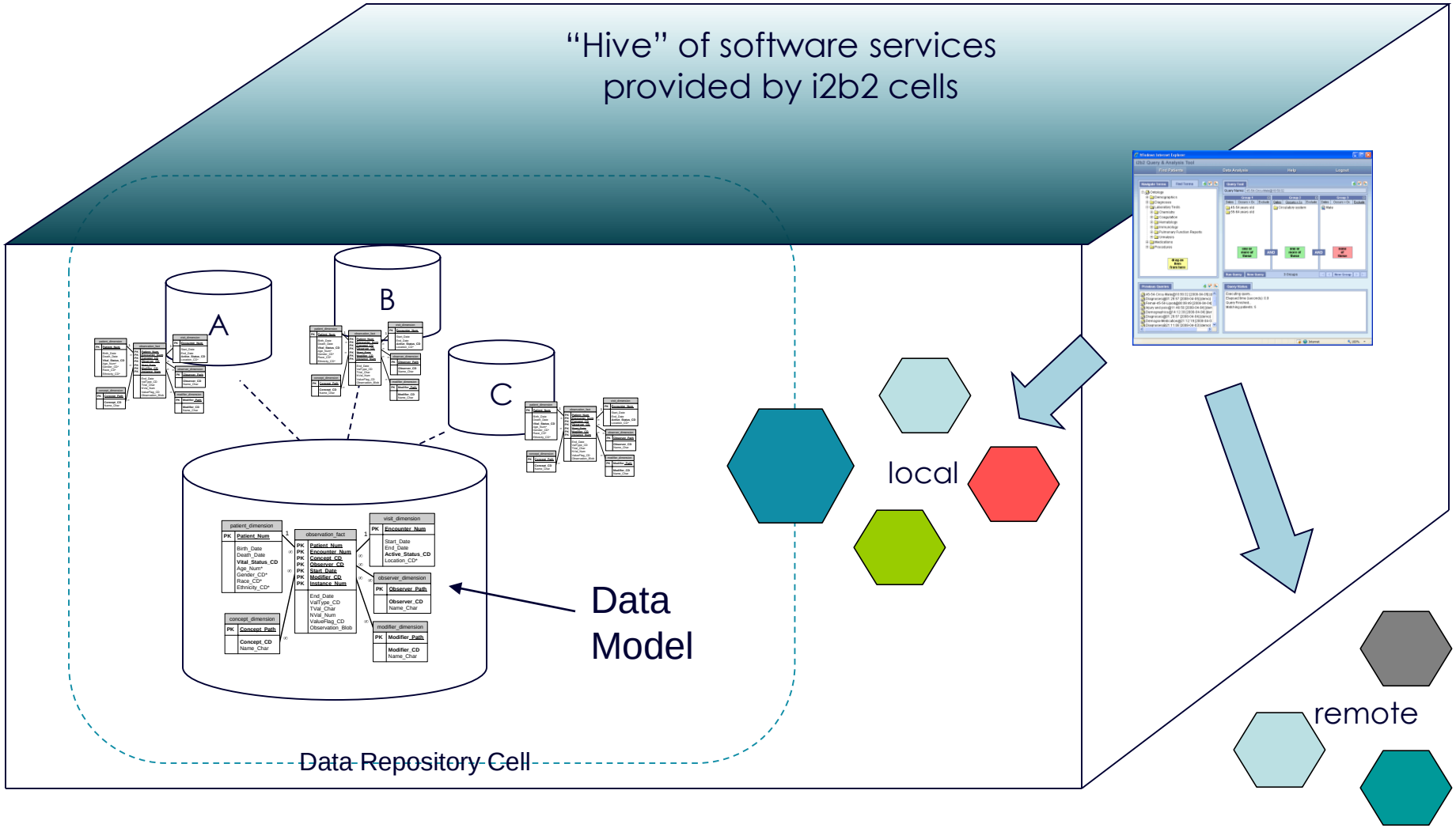
i2b2 Cell: The Canonical Software Module



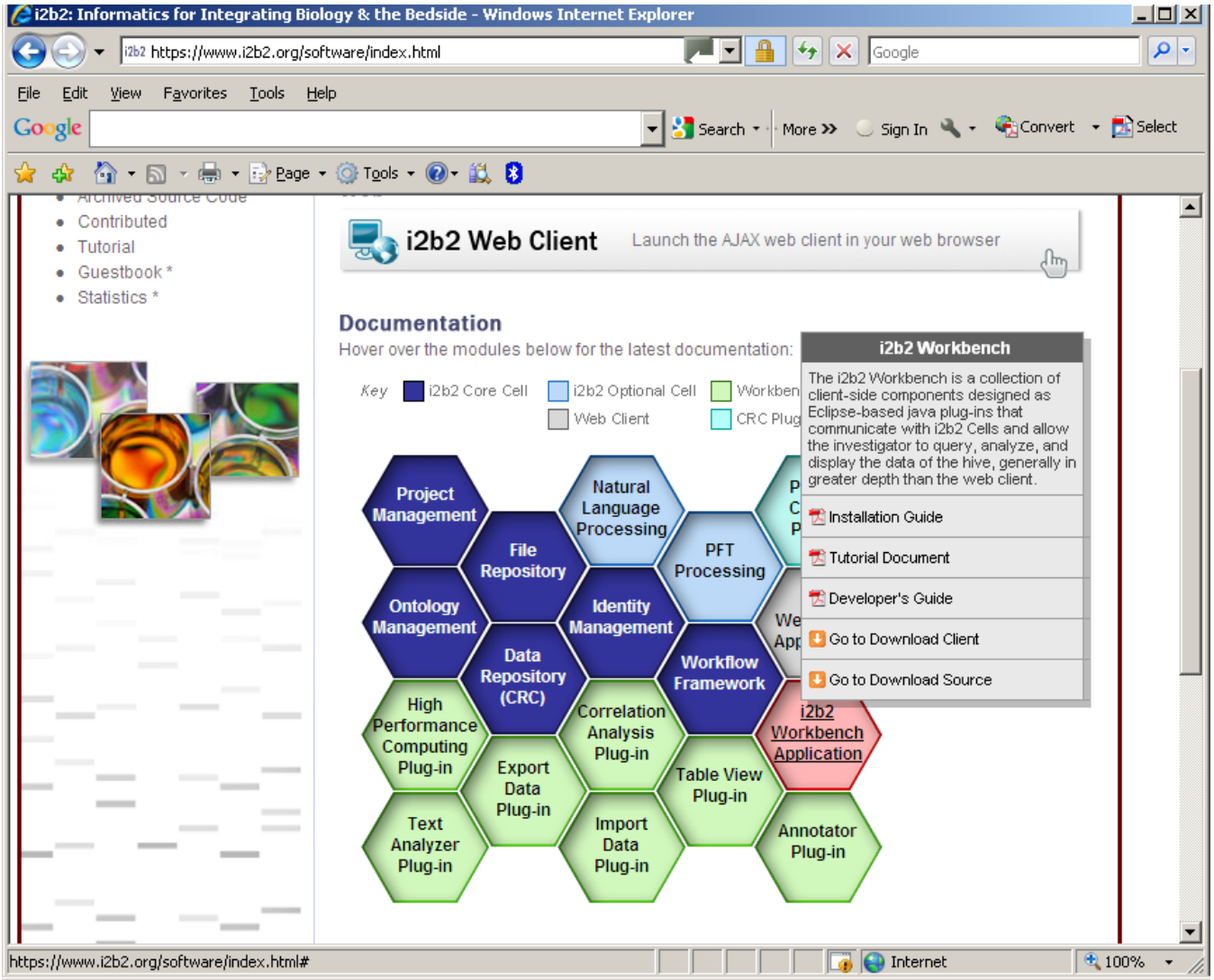
HTTP XML

(minimum: RESTful)

An i2b2 Environment (the Hive) is built from i2b2 Cells



I2b2 Software components are distributed as open source



Implementations

CTSA's

- Boston University
- Case Western Reserve University (*including Cleveland Clinic*)
- Children's National Medical Center (GWU), Washington D.C.
- Duke University
- Emory University (*including Morehouse School of Medicine and Georgia Tech*)
- Harvard University (*including Beth Israel Deaconness Medical Center, Brigham and Women's Hospital, Children's Hospital Boston, Dana Farber Cancer Center, Joslin Diabetes Center, Massachusetts General Hospital*)
- Medical University of South Carolina
- Medical College of Wisconsin
- Oregon Health & Science University
- Penn State MIlton S. Hershey Medical Center
- Tufts University
- University of Alabama at Birmingham
- University of Arkansas for Medical Sciences
- University of California Davis
- University of California, Irvine
- University of California, Los Angeles*
- University of California, San Diego*
- University of California San Francisco
- University of Chicago
- University of Cincinnati (including *Cinncinati Children's Hospital Medical Center*)
- University of Colorado Denver (including *Children's Hospital Colorado*)
- University of Florida
- University of Kansas Medical Center
- University of Kentucky Research Foundation
- University of Massachusetts Medical School, Worcester
- University of Michigan
- University of Pennsylvania (including *Children's Hospital of Philadelphia*)
- University of Pittsburgh (including their *Cancer Institute*)
- University of Rochester School of Medicine and Dentistry
- University of Texas Health Sciences Center at Houston
- University of Texas Health Sciences Center at San Antonio
- University of Texas Medical Branch (Galveston)
- University of Texas Southwestern Medical Center at Dallas
- University of Utah
- University of Washington
- University of Wisconsin - Madison (*including Marshfield Clinic*)
- Virginia Commonwealth University
- Weill Cornell Medical College

Academic Health Centers (does not include AHCs that are part of a CTSA):

- Arizona State University
- City of Hope, Los Angeles
- Georgia Health Sciences University, Augusta
- Hartford Hospital, CN
- HealthShare Montana
- Massachusetts Veterans Epidemiology Research and Information Center (MAVERICK), Boston
- Nemours
- Phoenix Children's Hospital
- Regenstrief Institute
- Thomas Jefferson University
- University of Connecticut Health Center
- University of Missouri School of Medicine
- University of Tennessee Health Sciences Center
- Wake Forest University Baptist Medical Center

HMOs:

- Group Health Cooperative
- Kaiser Permanente

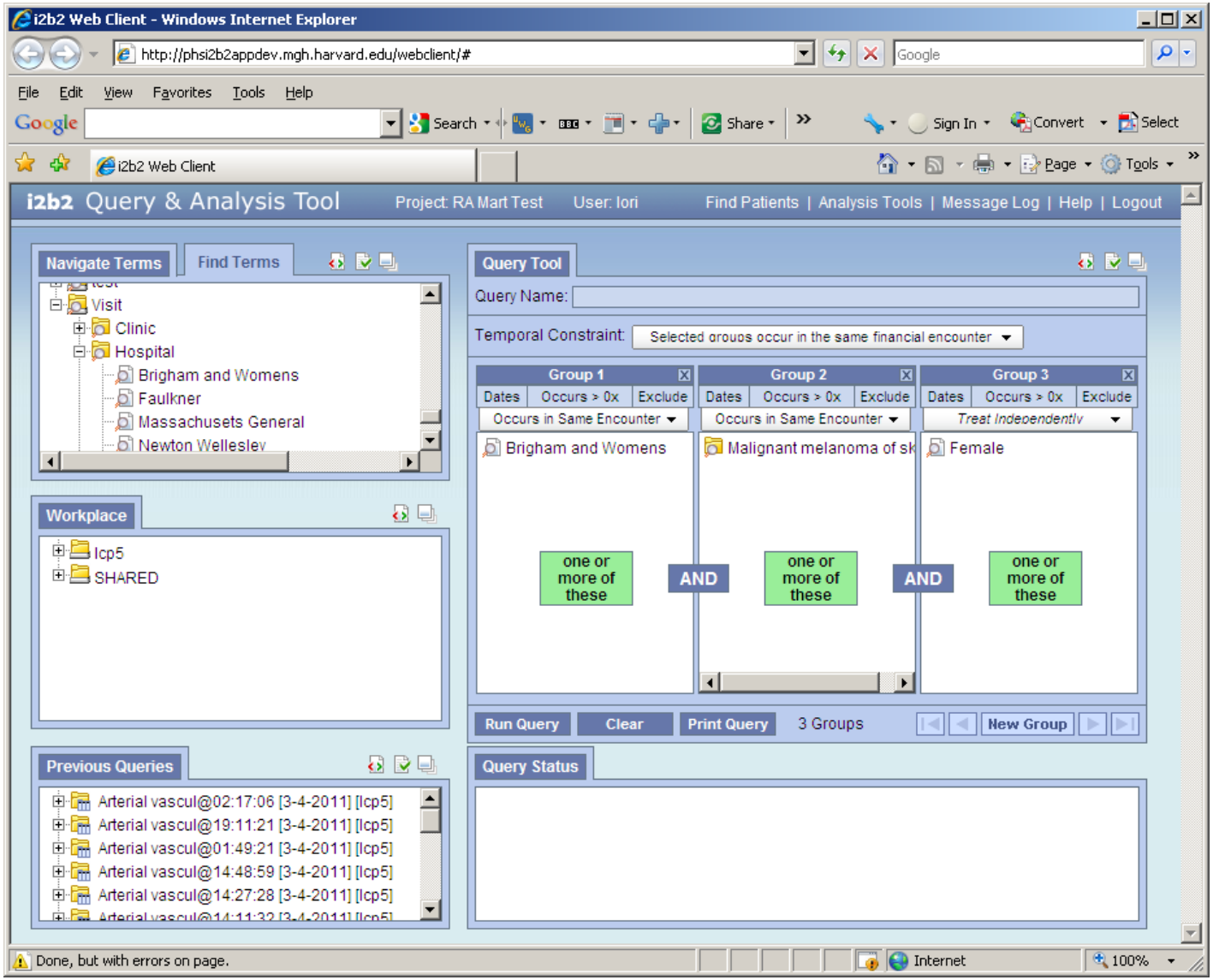
International:

- Georges Pompidou Hospital, Paris, France
- Hospital of the Free University of Brussels, Belgium
- Inserm U936, Rennes, France
- Institute for Data Technology and Informatics (IDI), NTNU, Norway
- Institute for Molecular Medicine Finland (FIMM)
- Karolinska Institute, Sweden
- Landspitali University Hospital, Reykjavik, Iceland
- Tokyo Medical and Dental University, Japan
- University of Bordeau Segalen, France
- University of Erlangen-Nuremberg, Germany
- University of Goettingen, Goettingen, Germany
- University of Leicester and Hospitals, England (Biomed. Res. Informatics Ctr. for Clin. Sci)
- University of Pavia, Pavia, Italy
- University of Seoul, Seoul, Korea

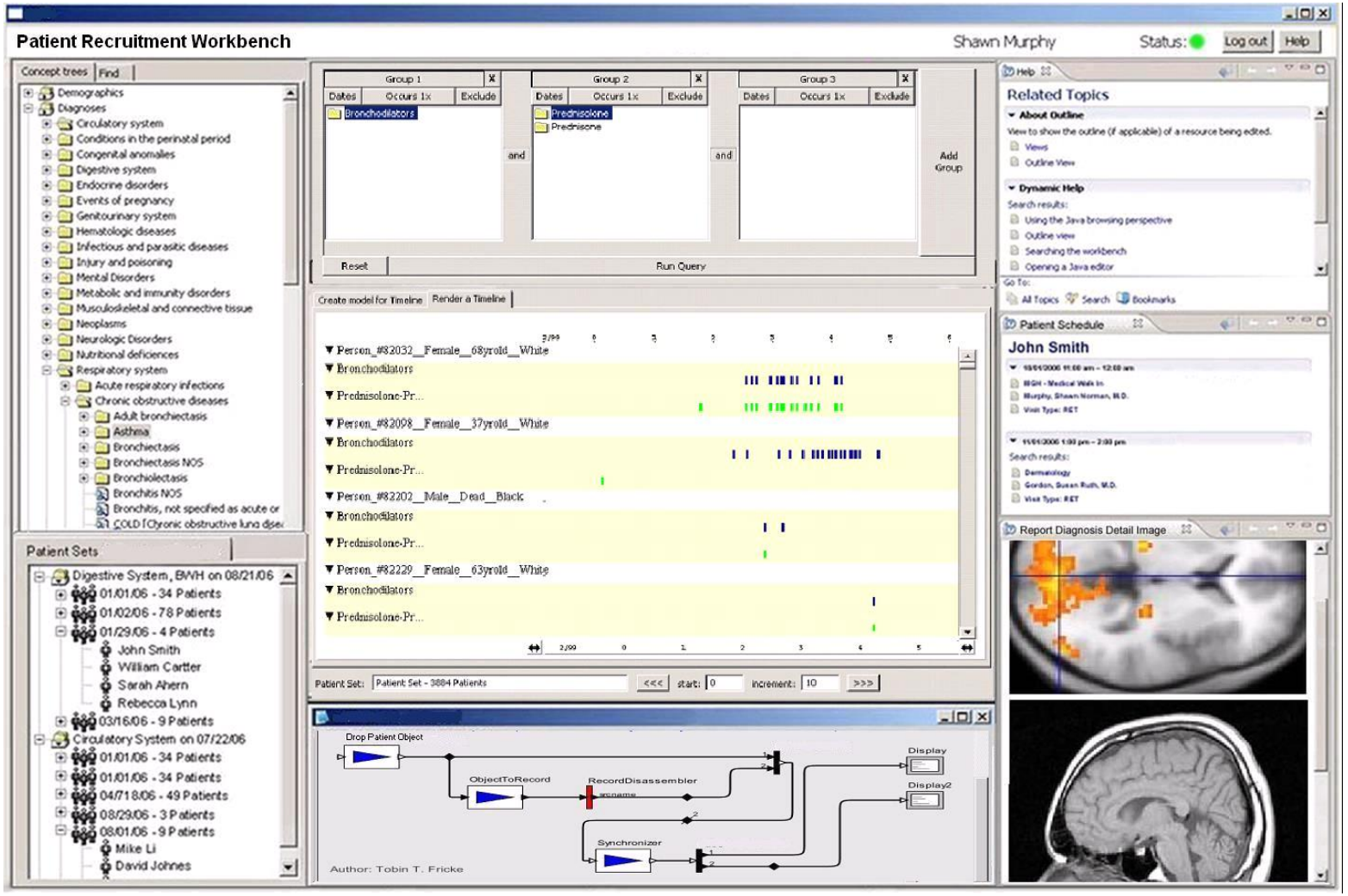
Companies:

- Johnson and Johnson (TransMART)
- GE Healthcare Clinical Data Services

Interogation can occur through i2b2 web client



I2b2 Workbench provides a detailed patient view for Investigator



Psychological Medicine (2012), **42**, 41–50. © Cambridge University Press 2011
doi:10.1017/S0033291711000997

ORIGINAL ARTICLE

Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model

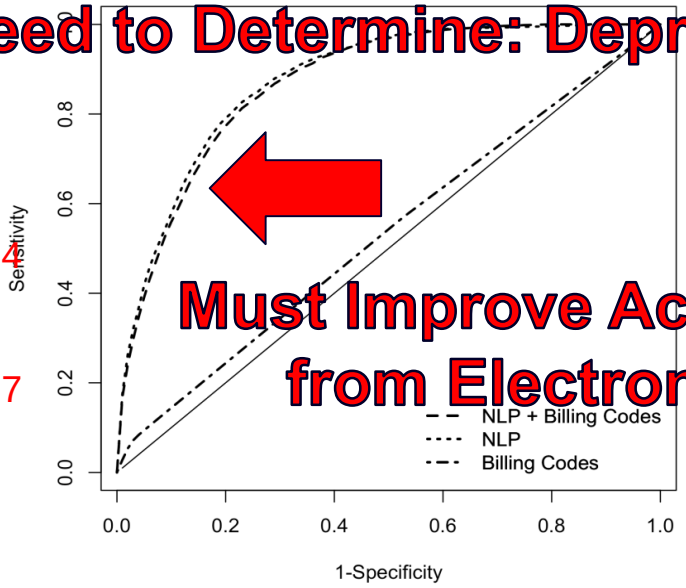
R. H. Perlis[1,2*], D. V. Iosifescu[1,3], V. M. Castro[4], S. N. Murphy[5], V. S. Gainer[4], J. Minnier[6], T. Cai[6], S. Goryachev[4], Q. Zeng[7], P. J. Gallagher[2], M. Fava[1], J. B. Weilburg[1], S. E. Churchill[8], I. S. Kohane[9] and J. W. Smoller[2]

Use Phenotyping Algorithms to define cohorts of treatment-resistant and treatment-responsive depression

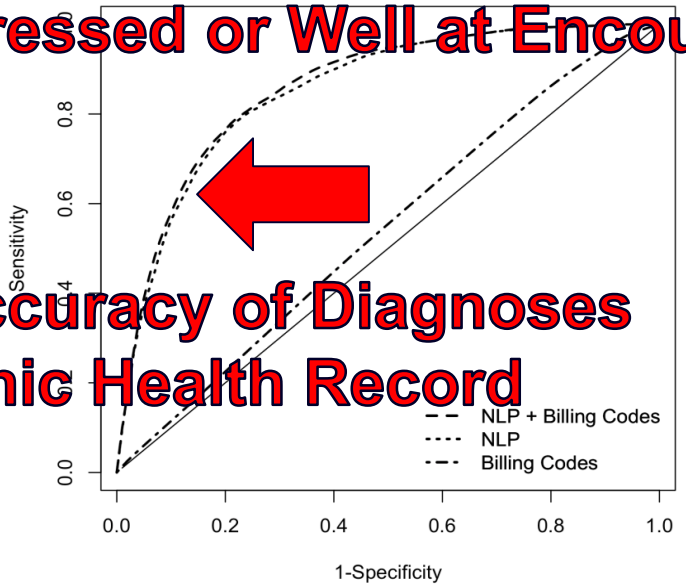
Need to Determine: Depressed or Well at Encounter

Initially:
AUC = 0.54

Finally:
AUC = 0.87



Must Improve Accuracy of Diagnoses from Electronic Health Record

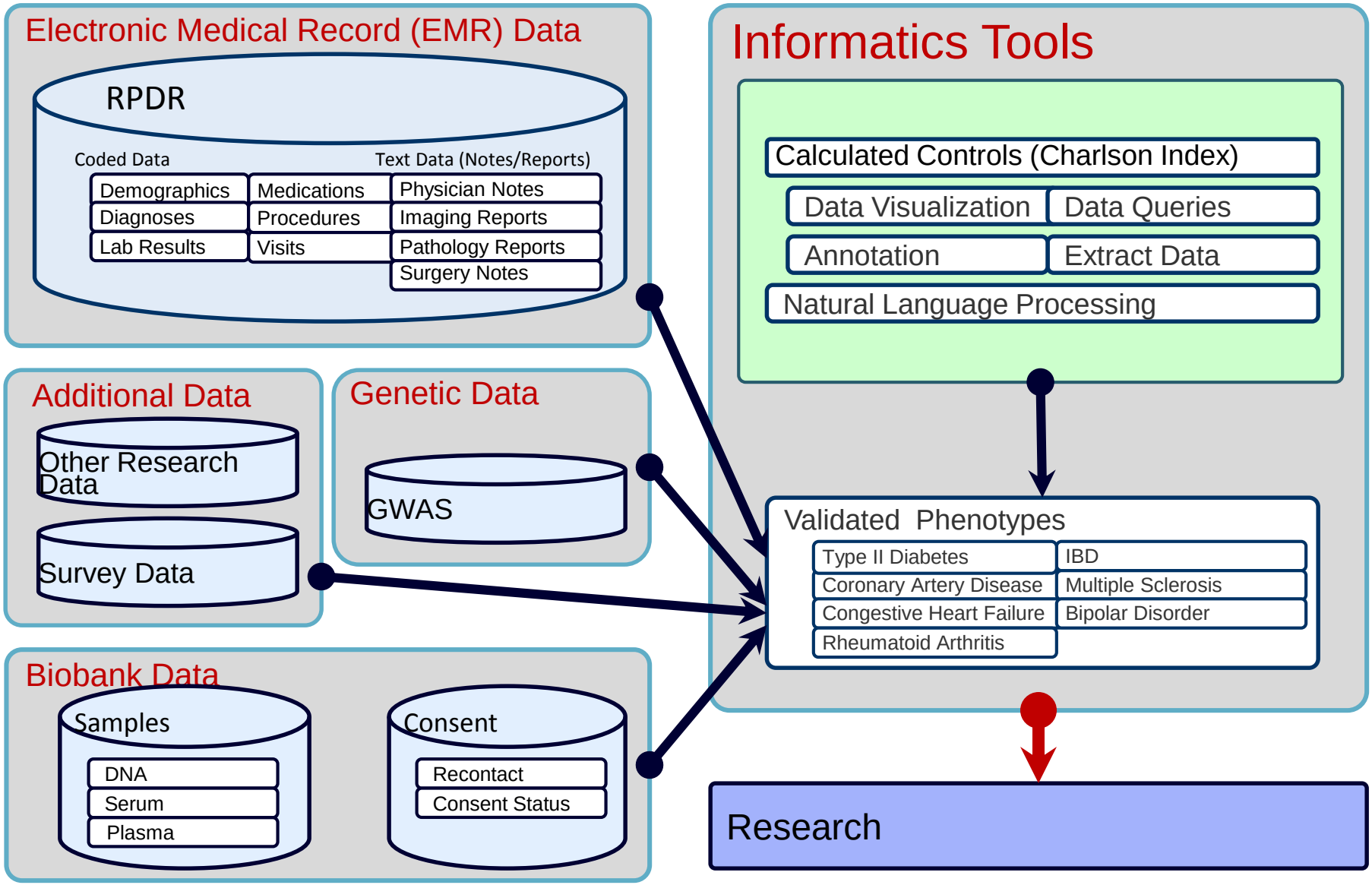


Initially:
AUC = 0.55

Finally:
AUC = 0.86

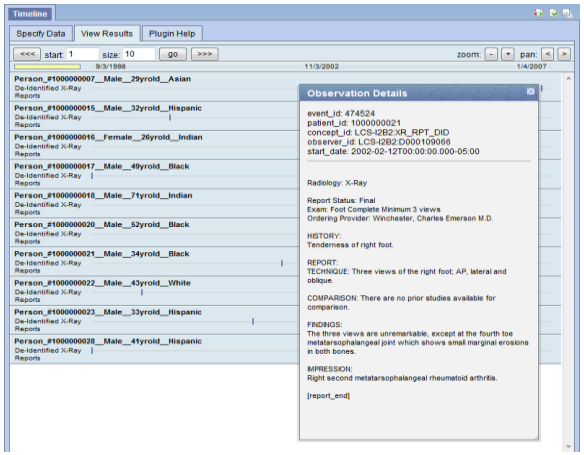
Clinical Status	Model	Specificity	Sensitivity	Precision	AUC
Depressed	Billing Codes	0.95	0.09 (0.03)	0.57 (0.14)	0.54 (0.02)
Depressed	NLP	0.95	0.42 (0.05)	0.78 (0.02)	0.88 (0.02)
Depressed	NLP + Billing Codes	0.95	0.39 (0.06)	0.78 (0.02)	0.87 (0.02)
Well	Billing Codes	0.95	0.06 (0.02)	0.26 (0.27)	0.55 (0.03)
Well	NLP	0.95	0.37 (0.06)	0.86 (0.02)	0.85 (0.02)
Well	NLP + Billing Codes	0.95	0.39 (0.07)	0.85 (0.02)	0.86 (0.02)

Data Integration | Phenotype Discovery Center

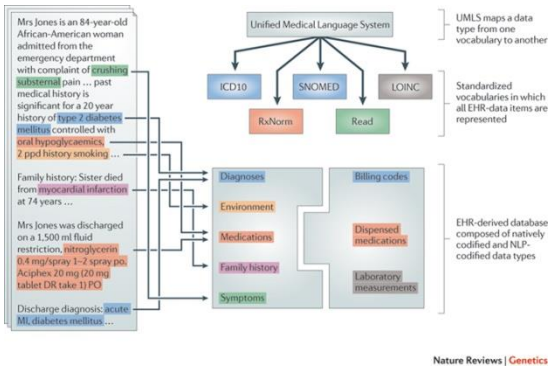


Curating a Disease Algorithm

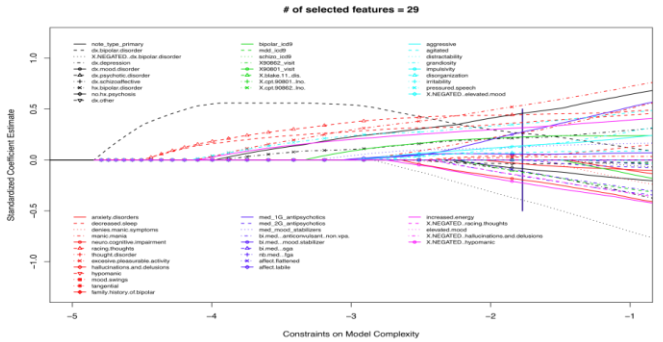
1. Create a gold standard training set.



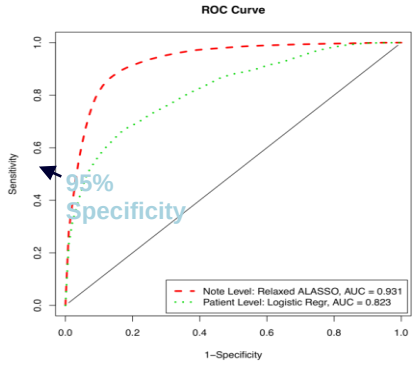
2. Create a comprehensive list of features from patient's electronic data that describe the disease of interest



3. Develop the classification algorithm. Using the data analysis file and the training set from step 1, assess the frequency of each variable. Remove variables with low prevalence. Apply adaptive LASSO penalized logistic regression to identify highly predictive variables for the algorithm

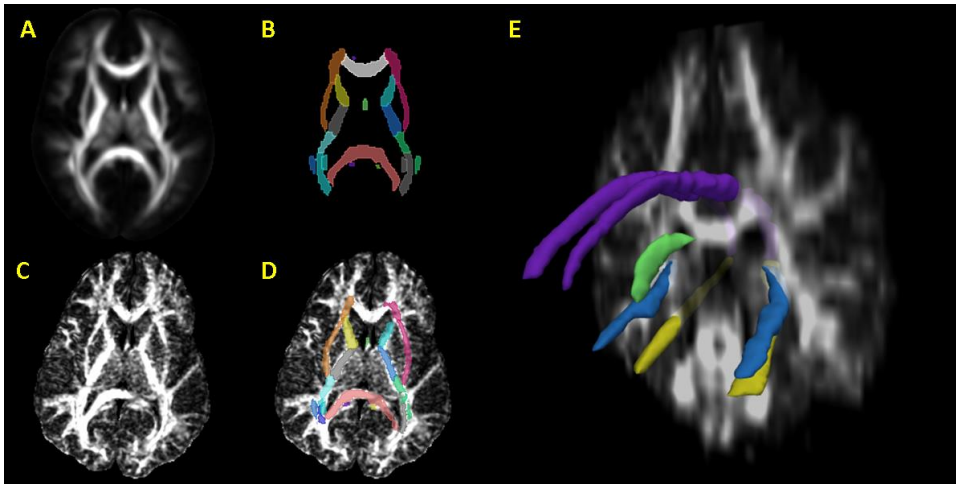


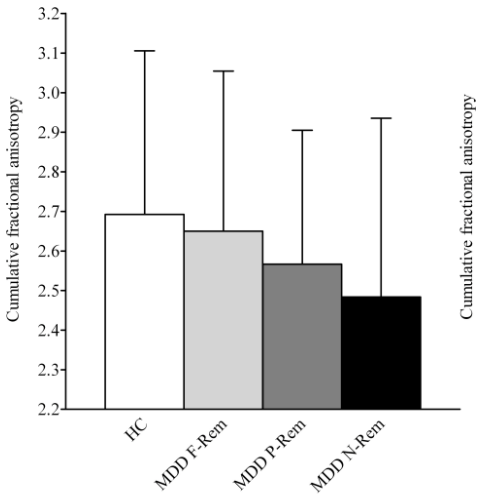
4. Apply the algorithm to all subjects in the superset and assign each subject a probability of having the phenotype

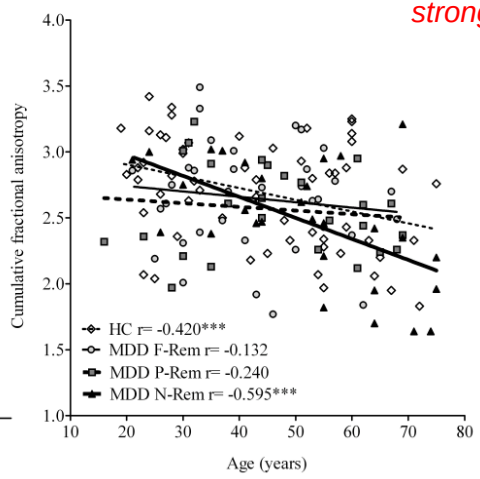


White matter abnormalities associated with treatment-resistant depression

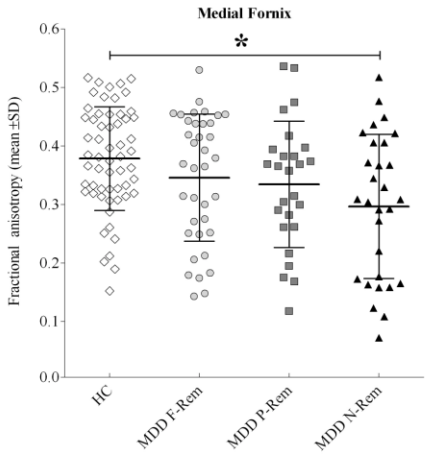
- Scans collected as part of routine clinical care
- Diffusion tensor imaging in 150 pts
- Age-related decline in white matter integrity increases with treatment resistant depression







Medial fornix shows strongest effect



Hoogenboom et al. World J Biol Psychiatry, 2012

Biobank Portal | Curated Diseases

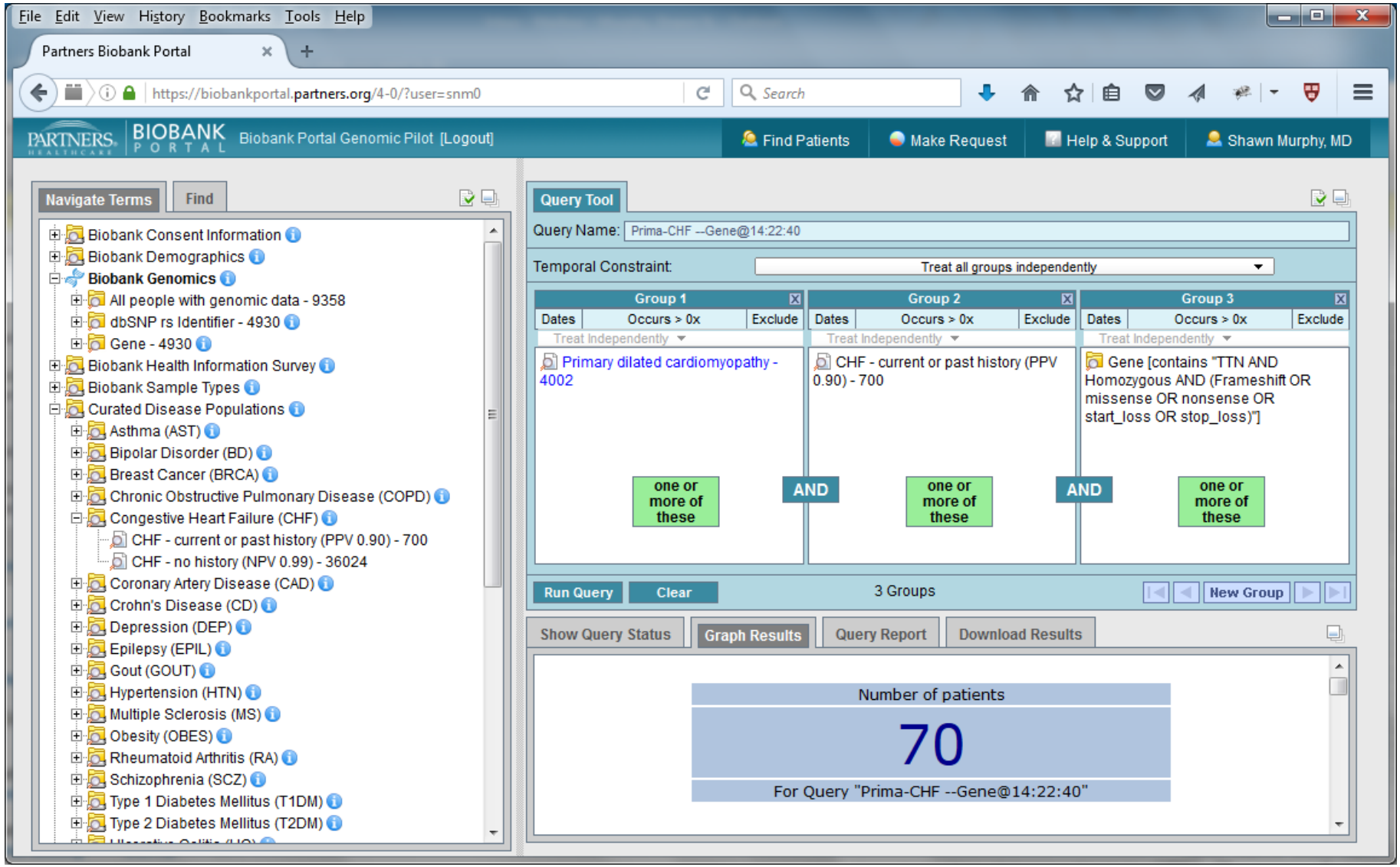
Validated Phenotype	Count*	Predictive Positive Value
Bipolar Disease	71	89%
Congestive Heart Failure	387	90%
Coronary Artery Disease	2,420	97%
Crohn's Disease	453	90%
Multiple Sclerosis	94	90%
Rheumatoid Arthritis	550	90%
Type 2 Diabetes Mellitus	1,887	97%
Ulcerative Colitis	330	90%

Healthy Controls based on Charlson Index	Count**
0 – 10-year survival probability is >98.3%	2,206
1 – 10-year survival probability is >95.87%	4,343
2 – 10-year survival probability is >90.15%	6,545

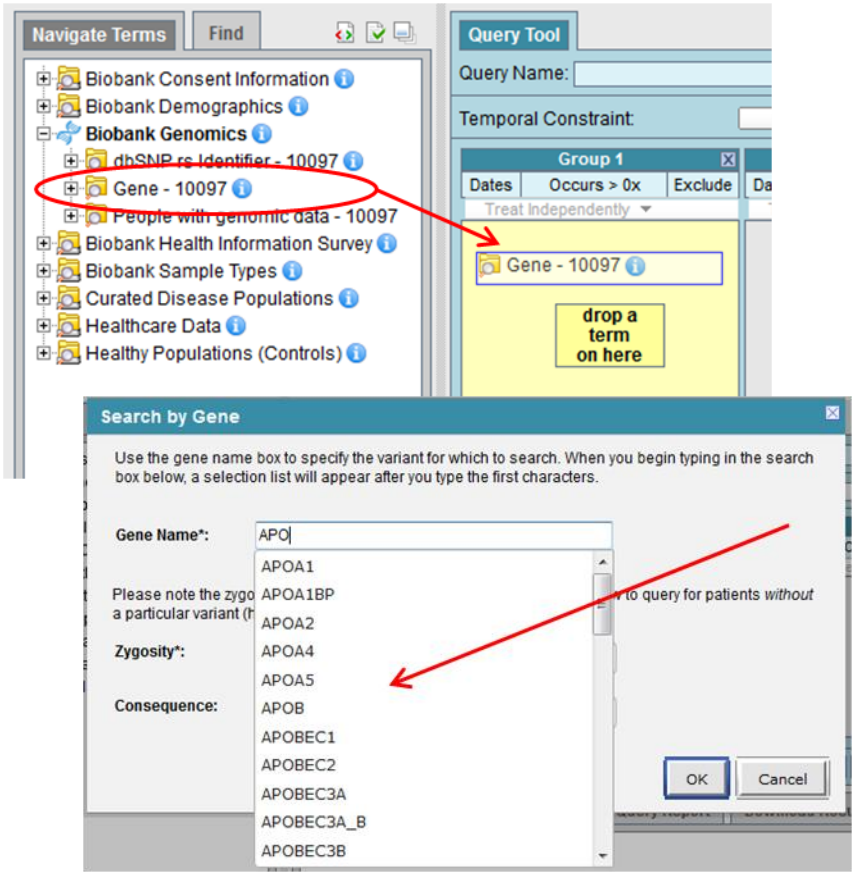
* Based on 15,880 patients

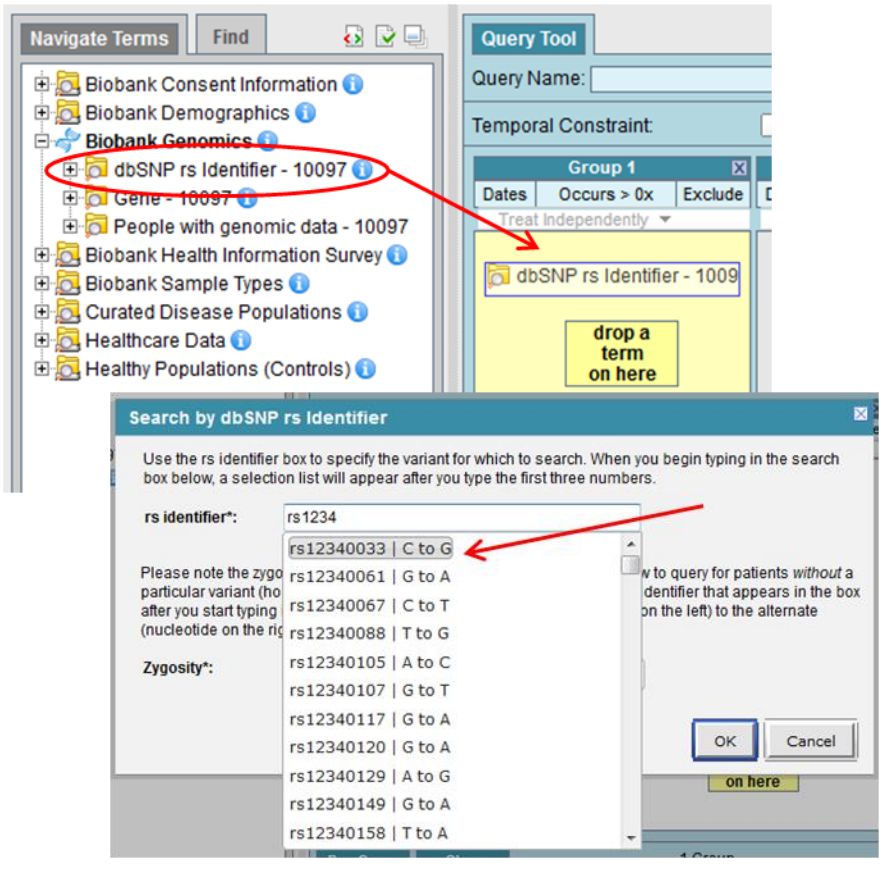
** Based on 21,300 patients

High Quality Phenotypes available for Genetic Studies



Genotype Data

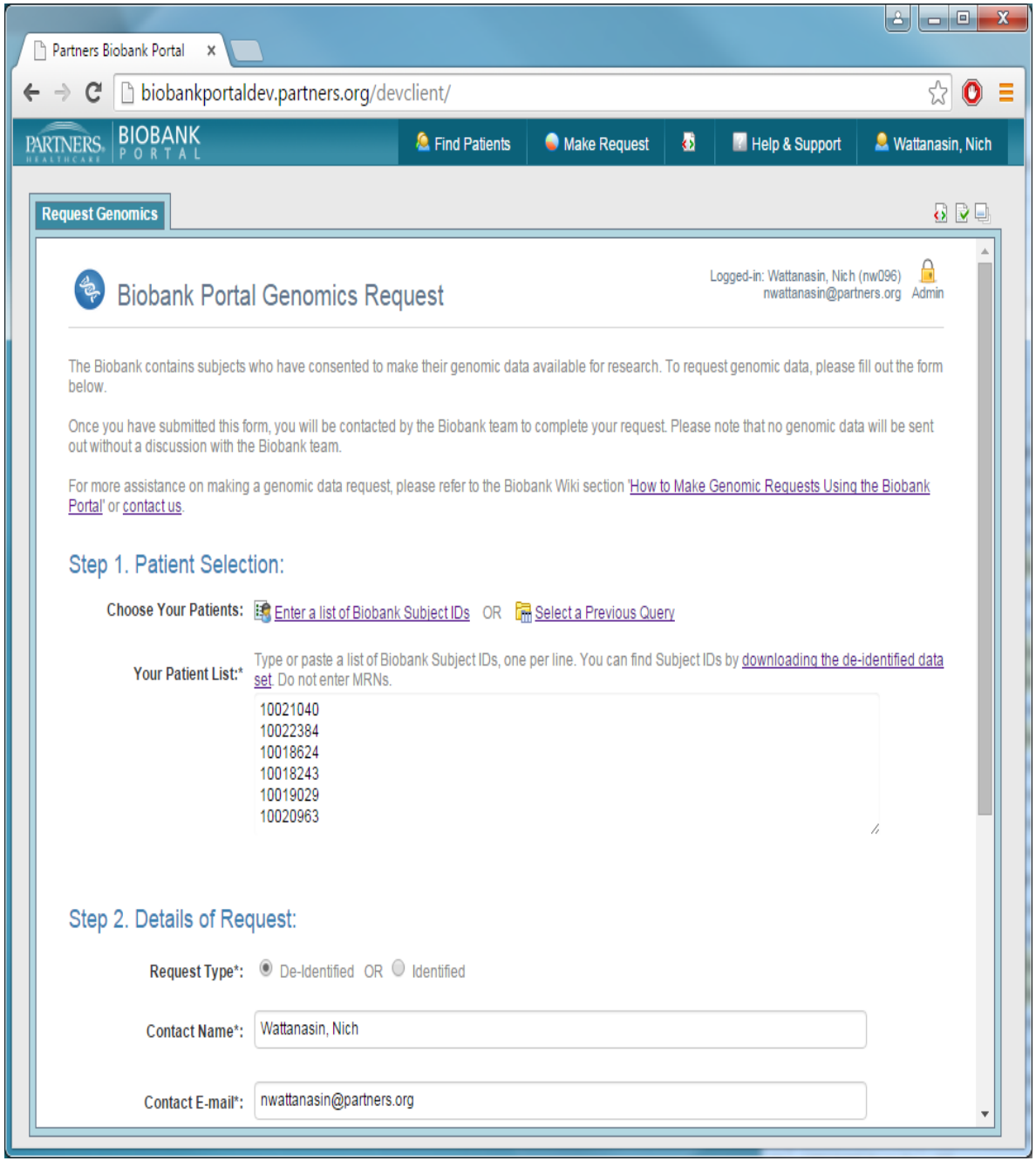




TTN

- 3349 SNP or indels
- 1680 Homozygous
- 1336 subjects with protein altering (frameshift, missense, nonsense, start loss, stop loss) variant

Partners Biobank Portal – Request Genetic Data



High Throughput Methods for supporting Translational Research

- Set of patients is selected from medical record data in a high throughput fashion
- Investigators explore phenotypes of these patients using i2b2 tools and a translational team developed to work specifically with medical record data
- Distributed networks cross institutional boundaries for phenotype selection, public health, and hypothesis testing
- Personalized medicine is delivered into clinical care

eMERGE network

ELECTRONIC MEDICAL RECORDS AND GENOMICS

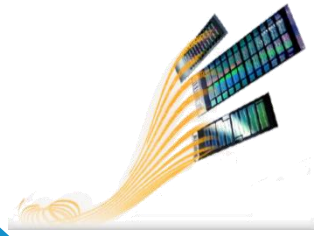
2500

25,000 Network-wide

Sequencing 100 high-priority genes

PARTNERS HEALTHCARE BIOBANK

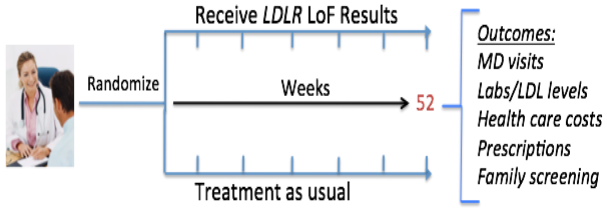
25,000



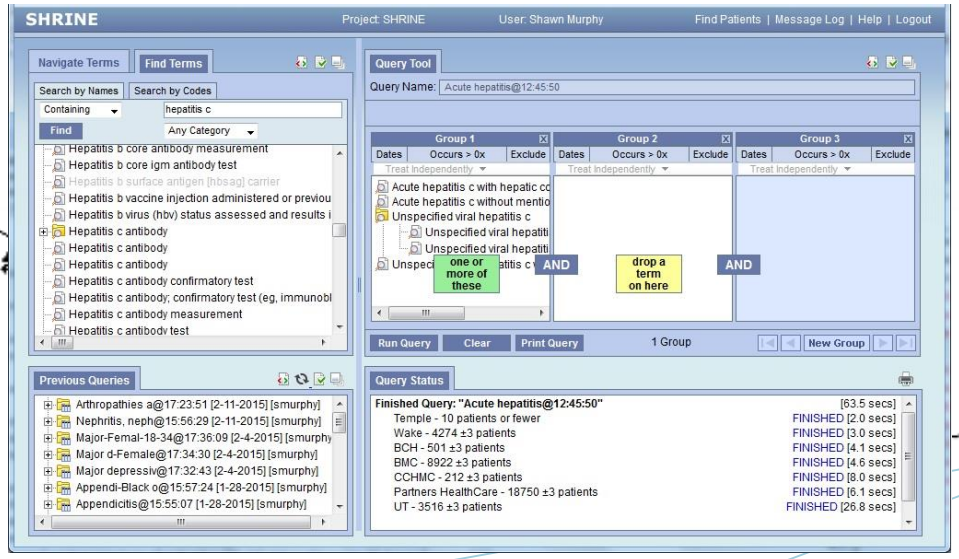
Genotyping

Discovery

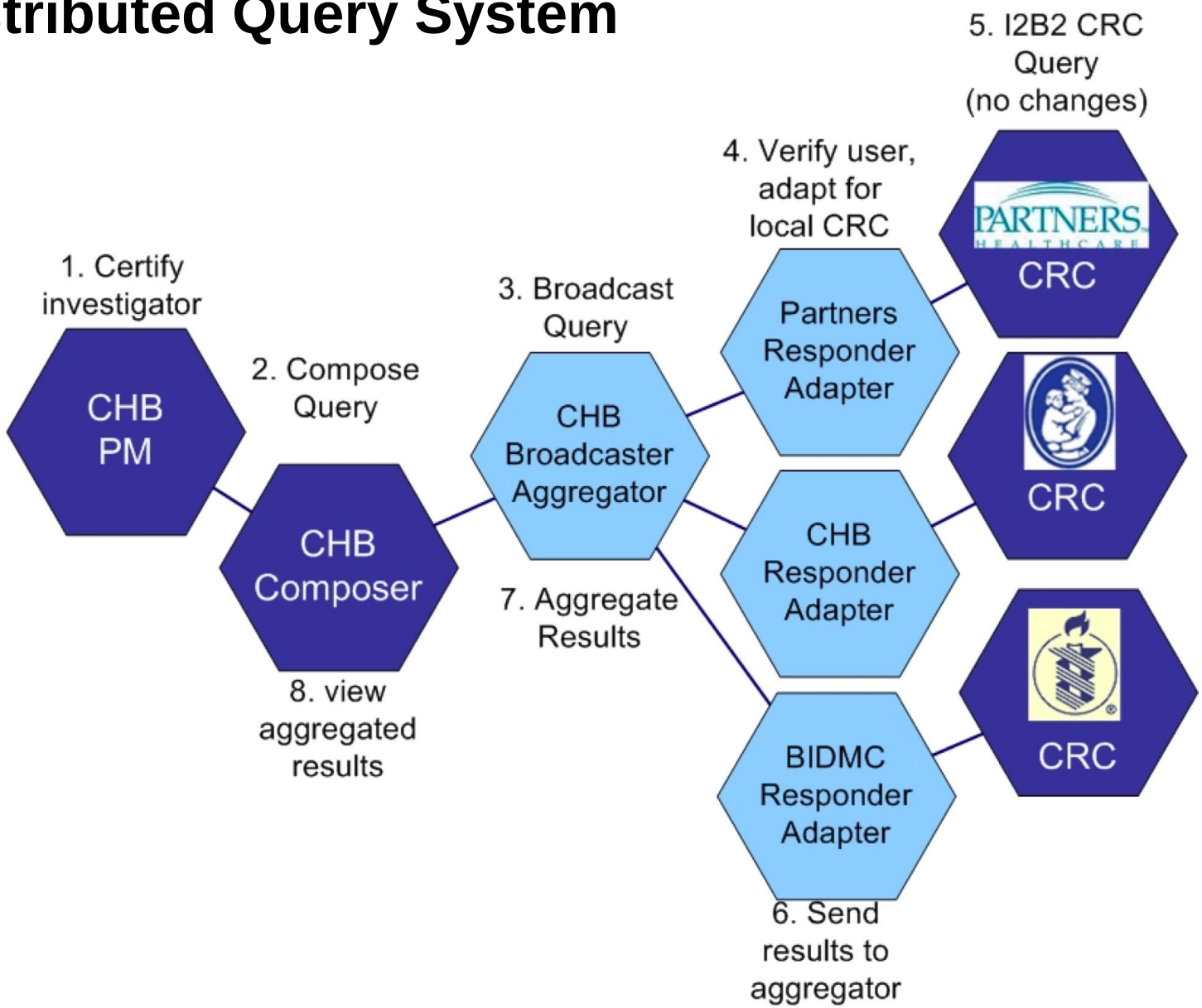
Penetrance and Pleiotropy



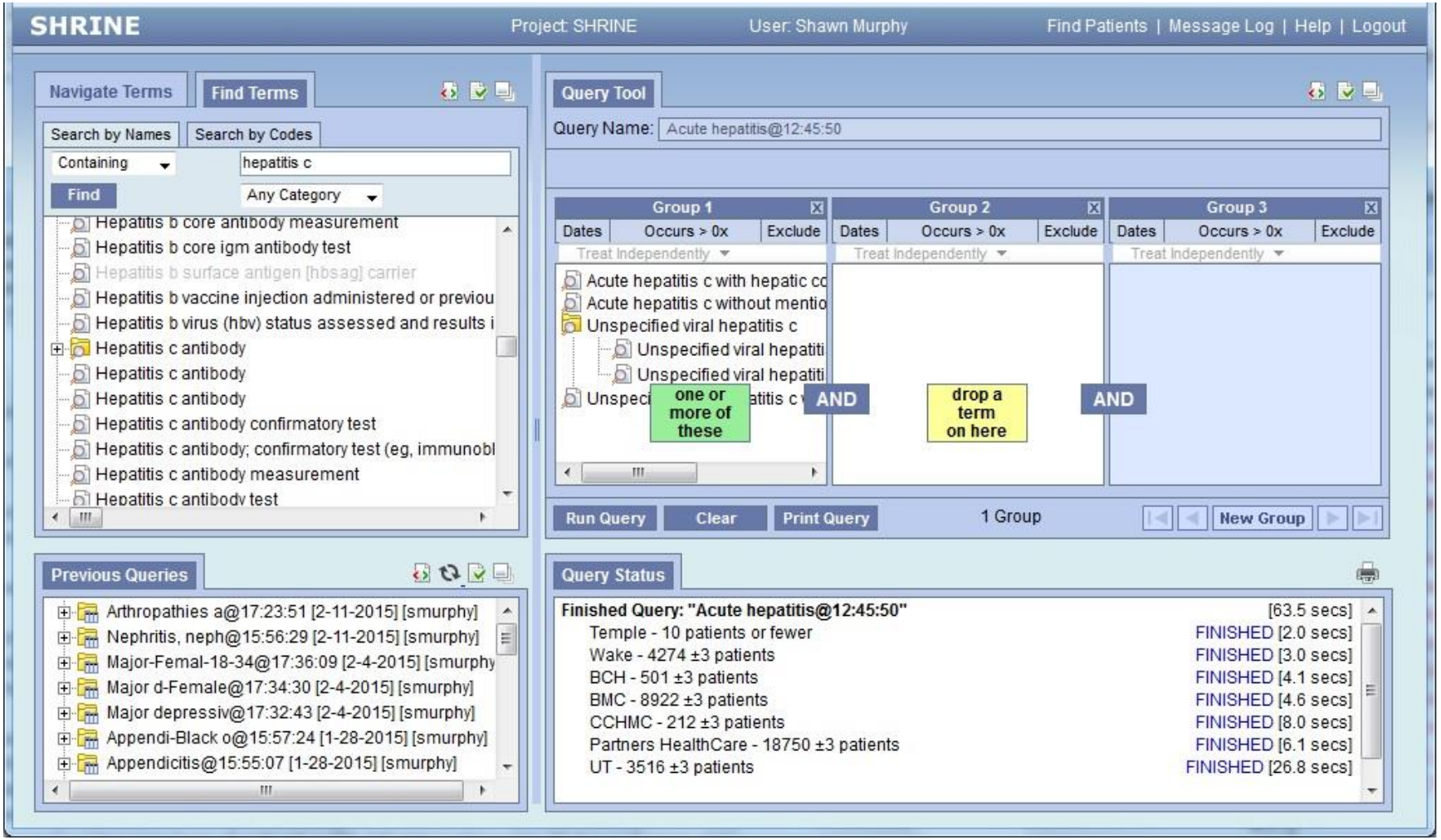
Federated Queries in PCORNet



Distributed Query System



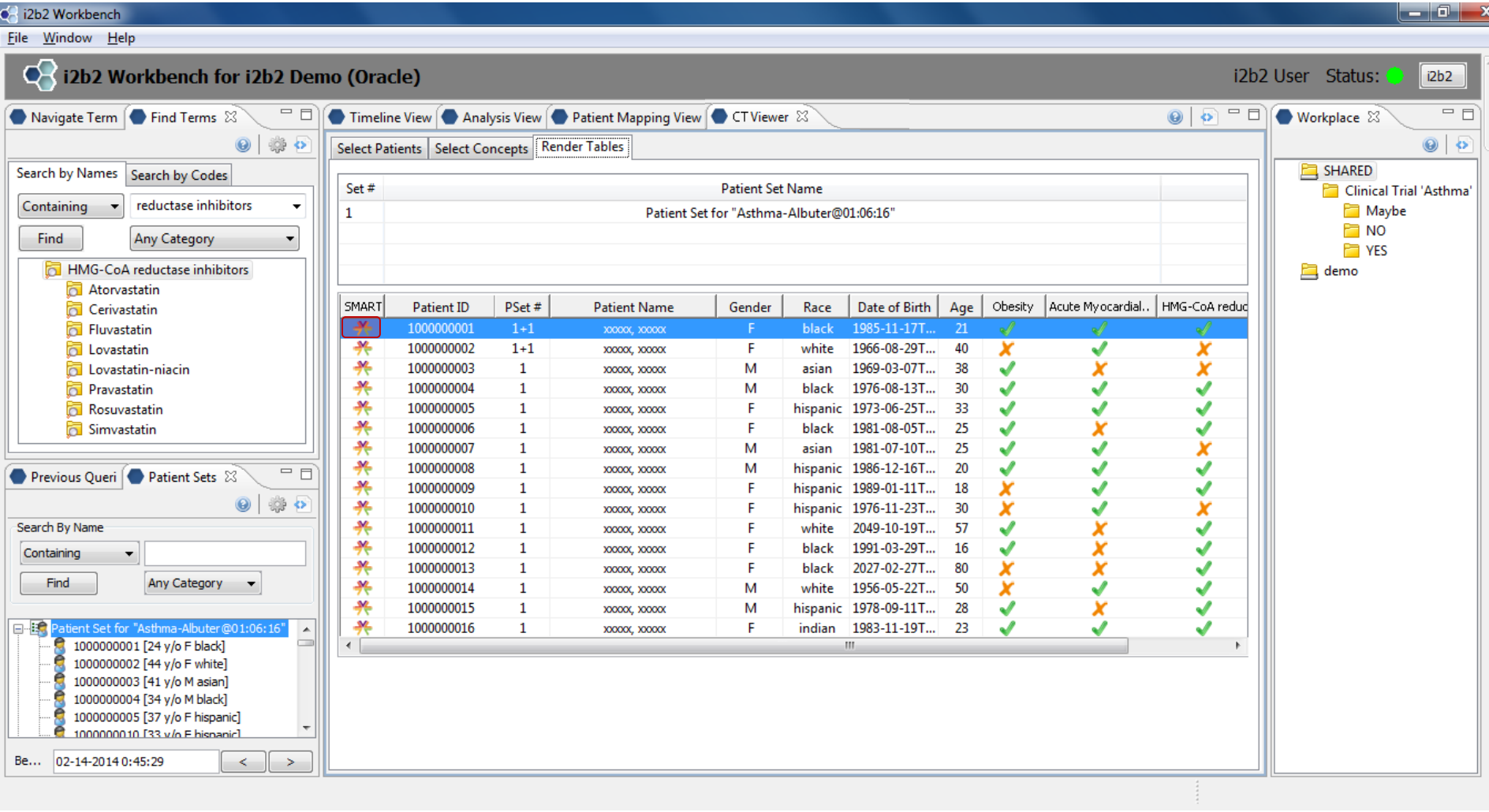
Run Query Using SCILHS-SHRINE



Workflow at the sites to find patients for a clinical trial:

- After a query is run across the “SHRINE” network, the query is automatically saved at every site
- The query saved at each site is transformed into a patient set
- The patient set is studied and sorted for the specific patients eligible for the Clinical Trial

Review Patients at Sites



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- Personalized medicine is delivered into clinical care

Personalized Medicine for the Everyday Clinician - Finding similar patients

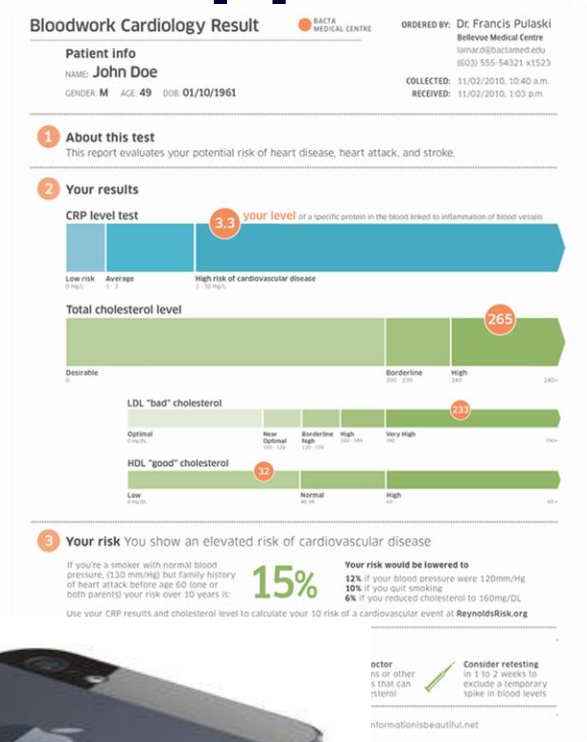
- Finding similar patients help us understand what is disease and what is normal, to distinguish between several disease states, help predict successful therapies, and to help determine next steps in potentially very expensive diagnostic pathways

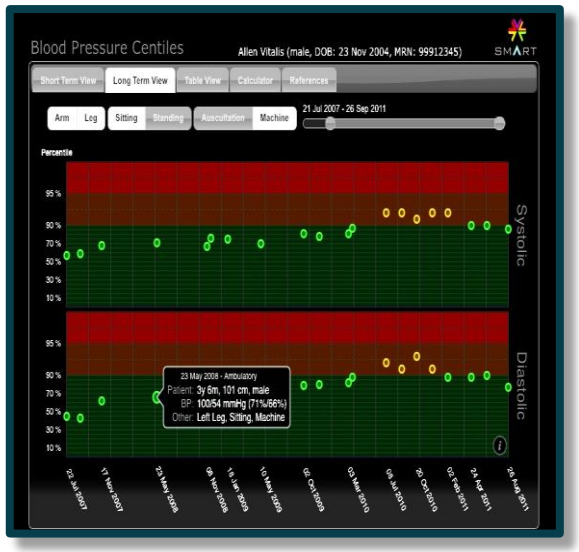
- This is an opportunity for combining the EHR, Big Data Queries, and SMART Apps

- Apply the approaches we have used to conduct scientific research to Provider and Patient engaging visualizations

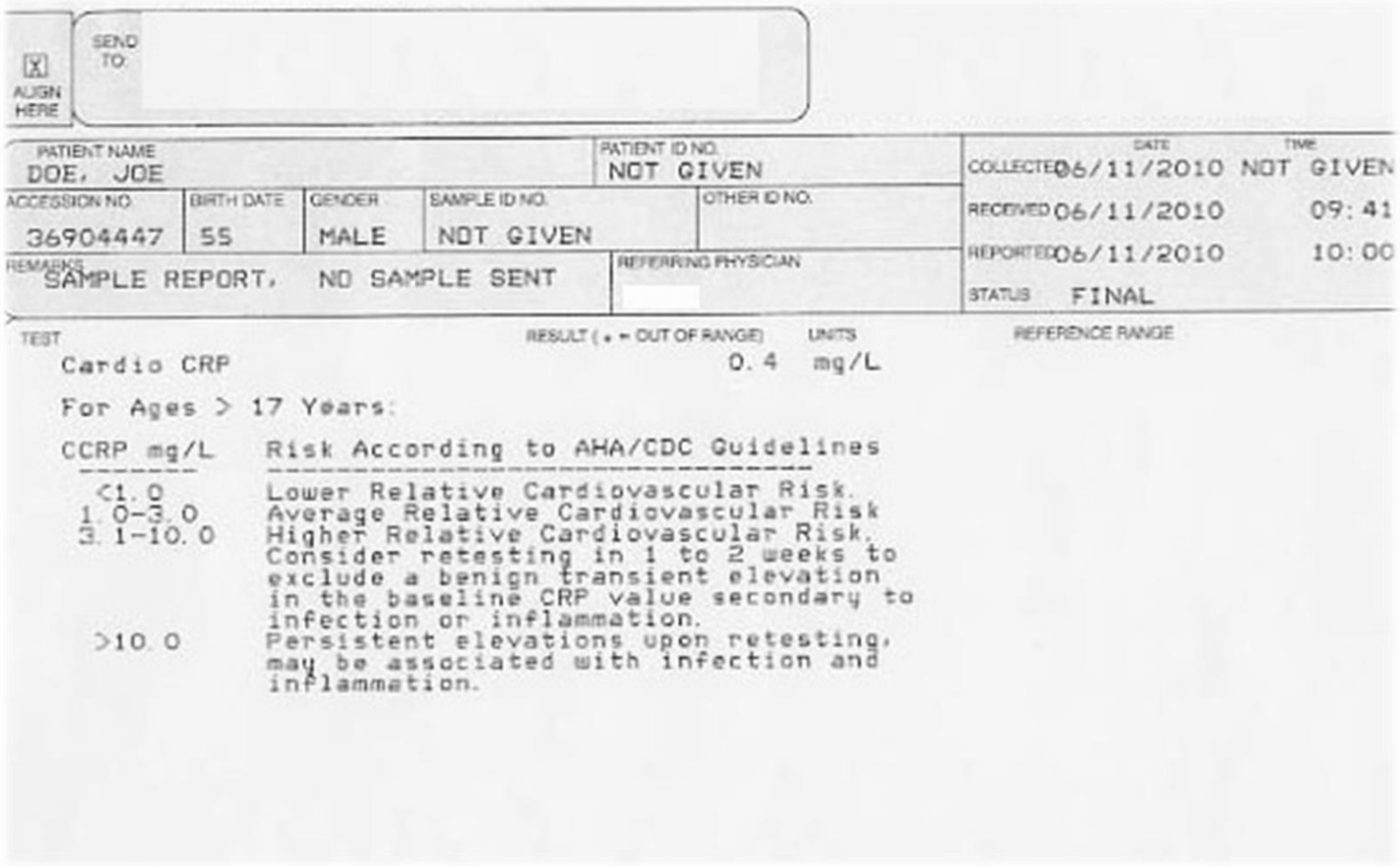
Designing the App Store for Health

SMART





State-of-the-Art ???



SIGN HERE

SEND TO:

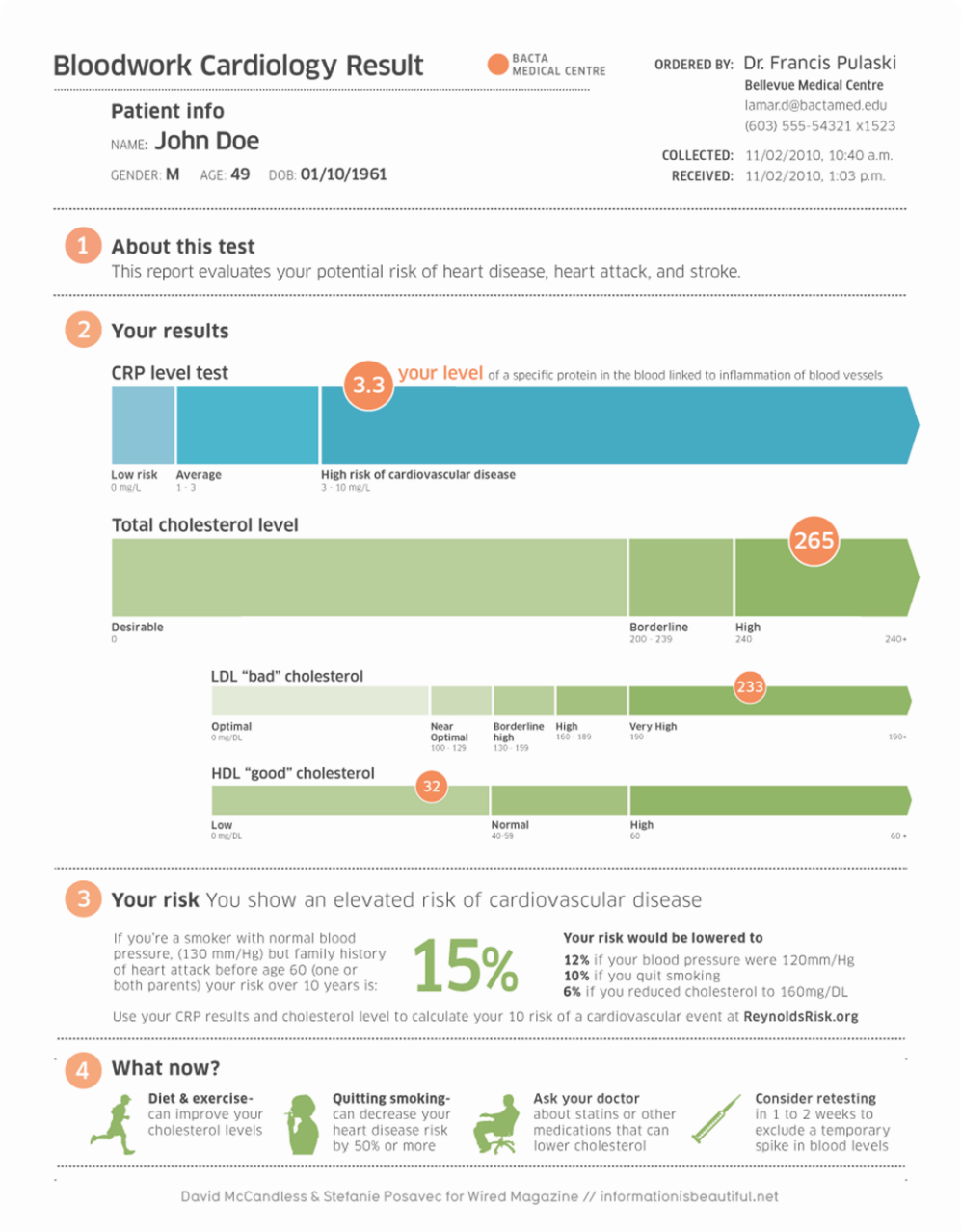
PATIENT NAME				PATIENT ID NO.		DATE	TIME
DOE, JOE				NOT GIVEN			
ACCESSION NO.	BIRTH DATE	GENDER	SAMPLE ID NO.	OTHER ID NO.	COLLECTED	06/11/2010	NOT GIVEN
36904447	55	MALE	NOT GIVEN		RECEIVED	06/11/2010	09:41
REMARKS			REFERRING PHYSICIAN		REPORTED	06/11/2010	10:00
SAMPLE REPORT, NO SAMPLE SENT					STATUS	FINAL	

TEST	RESULT (* = OUT OF RANGE)	UNITS	REFERENCE RANGE
Cardio CRP	0.4	mg/L	

For Ages > 17 Years:

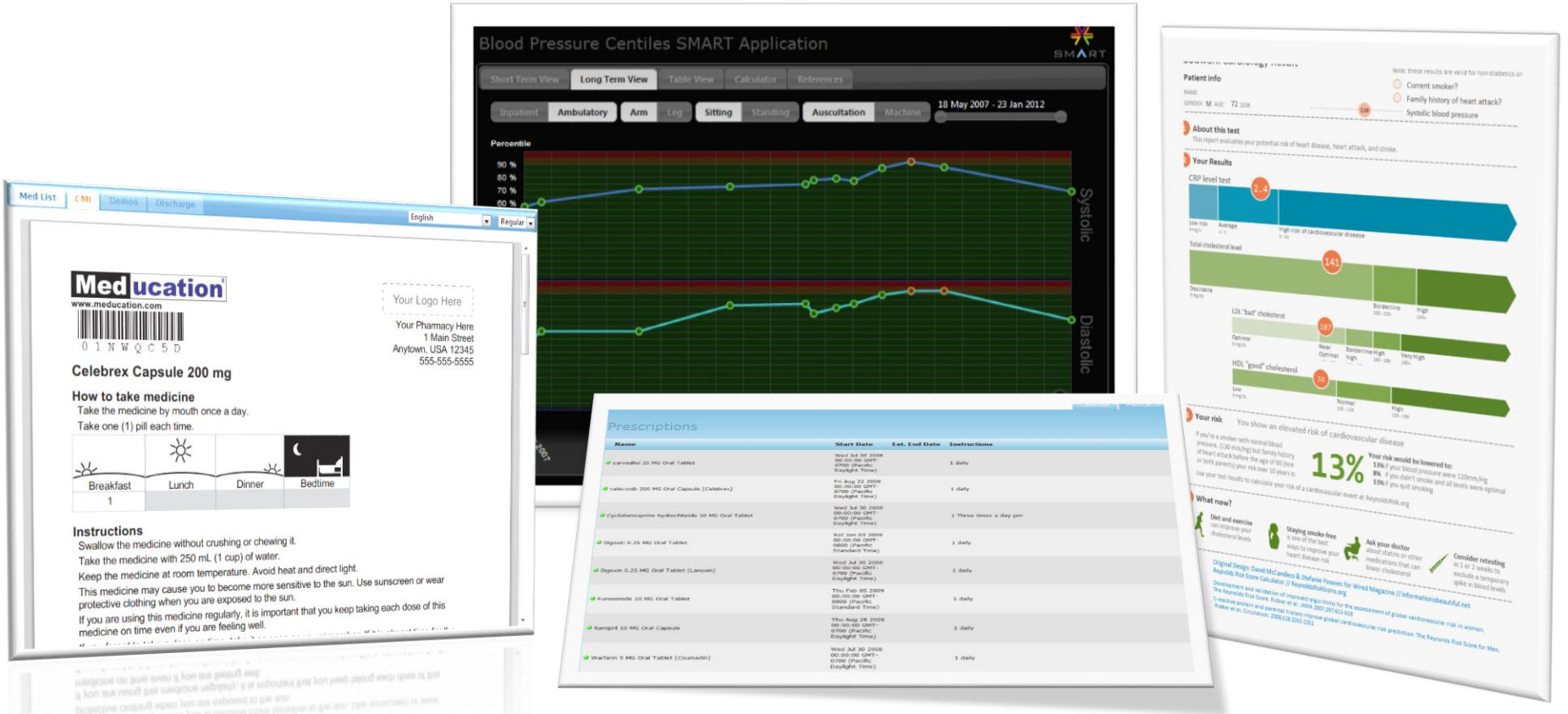
CCRP mg/L	Risk According to AHA/CDC Guidelines
<1.0	Lower Relative Cardiovascular Risk.
1.0-3.0	Average Relative Cardiovascular Risk
3.1-10.0	Higher Relative Cardiovascular Risk. Consider retesting in 1 to 2 weeks to exclude a benign transient elevation in the baseline CRP value secondary to infection or inflammation.
>10.0	Persistent elevations upon retesting, may be associated with infection and inflammation.

An
Inspired Design
from Dave McCandless
(cc license)

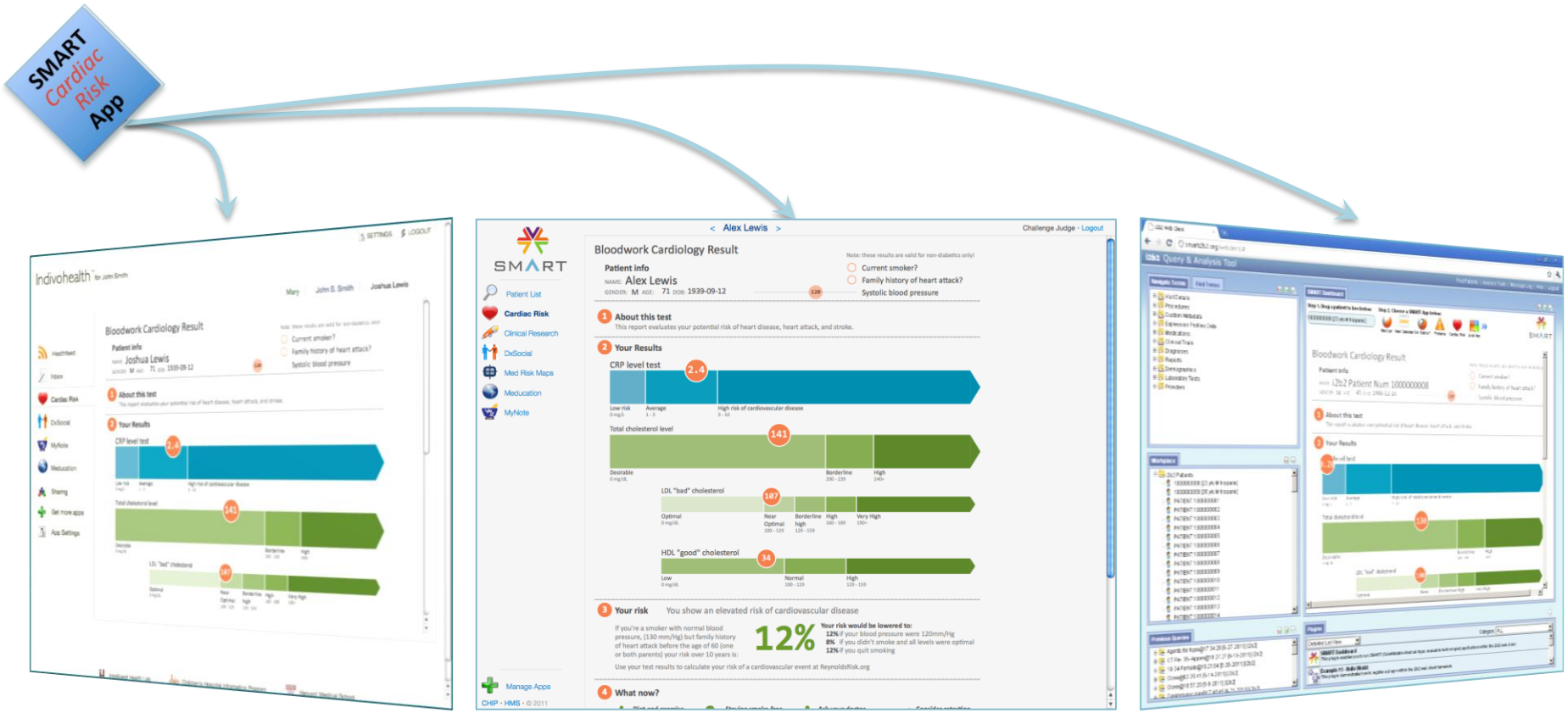


Out of the Box - SMART Apps can link Big Data to the EMR

- Substitutable Medical Application and Reusable Technology – Started with grant form the Office of the National Coordinator
- Paradigm is similar to Mobile Apps with a proposed standard interface using FHIR (Fast Healthcare Interoperable Resource)



1 SMART App in 3 SMART Systems



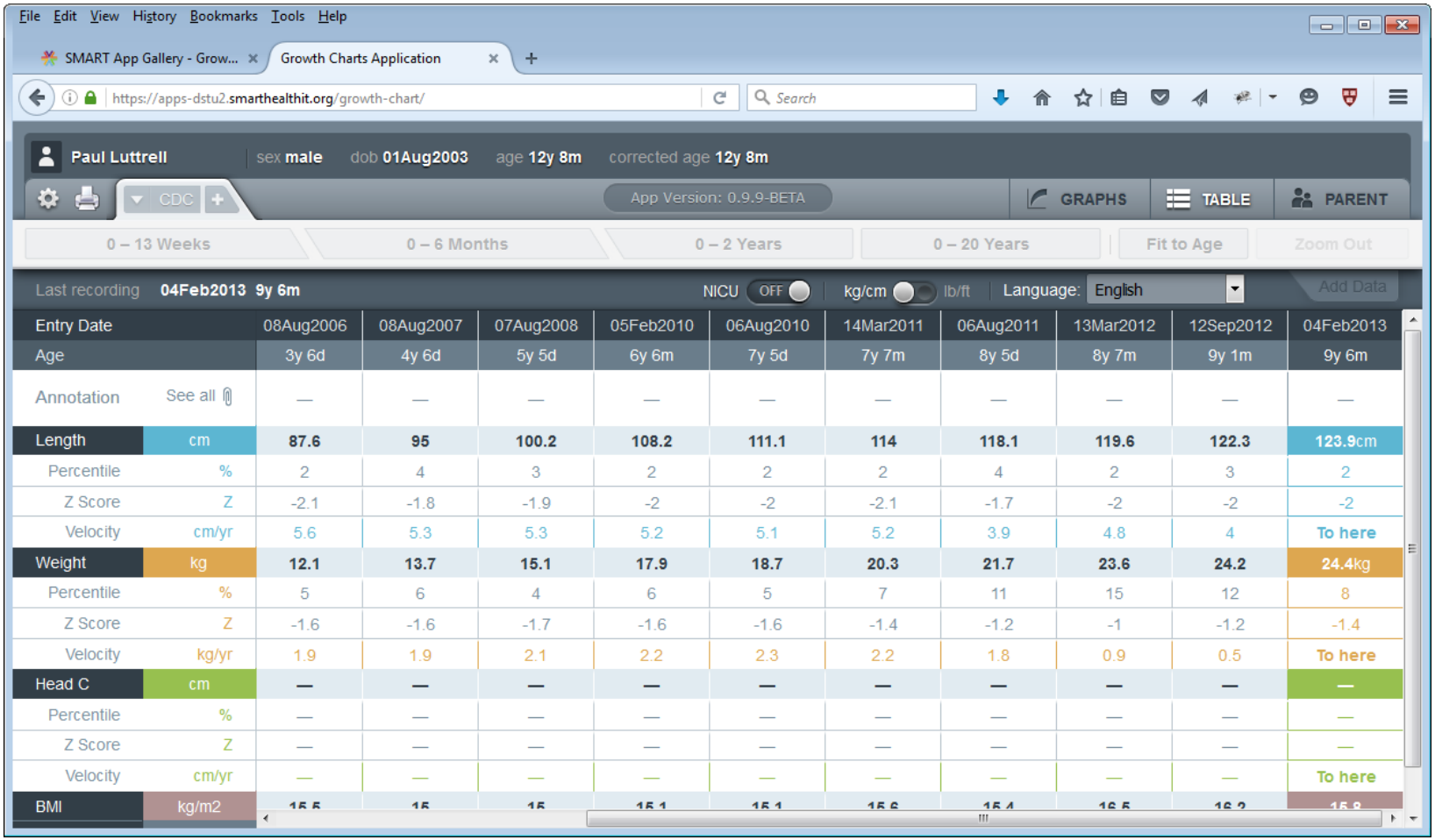
What Big Data can do for the Everyday Clinician Finding Similar Patients

- Looking at similar patients can help predict:
  - Future outcomes and responses to therapy
  - Course of disease
  - Penetrance of genetic variants
  - Likelihood that a diagnostic pathway might be fruitful

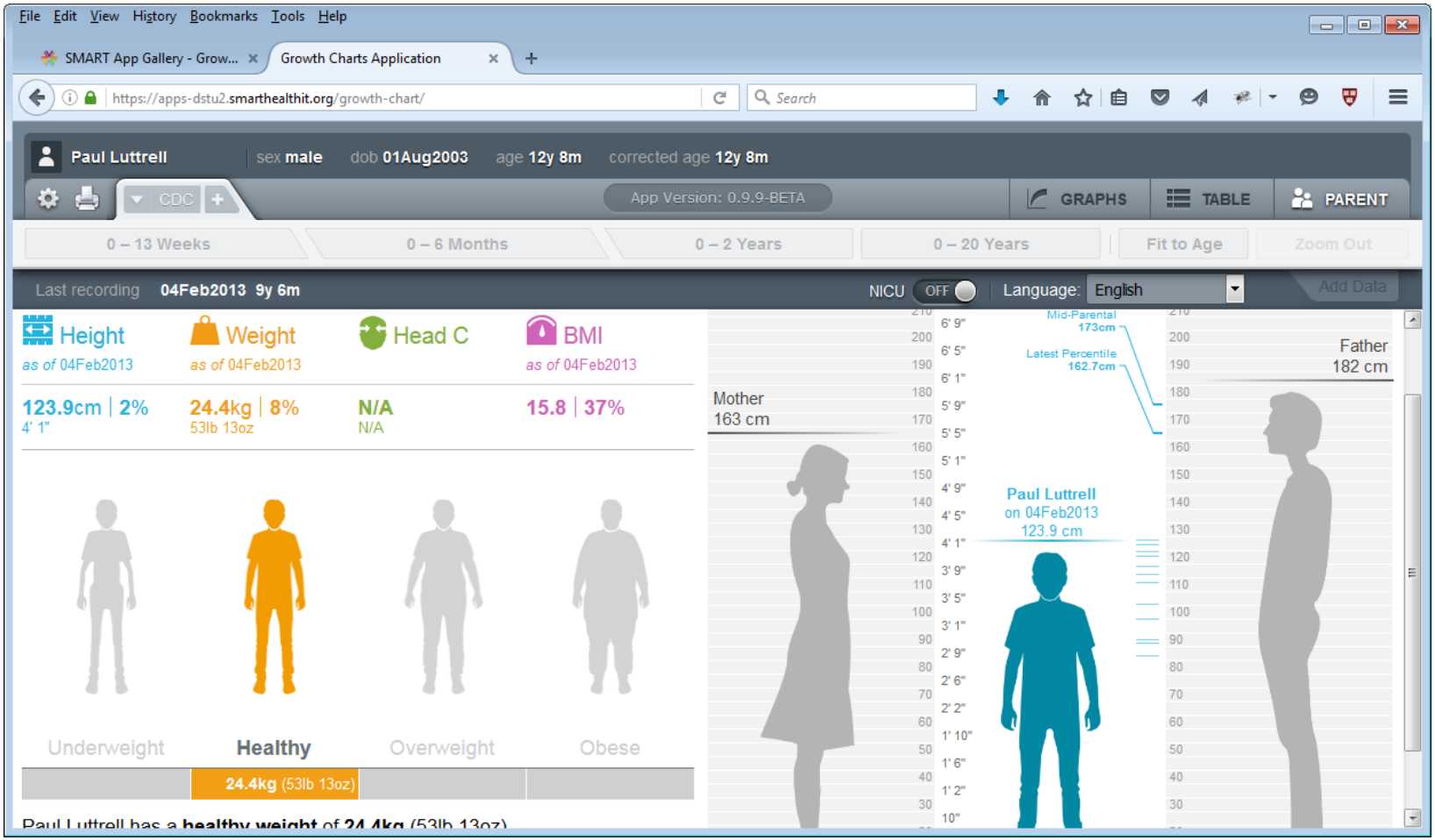
- Big Data Commons is an opportunity for combining data from the Electronic Health Record, Specialized Health Databases, Analytics from Big Data Queries, and presentation in SMART Apps

- Presentation of results can be greatly enhanced with engaging visualizations for the provider making difficult, complex decisions

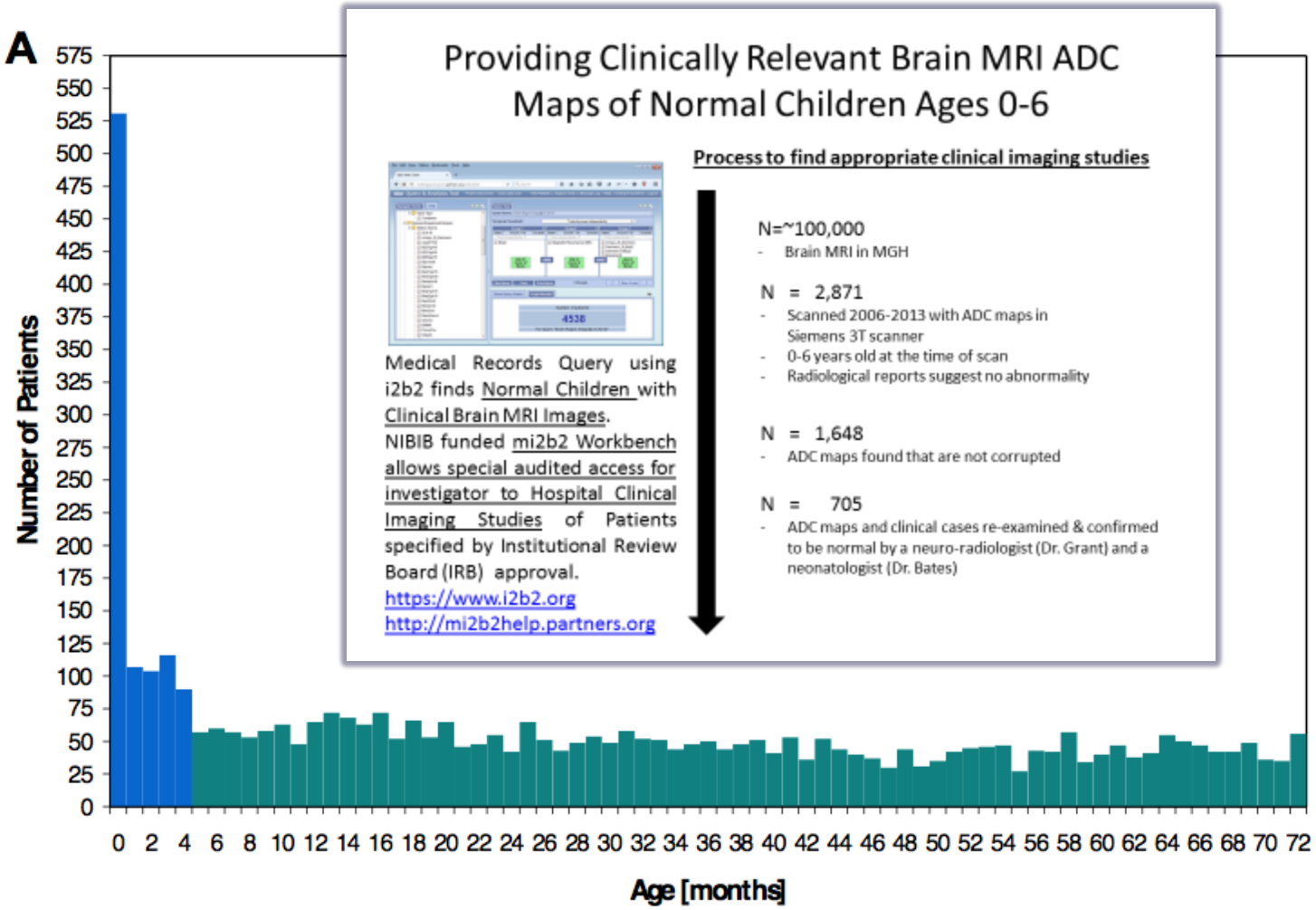
https://gallery.smarthealthit.org/boston-childrens-hospital/growth-chart



Entry Date		08Aug2006	08Aug2007	07Aug2008	05Feb2010	06Aug2010	14Mar2011	06Aug2011	13Mar2012	12Sep2012	04Feb2013
Age		3y 6d	4y 6d	5y 5d	6y 6m	7y 5d	7y 7m	8y 5d	8y 7m	9y 1m	9y 6m
Annotation	See all	—	—	—	—	—	—	—	—	—	—
Length	cm	87.6	95	100.2	108.2	111.1	114	118.1	119.6	122.3	123.9cm
Percentile	%	2	4	3	2	2	2	4	2	3	2
Z Score	Z	-2.1	-1.8	-1.9	-2	-2	-2.1	-1.7	-2	-2	-2
Velocity	cm/yr	5.6	5.3	5.3	5.2	5.1	5.2	3.9	4.8	4	To here
Weight	kg	12.1	13.7	15.1	17.9	18.7	20.3	21.7	23.6	24.2	24.4kg
Percentile	%	5	6	4	6	5	7	11	15	12	8
Z Score	Z	-1.6	-1.6	-1.7	-1.6	-1.6	-1.4	-1.2	-1	-1.2	-1.4
Velocity	kg/yr	1.9	1.9	2.1	2.2	2.3	2.2	1.8	0.9	0.5	To here
Head C	cm	—	—	—	—	—	—	—	—	—	—
Percentile	%	—	—	—	—	—	—	—	—	—	—
Z Score	Z	—	—	—	—	—	—	—	—	—	—
Velocity	cm/yr	—	—	—	—	—	—	—	—	—	To here
BMI	kg/m2	15.5	15	15	15.1	15.1	15.6	15.4	16.5	16.2	15.8

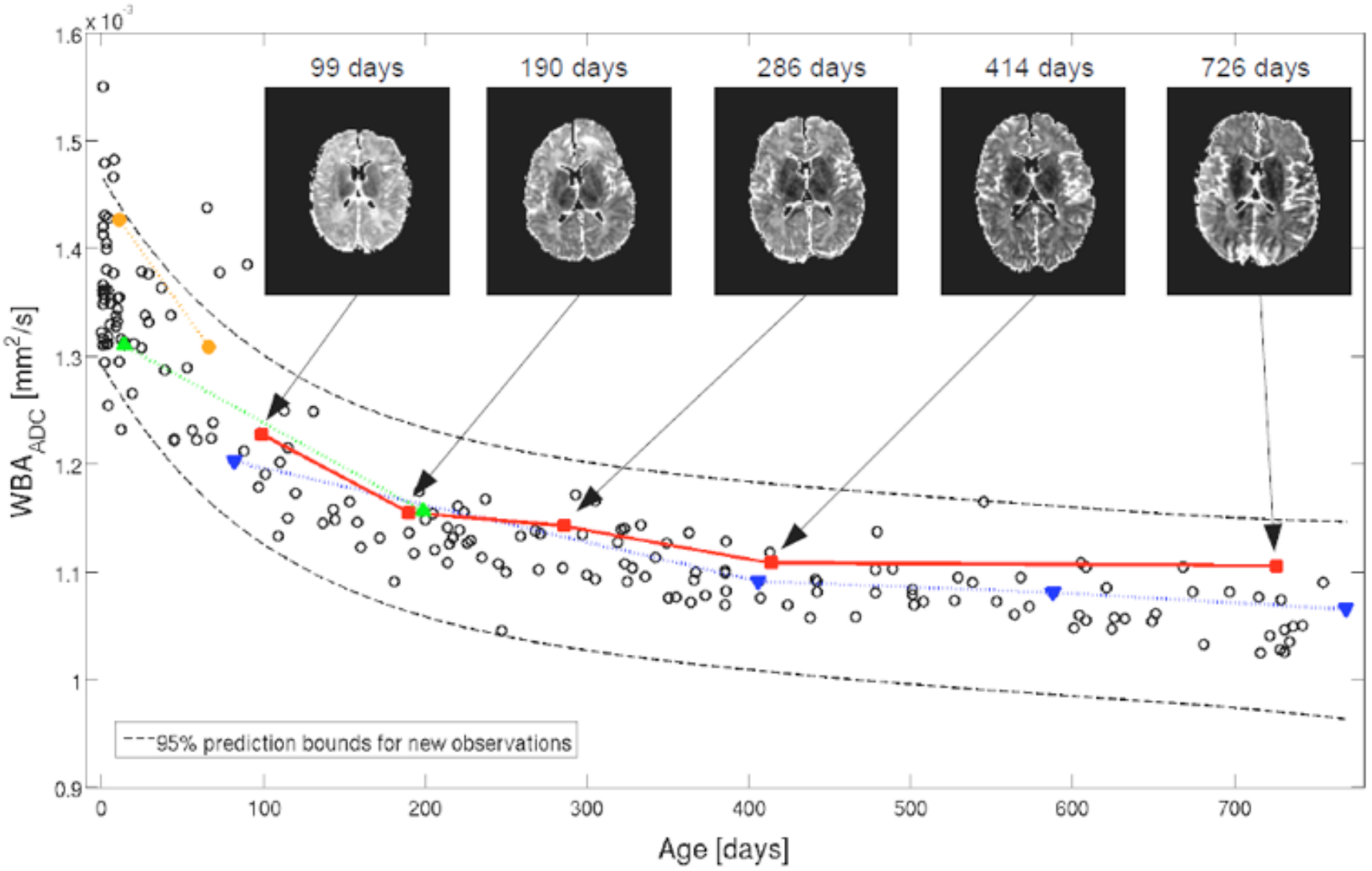

File Edit View History Bookmarks Tools Help
SMART App Gallery - Grow...
Growth Charts Application
https://apps-dstu2.smarthealthit.org/growth-chart/
Search
Paul Luttrell
sex male
dob 01Aug2003
age 12y 8m
corrected age 12y 8m
CDC
App Version: 0.9.9-BETA
GRAPHS
TABLE
PARENT
0 – 13 Weeks
0 – 6 Months
0 – 2 Years
0 – 20 Years
Fit to Age
Zoom Out
Last recording 04Feb2013 9y 6m
NICU OFF
Language: English
Add Data
Height
as of 04Feb2013
123.9cm | 2%
4' 1"
Weight
as of 04Feb2013
24.4kg | 8%
53lb 13oz
Head C
N/A
N/A
BMI
as of 04Feb2013
15.8 | 37%
Underweight
Healthy
Overweight
Obese
24.4kg (53lb 13oz)
Paul Luttrell has a healthy weight of 24.4kg (53lb 13oz)
Mother
163 cm
Mid-Parental
173cm
Latest Percentile
162.7cm
Father
182 cm
Paul Luttrell
on 04Feb2013
123.9 cm

Find Normal MRI's at All Ages 0-6 y/o



Number of patients who had a brain MRI scan at a particular age in months from 0 to 6 years (A) and in weeks from 0 to 4 months (B)

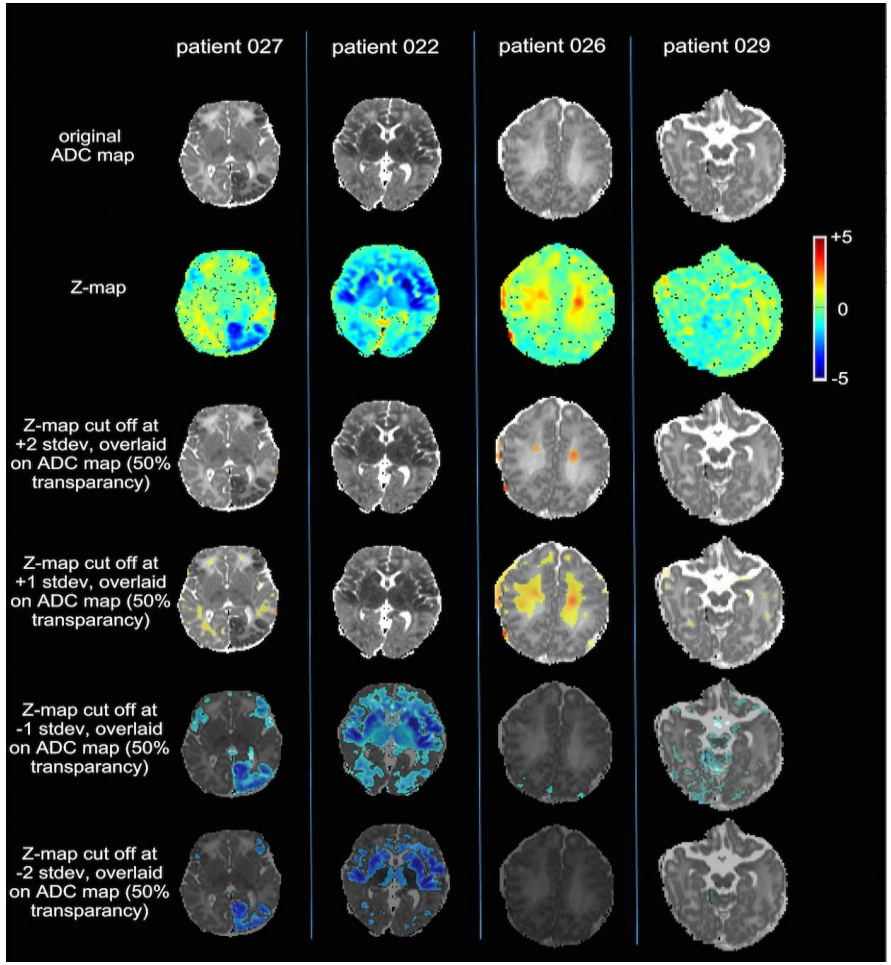
Determining a Normal Child's MRI



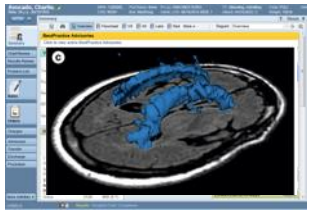
Atlases provide a visual guide for Radiology Decision Support, such as determining Perinatal Hypoxic Ischemic Encephalopathy

ADC map from 4 infants:
Each statistically compared to age matched atlas yields visual guide to pathology

Quantitative analysis tools + large data sets = Great insights for practicing doctors

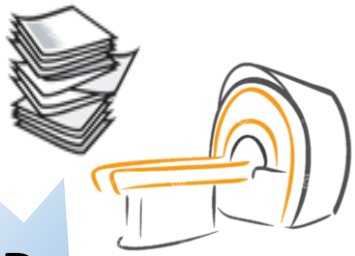


PARTNERS CLINICAL DEVELOPMENT ENVIRONMENT



CLINICAL ENVIRONMENT (eCARE)

eCare AI



Clinical Data

INTEGRATION ENVIRONMENT (HIP)

RESEARCH ENVIRONMENT (RPDR)

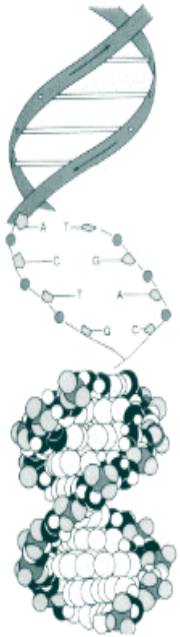
AI Applications

Structured Data

COMPUTATIONAL ENVIRONMENT (CDSC, PDC, other)

Tribute to…

- I2b2 Core Team
  - Isaac Kohane
  - Susanne Churchill
  - Michael Mendis
  - Christopher Herrick
  - Griffin Weber
  - Paul Avillach
  - Lori Phillips
  - Janice Donahoe
  - Nich Wattanasin
  - David Wang
  - Vivian Gainer
  - Victor Castro
  - Andrew Cagan
  - Wayne Chan
- SMART Apps Team
  - Calum MacRae
  - Sandy Aronson
  - Mike Oats
  - Layne Ainsworth
  - Kenneth Mandl
  - Joshua Mandel
- Radiology (mi2b2) Team
  - Randy Gollub
  - P Ellen Grant
  - Kathy Andriole
  - Kallirroi Retzepi
  - Rudolph Pienaar
  - Lilla Zollei
  - Yangming Ou



I2b2, SHRINE, and SMART Information and Software on the Web

i2b2 Homepage (https://www.i2b2.org)

i2b2 Software (https://www.i2b2.org/software)

i2b2 Community Site (https://community.i2b2.org)

SMART Platforms Homepage (http://smarthealthit.org)

Partners Healthcare, NIH/NCBC/BD2K; /NIMH; /NCATS; /NIBIB; /NHGRI

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NIH U54 LM008748
NIH U01 HG008685
PCORI 282364.5077585.0007
NIH U54 HG007963
NIH R01 AT006364
NIH R01 AT005280
NIH P01 AT006663

THANK YOU