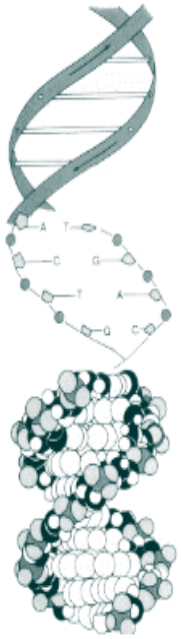


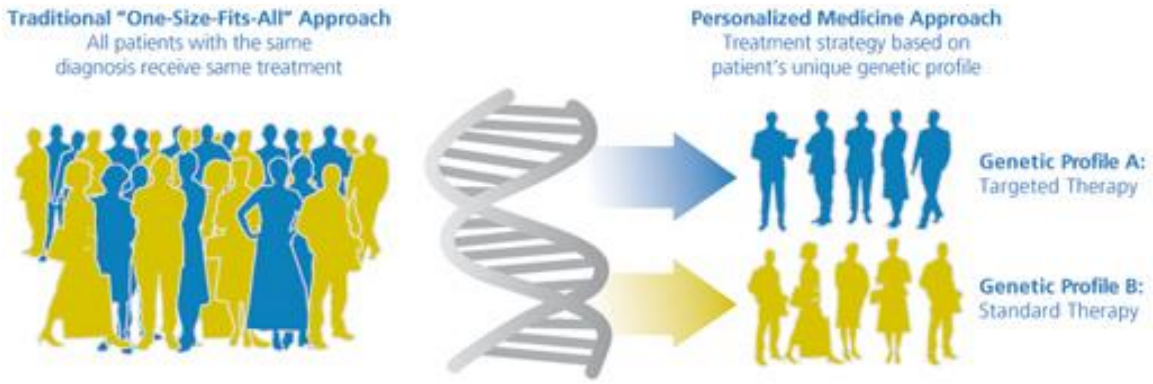
Instrumenting the Health Care Enterprise for Discovery in the Course of Clinical Care

Shawn Murphy MD, Ph.D.

Chief Research Information Officer

Harvard Medical School / Mass General Brigham

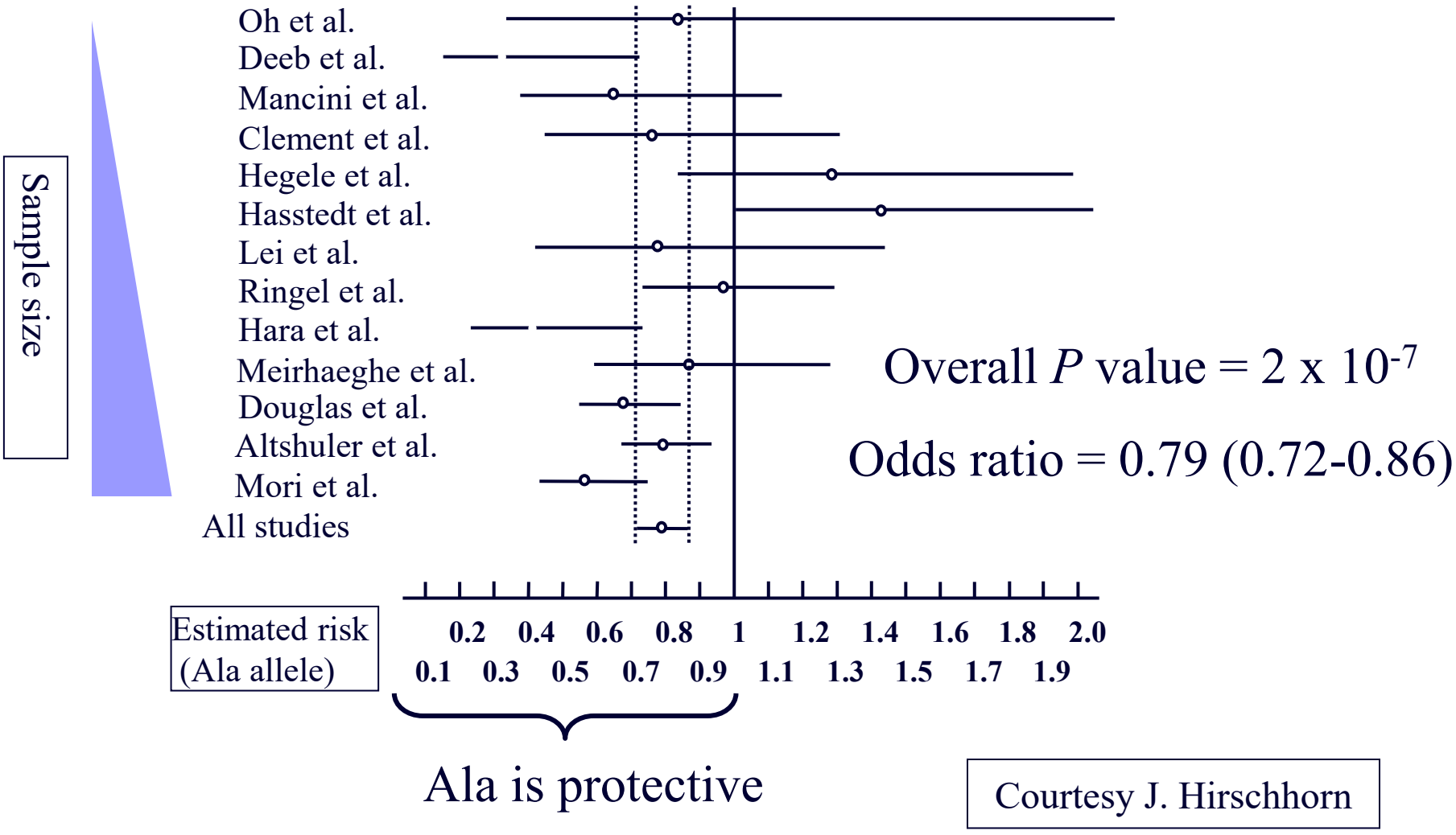
Personalized Medicine and Genomic technology are critical to managing populations



- 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 Machine Learning 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
- Digital medicine is delivered into clinical care through Digital Twin

Data problems that make working with Electronic Healthcare Data to conduct research difficult

- 1) There are significant risks of a data breach which will result in very large fines and loss of confidence in the hospitals where the breach occurred.

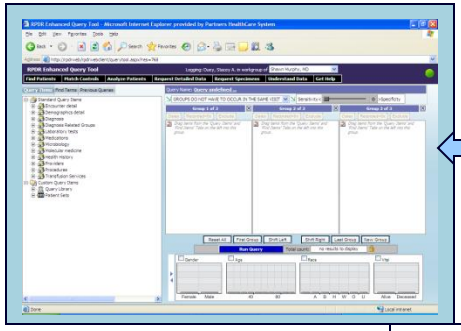
- 2) The data are not collected for research purposes, and therefore the data can be poorly structured with significant omissions, biases, and inaccuracies.

Research Patient Data Registry (RPDR) at Mass General Brigham to find patient cohorts and distribute data

1) Queries for aggregate patient numbers

- Warehouse of in & outpatient clinical data
- 6.7 million Mass General Brigham patients
- 2.6 billion diagnoses, medications, genomics, 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 detailed patient data

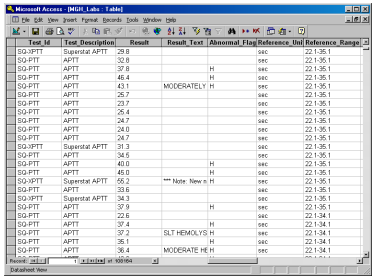
- Start with list of specific patients, usually from (1)
- Authorized use by IRB Protocol
- Returns contact and PCP information, demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology, reports (discharge, LMR, operative, radiology, pathology, cardiology, pulmonary,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

0000004
2185793
...
...

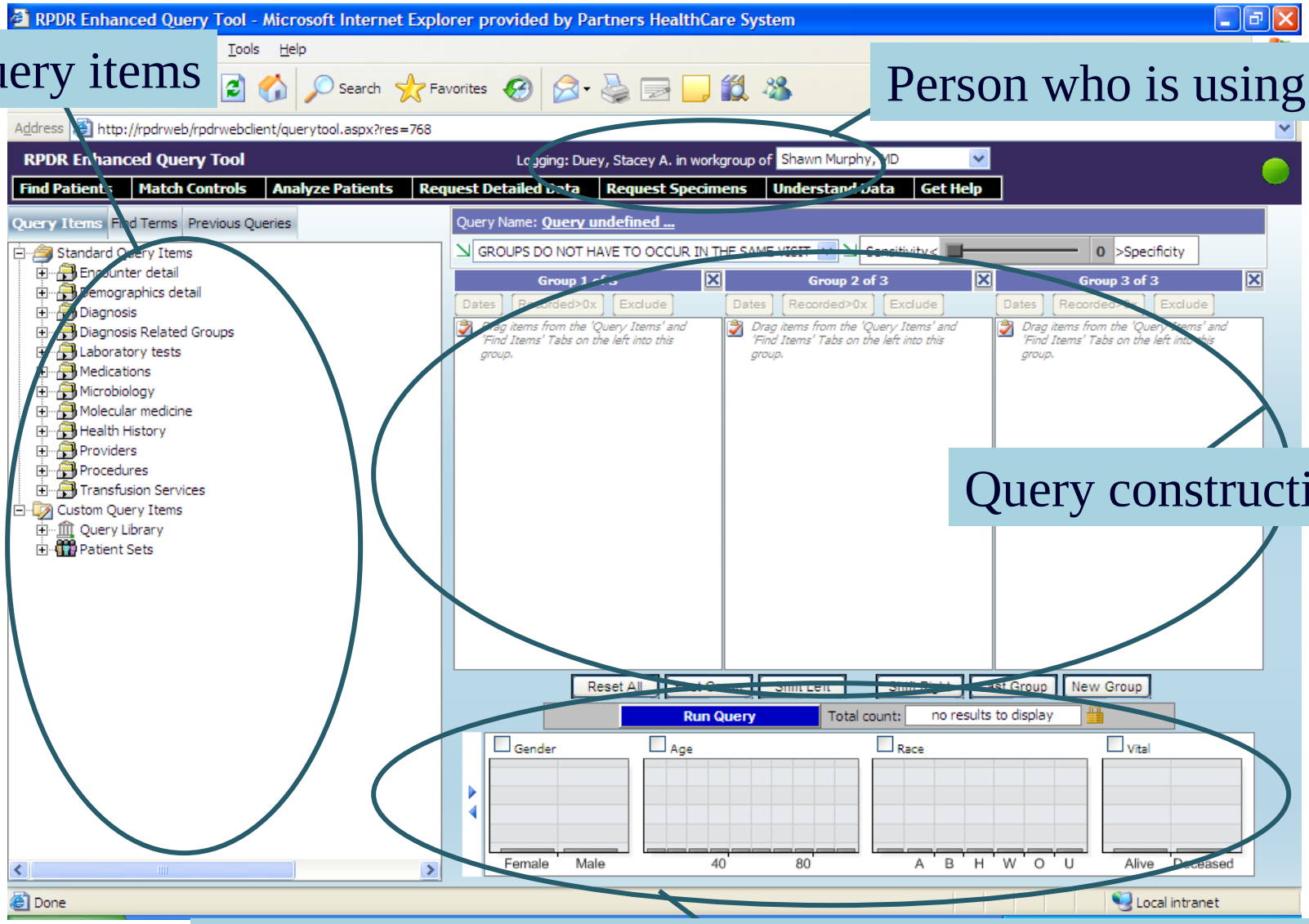
OR

0000004
2185793
...
...

Real identifiers



FINDING PATIENTS

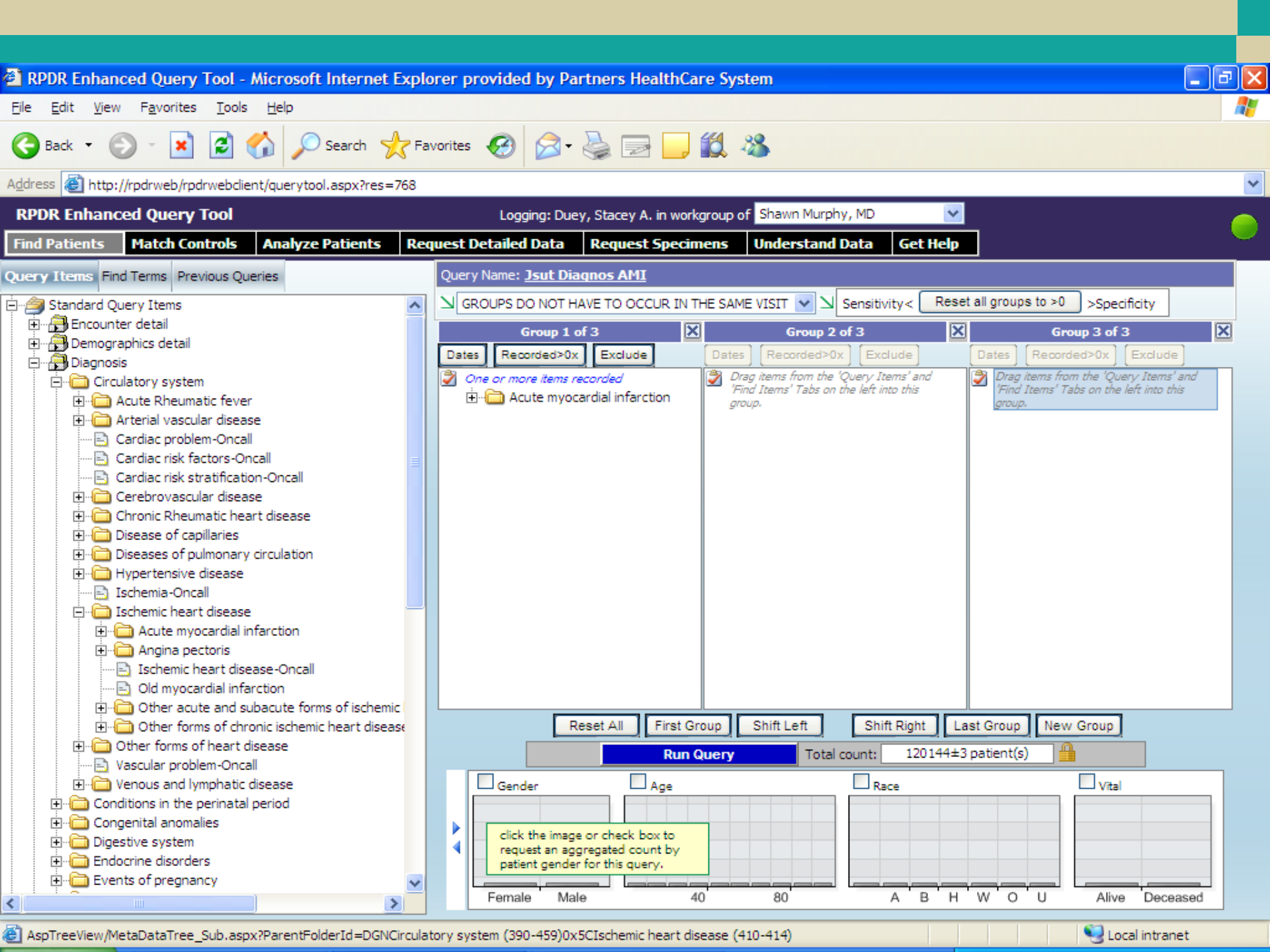


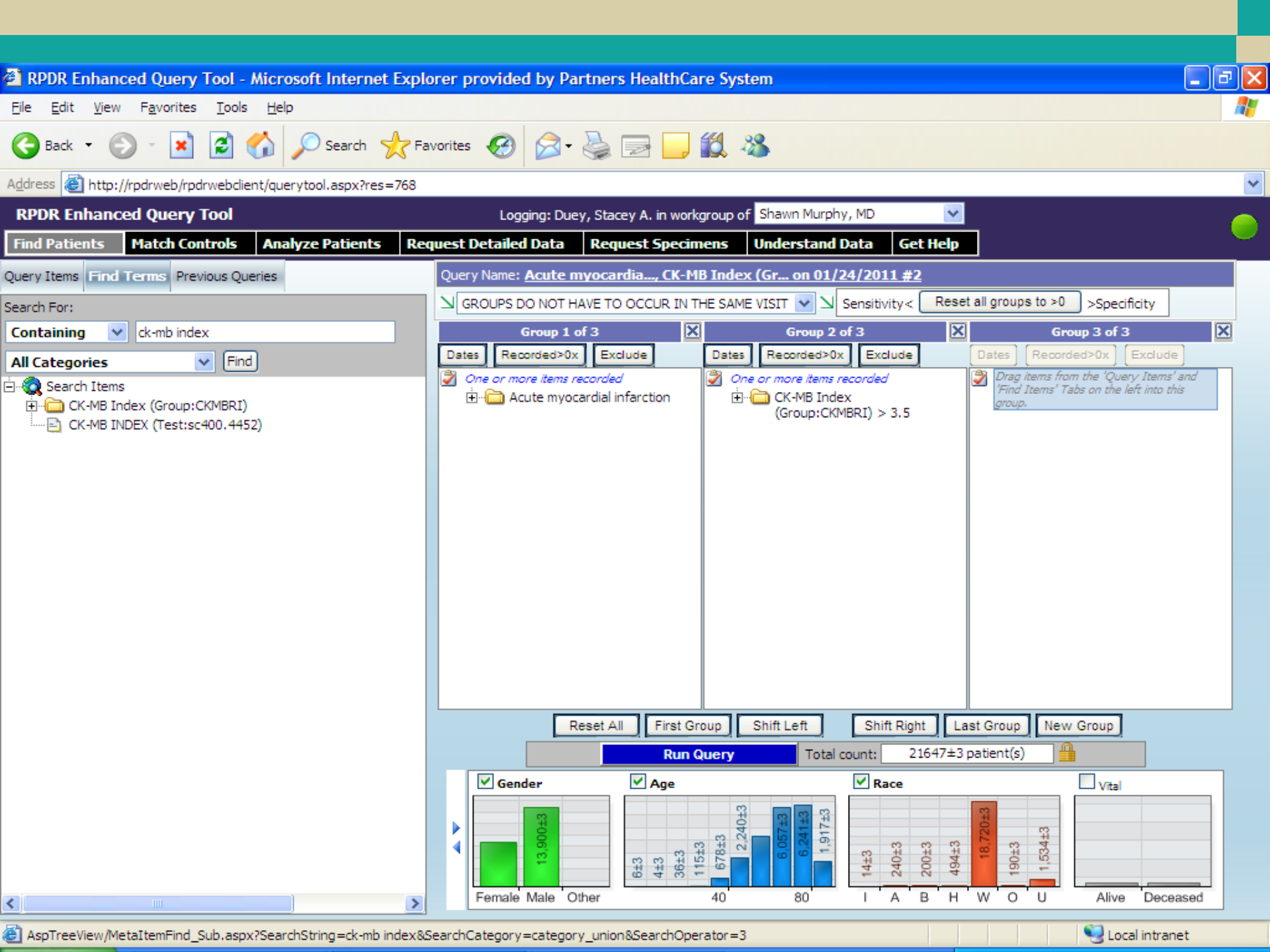
Query items

Person who is using tool

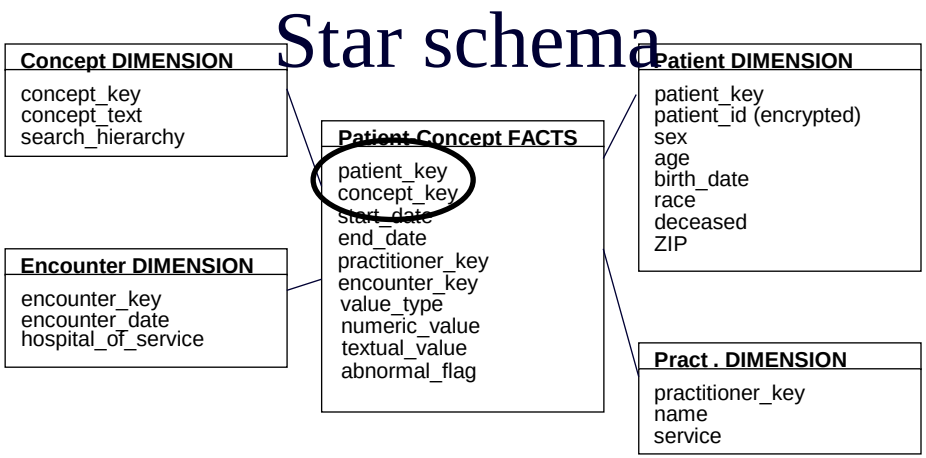
Query construction

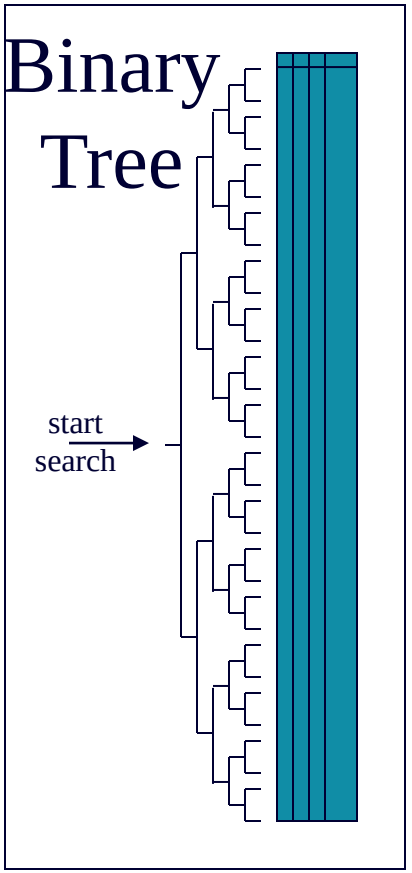
Results - broken down by number distinct of patients

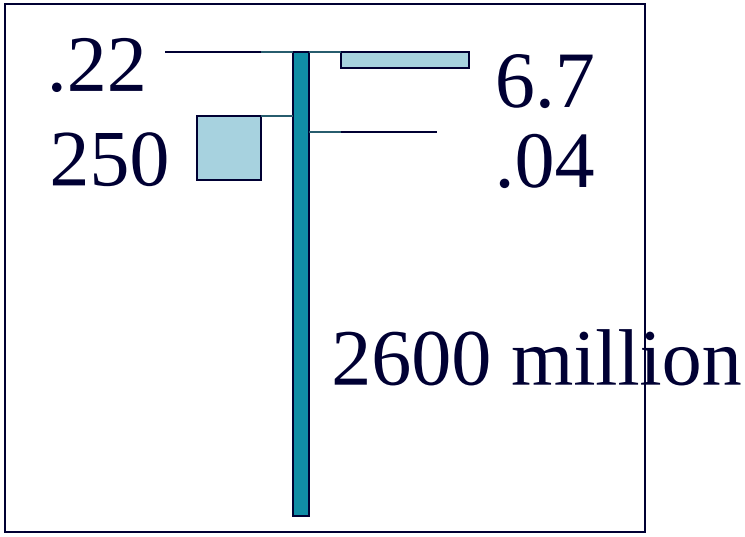

RPDR Enhanced Query Tool - Microsoft Internet Explorer provided by Partners HealthCare System
File Edit View Favorites Tools Help
Back Search Favorites
Address http://rpdrweb/rpdrwebclient/querytool.aspx?res=768
RPDR Enhanced Query Tool
Logging: Duey, Stacey A. in workgroup of Shawn Murphy, MD
Find Patients
Match Controls
Analyze Patients
Request Detailed Data
Request Specimens
Understand Data
Get Help
Query Items
Find Terms
Previous Queries
Standard Query Items
Encounter detail
Demographics detail
Diagnosis
Circulatory system
Acute Rheumatic fever
Arterial vascular disease
Cardiac problem-Oncall
Cardiac risk factors-Oncall
Cardiac risk stratification-Oncall
Cerebrovascular disease
Chronic Rheumatic heart disease
Disease of capillaries
Diseases of pulmonary circulation
Hypertensive disease
Ischemia-Oncall
Ischemic heart disease
Acute myocardial infarction
Angina pectoris
Ischemic heart disease-Oncall
Old myocardial infarction
Other acute and subacute forms of ischemic
Other forms of chronic ischemic heart disease
Other forms of heart disease
Vascular problem-Oncall
Venous and lymphatic disease
Conditions in the perinatal period
Congenital anomalies
Digestive system
Endocrine disorders
Events of pregnancy
Query Name: Jsut Diagnos AMI
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
Acute myocardial infarction
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: 120144±3 patient(s)
Gender
Age
Race
Vital
click the image or check box to request an aggregated count by patient gender for this query.
Female
Male
40
80
A
B
H
W
O
U
Alive
Deceased
AspTreeView/MetaDataTree_Sub.aspx?ParentFolderId=DGNCirculatory system (390-459)0x5CIschemic heart disease (410-414)
Local intranet

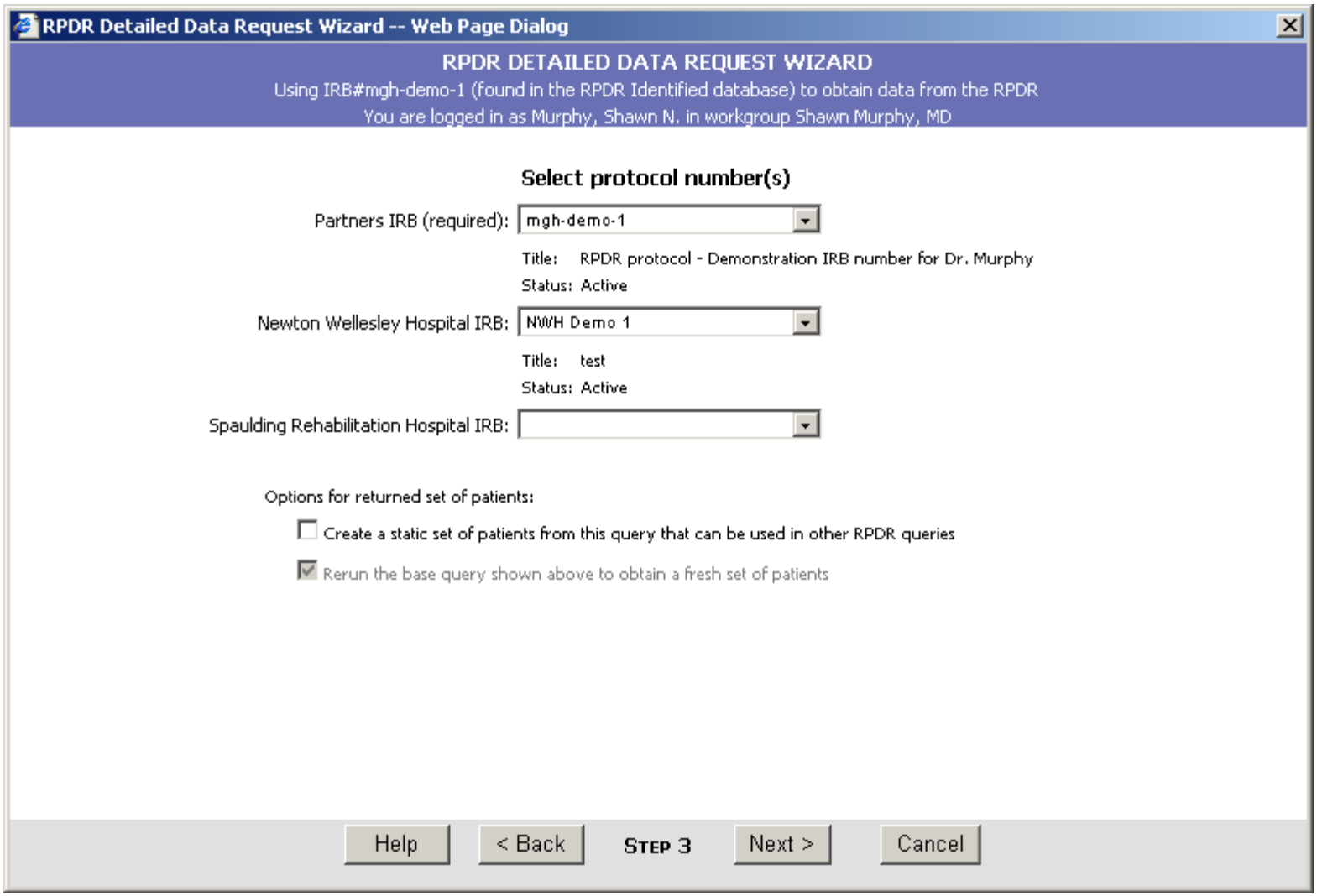

RPDR Enhanced Query Tool - Microsoft Internet Explorer provided by Partners HealthCare System
File Edit View Favorites Tools Help
Back Search Favorites
Address http://rpdrweb/rpdrwebclient/querytool.aspx?res=768
RPDR Enhanced Query Tool
Logging: Duey, Stacey A. in workgroup of Shawn Murphy, MD
Find Patients
Match Controls
Analyze Patients
Request Detailed Data
Request Specimens
Understand Data
Get Help
Query Items
Find Terms
Previous Queries
Search For:
Containing
ck-mb index
All Categories
Find
Search Items
CK-MB Index (Group:CKMBRI)
CK-MB INDEX (Test:sc400.4452)
Query Name: Acute myocardia..., CK-MB Index (Gr... on 01/24/2011 #2
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
Acute myocardial infarction
CK-MB Index
(Group:CKMBRI) > 3.5
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:
21647±3 patient(s)
Gender
Female Male Other
13,900±3
Age
6±3
4±3
36±3
115±3
678±3
2,240±3
6,057±3
6,241±3
1,917±3
40
80
Race
14±3
240±3
200±3
494±3
18,720±3
190±3
1,534±3
I A B H W O U
Vital
Alive Deceased
AspTreeView/MetaItemFind_Sub.aspx?SearchString=ck-mb index&SearchCategory=category_union&SearchOperator=3
Local intranet

Theory of Kimball translated to Healthcare Data

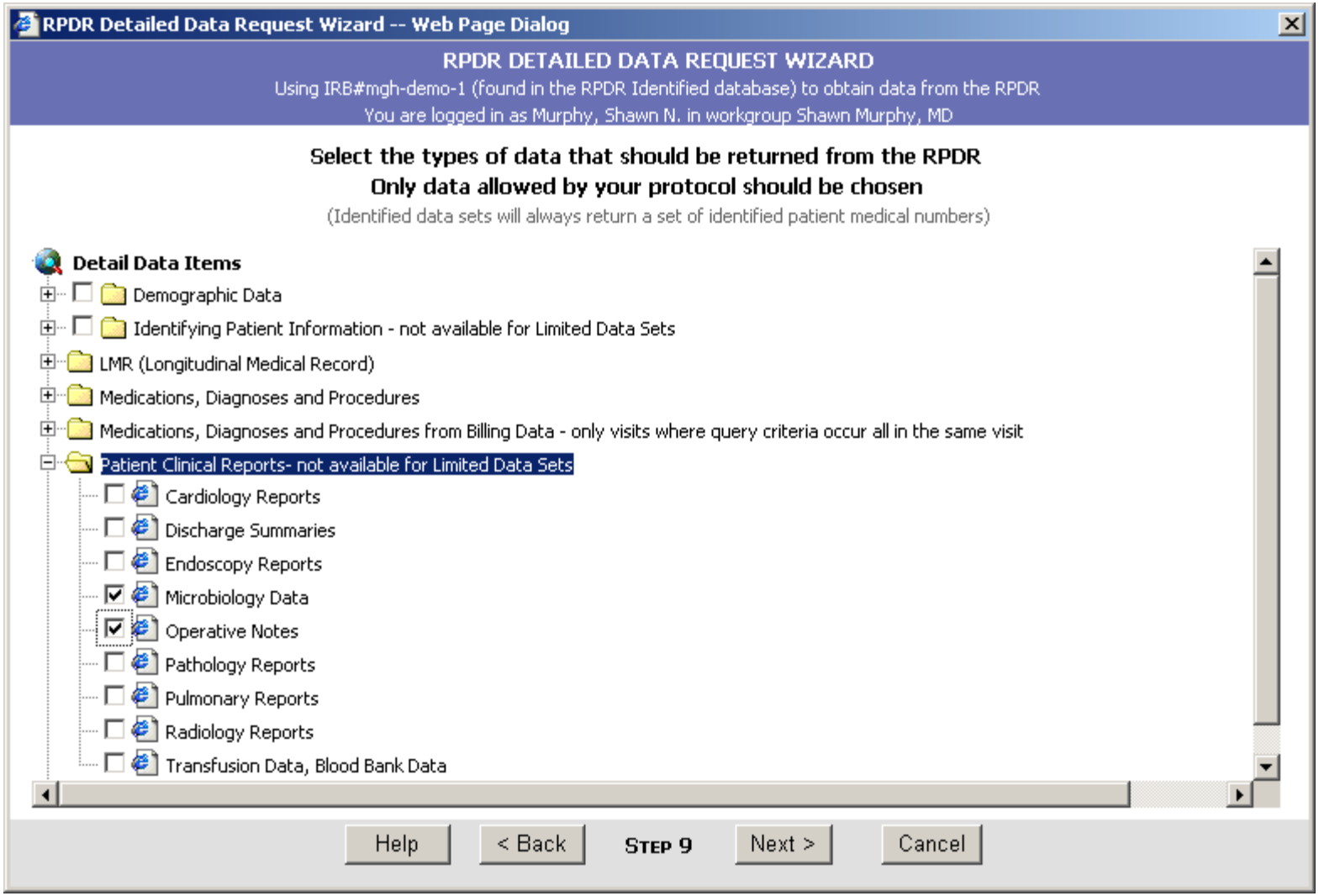




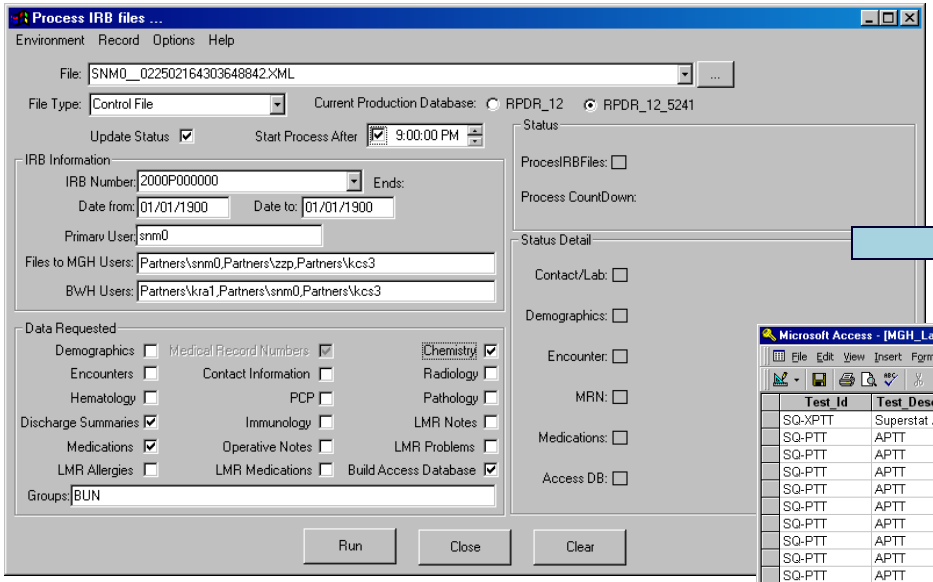



RPDR Detailed Data Request Wizard -- Web Page Dialog
RPDR DETAILED DATA REQUEST WIZARD
Using IRB#mgh-demo-1 (found in the RPDR Identified database) to obtain data from the RPDR
You are logged in as Murphy, Shawn N. in workgroup Shawn Murphy, MD
Select protocol number(s)
Partners IRB (required):
mgh-demo-1
Title: RPDR protocol - Demonstration IRB number for Dr. Murphy
Status: Active
Newton Wellesley Hospital IRB:
NWH Demo 1
Title: test
Status: Active
Spaulding Rehabilitation Hospital IRB:
Options for returned set of patients:
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

RPDR Detailed Data Request Wizard -- Web Page Dialog
RPDR DETAILED DATA REQUEST WIZARD
Using IRB#mgh-demo-1 (found in the RPDR Identified database) to obtain data from the RPDR
You are logged in as Murphy, Shawn N. in workgroup Shawn Murphy, MD
Please select if you would like a HIPAA-defined (deidentified) limited data set or an identified data set
What's a limited data set?
Limited Data Set
- The files that result from this request will be available in a protected file share with no special encryption.
Identified Data Set
- The text files that result from this request will be encrypted and the Microsoft Access file will be password protected. In order to access the data, a password will be provided.
Help
< Back
STEP 8
Next >
Cancel

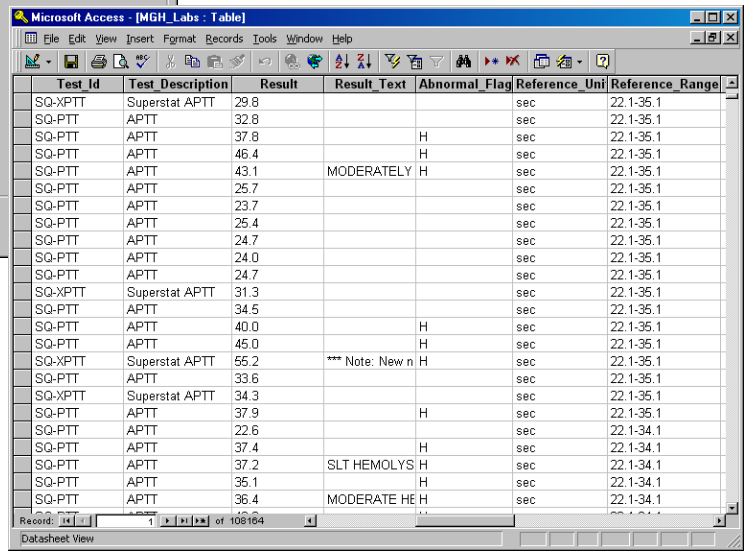

RPDR Detailed Data Request Wizard -- Web Page Dialog
RPDR DETAILED DATA REQUEST WIZARD
Using IRB#mgh-demo-1 (found in the RPDR Identified database) to obtain data from the RPDR
You are logged in as Murphy, Shawn N. in workgroup Shawn Murphy, MD
Select the types of data that should be returned from the RPDR
Only data allowed by your protocol should be chosen
(Identified data sets will always return a set of identified patient medical numbers)
Detail Data Items
Demographic Data
Identifying Patient Information - not available for Limited Data Sets
LMR (Longitudinal Medical Record)
Medications, Diagnoses and Procedures
Medications, Diagnoses and Procedures from Billing Data - only visits where query criteria occur all in the same visit
Patient Clinical Reports- not available for Limited Data Sets
Cardiology Reports
Discharge Summaries
Endoscopy Reports
Microbiology Data
Operative Notes
Pathology Reports
Pulmonary Reports
Radiology Reports
Transfusion Data, Blood Bank Data
Help
< Back
STEP 9
Next >
Cancel

Detailed data is gathered for request and distributed



Output files placed in special directory

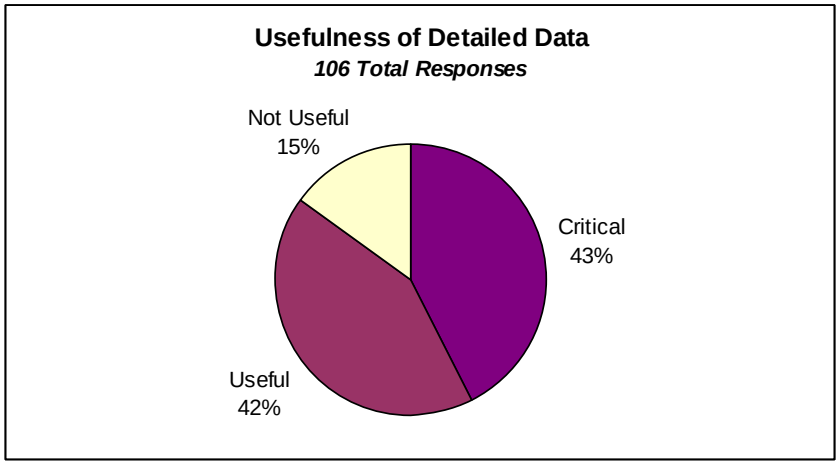
Data is gathered from RPDR and other MGB sources



Files include Small Database

One year's usage of RPDR

- 4526 registered users, 1113 new in just 2019
- 834 teams/year gathering data for research studies
- 4472 detailed patient data sets returned to these teams in 2019, containing data of 24.7 million patient records.
- From a survey of 153 teams
  - Importance of the data received from the RPDR was evaluated in relation to the study it was supporting.
  - Calculated over 4 years (FY15-FY19) the total agreement amounts were $2.27 Billion, making per year consumption critically dependent on RPDR $244 Million.



Rapid investigation of QTc prolongation

- *FDA warning 2011 for Celexa*

  Safety Announcement:
  [8-24-2011] "should no longer be used at doses greater than 40 mg per day because it can cause abnormal changes in the electrical activity of the heart."

- *But, did NOT include Lexapro (which is active ingredient of Celexa [s-enantiomer])*
- *Shown to be true with RPDR-derived data set with >38,000 EKGs obtained within 14 – 90 day window after medication initiated*

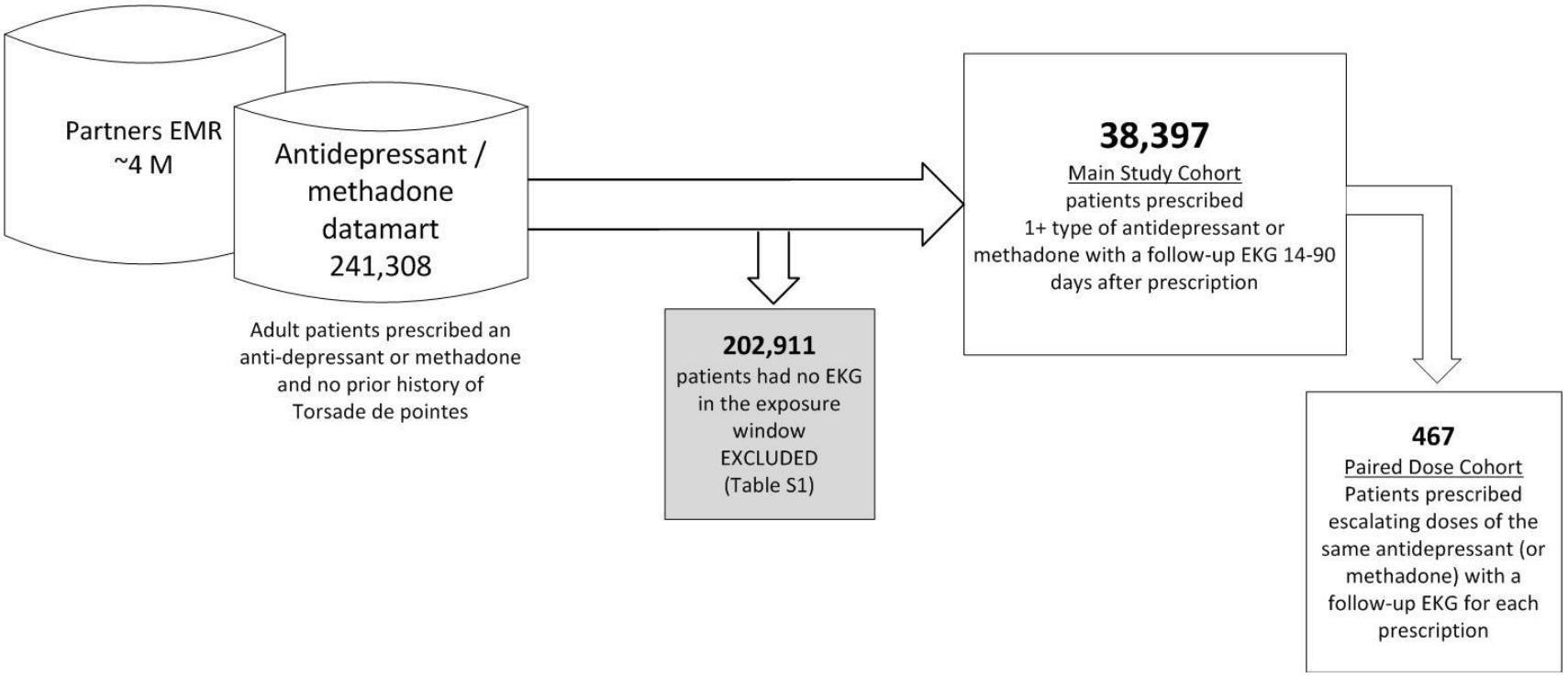
	Adjusted model†	
Anti-depressant	**prolongation**	**p-value**
SSRI		
Citalopram (Celexa)	2.85	0.004
Escitalopram (Lexapro)	3.80	< 0.001
Fluoxetine (Prozac)	1.44	0.150
Paroxetine (Paxil)	0.07	0.943
Sertraline (Zoloft)	0.87	0.383
Other anti-depressants		
Amitriptyline	4.10	< 0.001
Bupropion	-2.15	0.032
Duloxetine	0.60	0.547
Mirtazapine	-1.46	0.145
Nortriptyline	1.23	0.219
Venlafaxine	1.15	0.251
previously known prolonger		
Methadone	5.32	< 0.001

† Adjusted for age, gender, race, type of insurance, history of major depression, history of myocardial infarction and Charlson comorbidity score

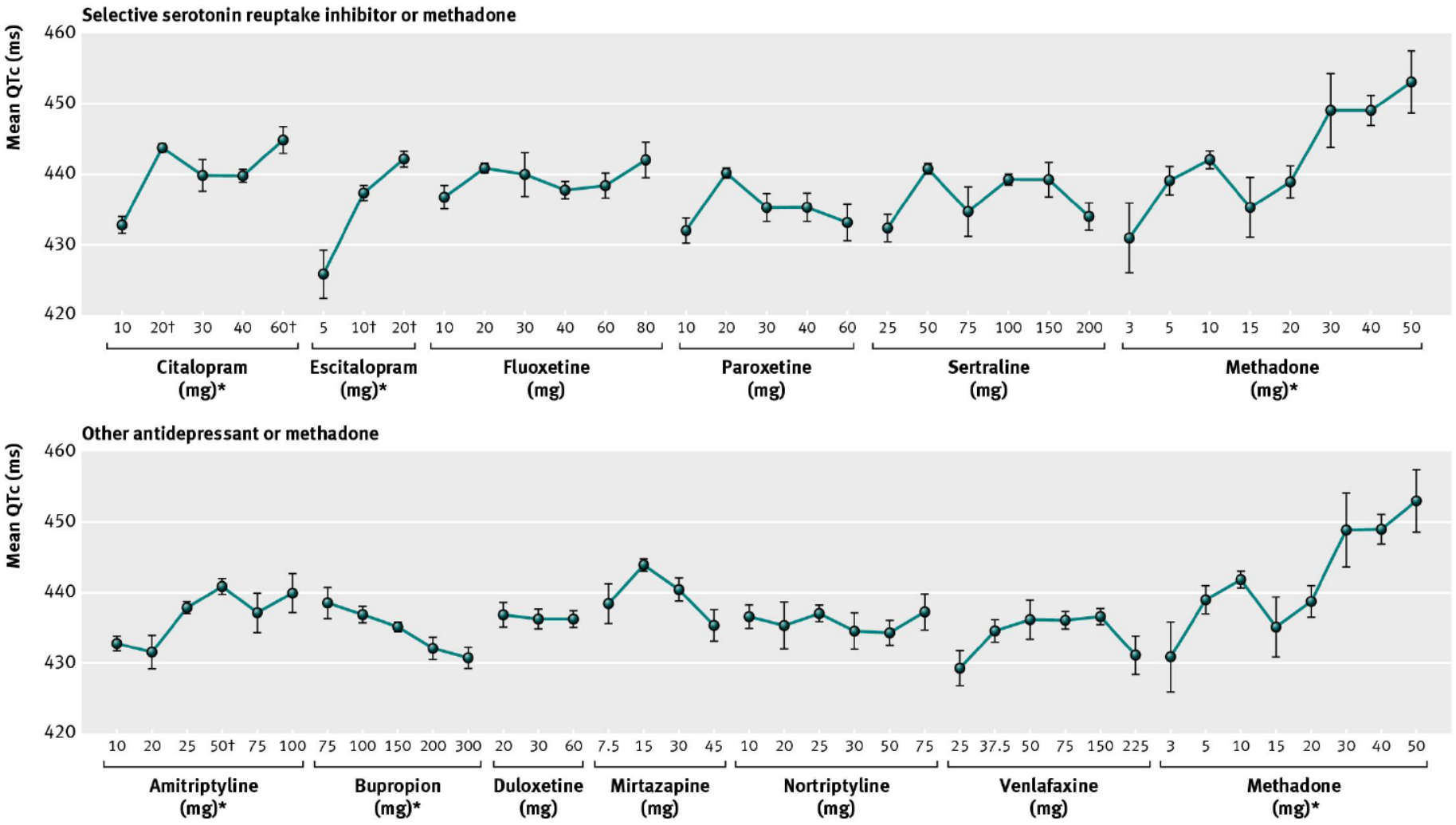
Roy Perlis MD, MSc and team

Relevant Cohorts of Patients are Gathered through RPDR and Detailed Data Obtained

- **Medication use by individual patients over time**
- **Patient EKG QTc values at various time points**



Results: QTc interval and medication use



* Dose a significant predictor of QTc in fully adjusted linear models at α=0.05
† QTc at specified dose is significantly different from that at prior dose in fully adjusted linear models at α=0.05

Mean (SD) corrected QT (QTc) interval recorded on electrocardiogram 14–90 days after prescription of antidepressant or methadone, by drug dose

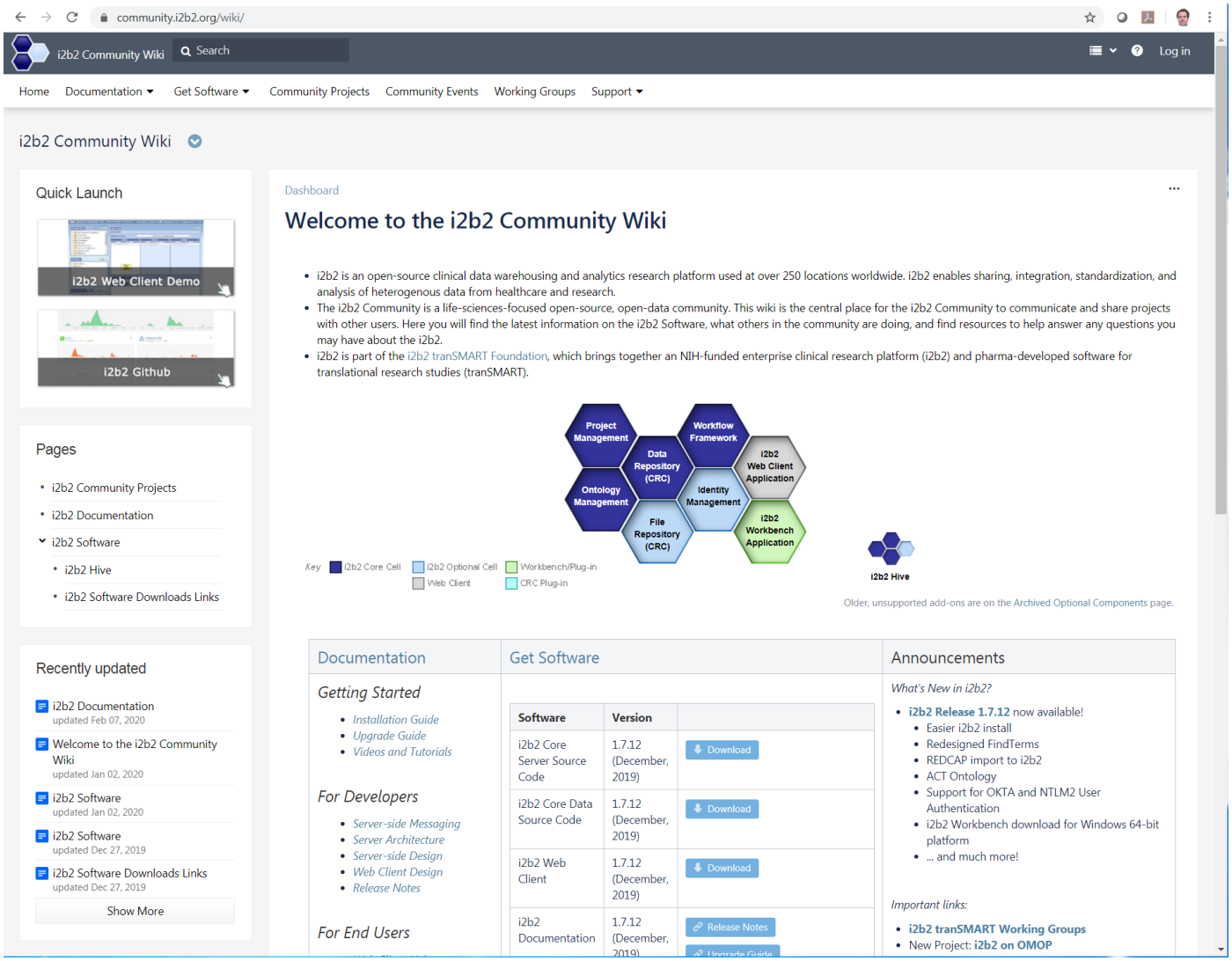
High Throughput Methods for supporting Translational Research

- Set of patients is selected from medical record data in a high throughput fashion
- Investigators explore phenotypes of these patients using Machine Learning 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
- Digital medicine is delivered into clinical care through Digital Twin

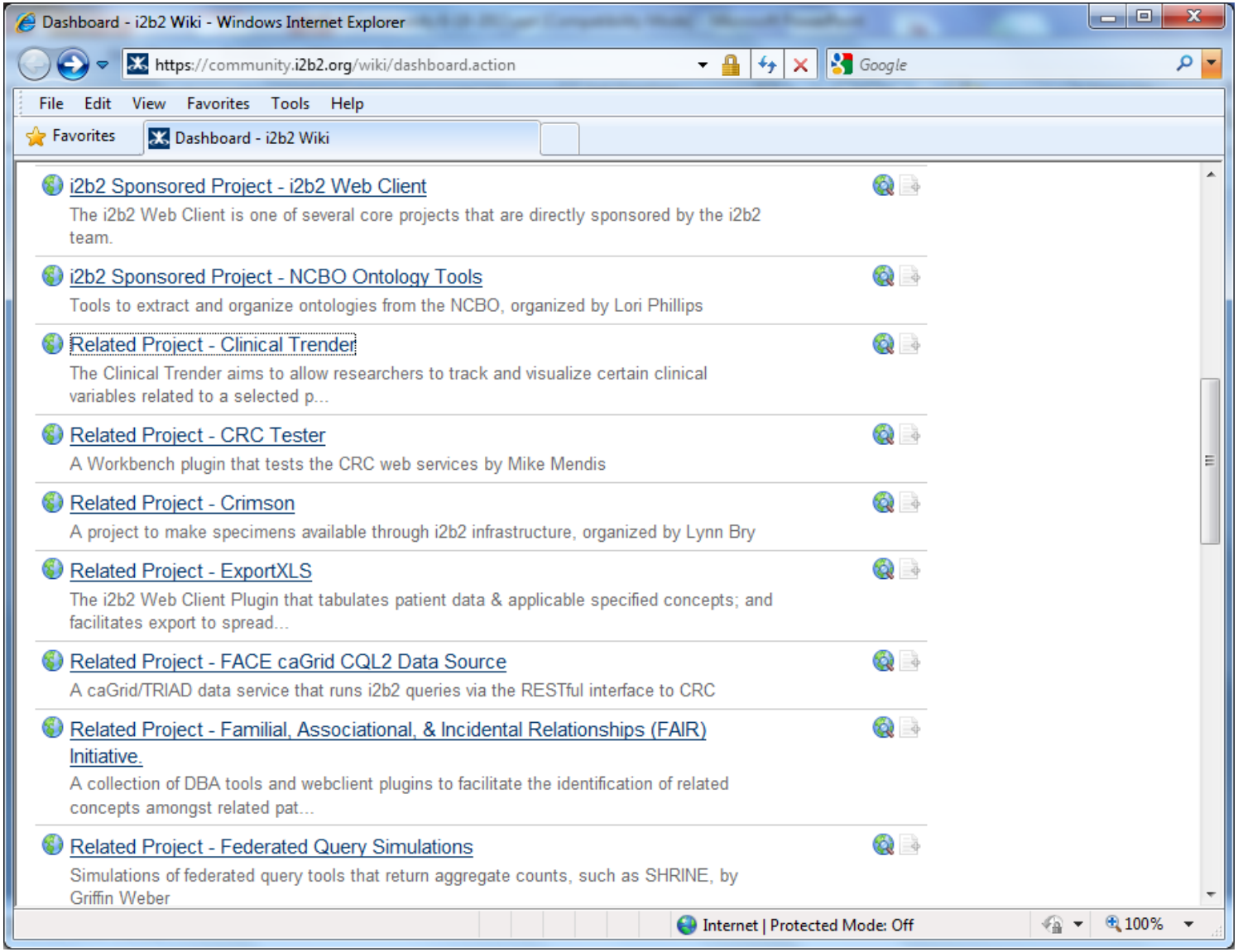
RPDR Evolved into international “Informatics for Integrating Biology and the Bedside (i2b2)” sponsored by the National Institutes of Health, what is it?

- 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

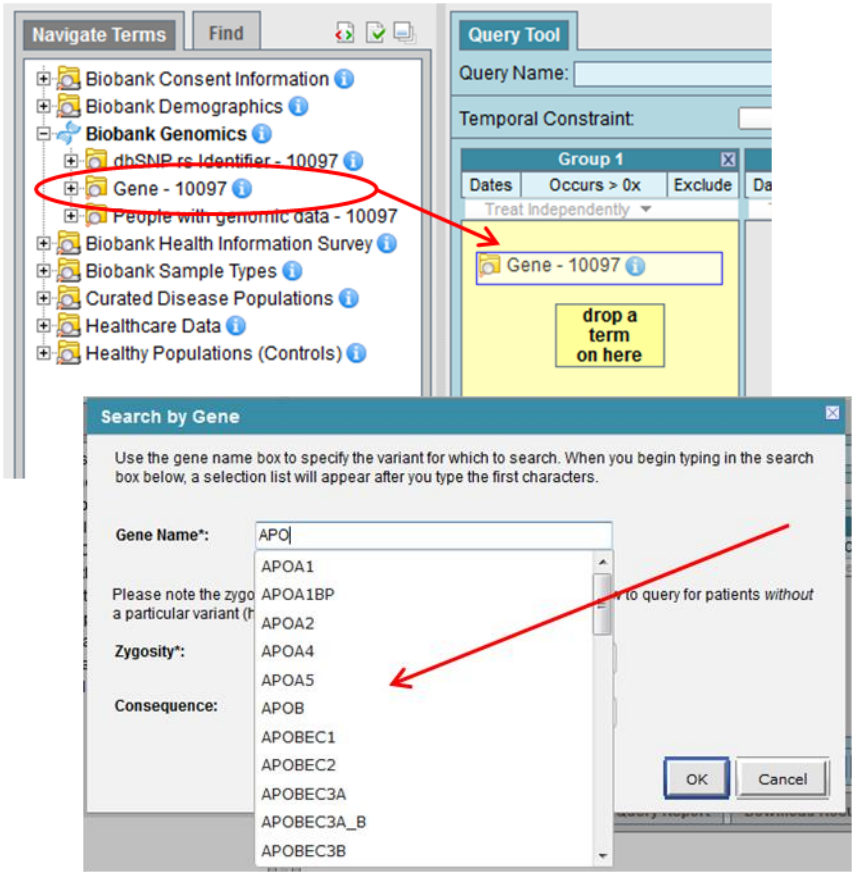
I2b2 Community Software distributed as open source

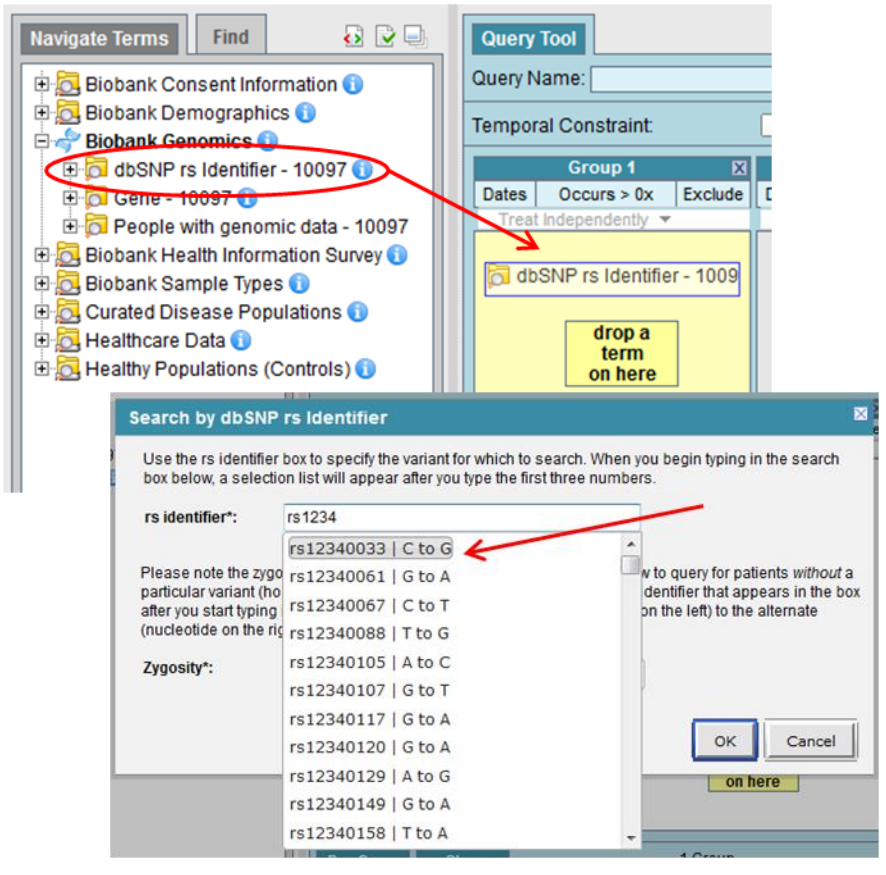


I2b2 Software adapts through new plugins



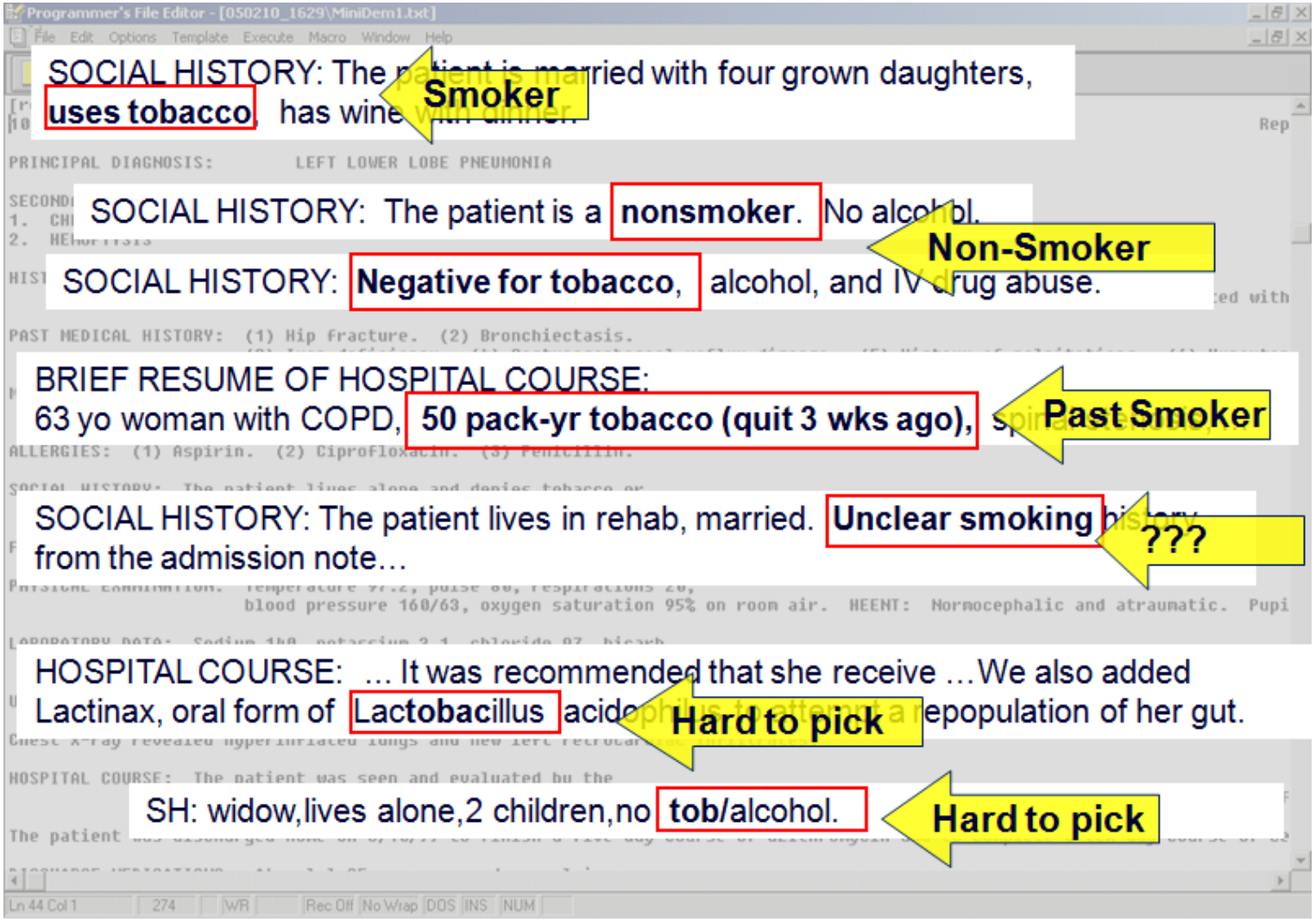
Genotype Data



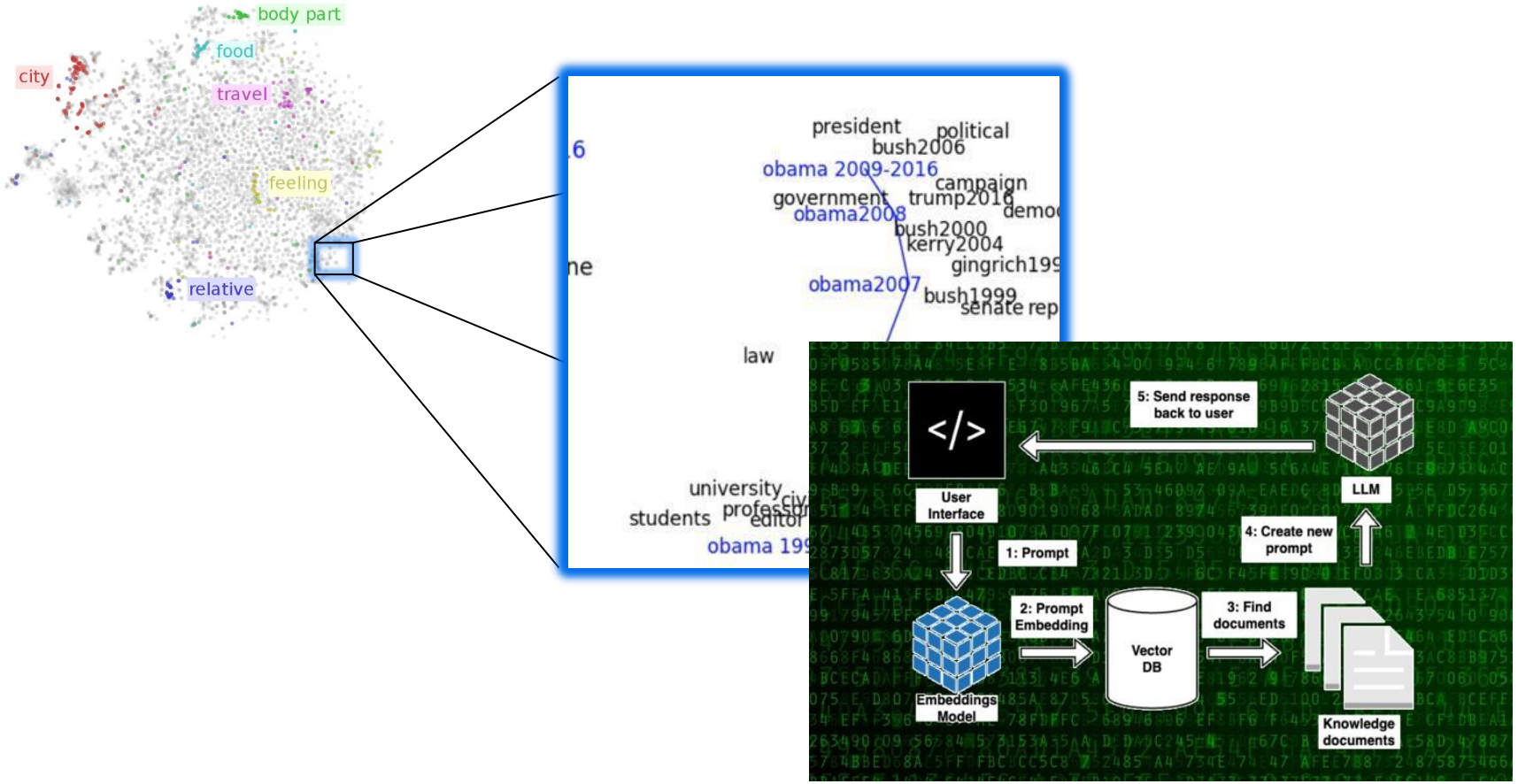


https://community.i2b2.org/wiki/display/IGD/Loading+Genomic+VCF+Files+into+i2b2

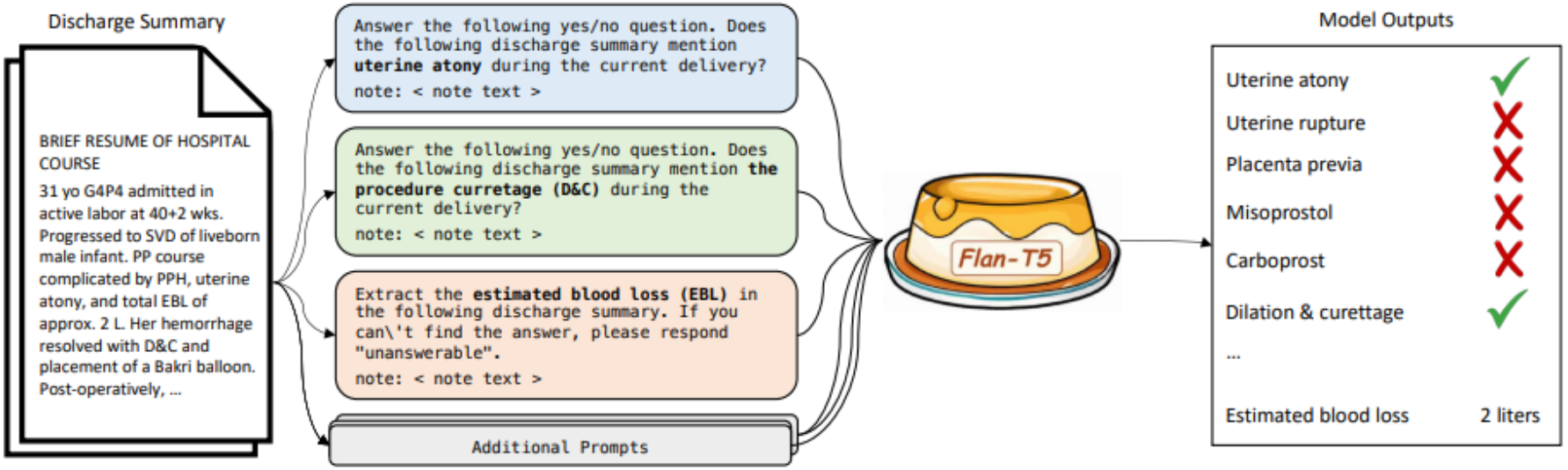
Use NLP to extract the relevant features from the set of patient notes.



LMM Enhanced interaction with Patient Representation

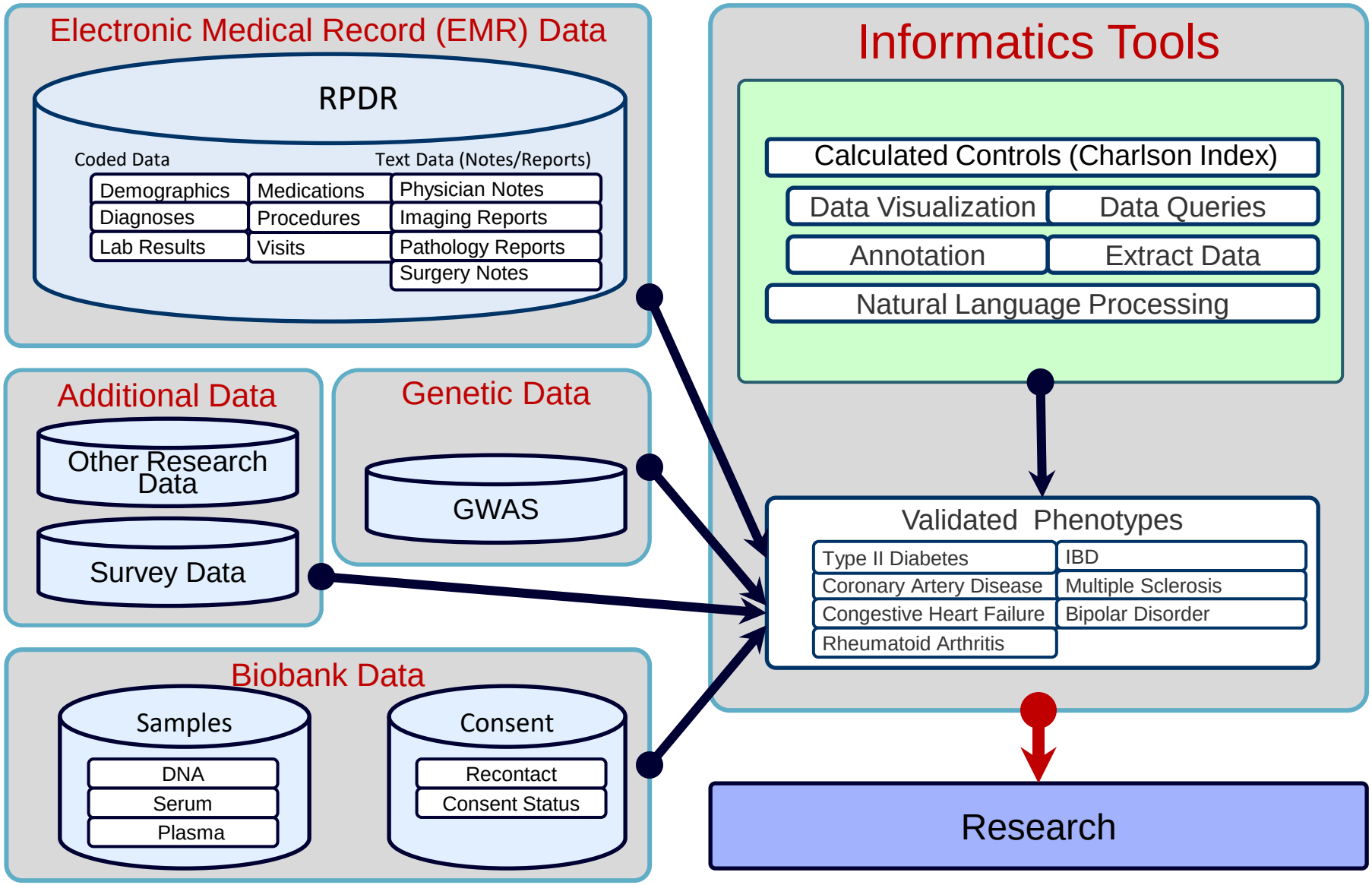


Medical conditions supported by description in chart



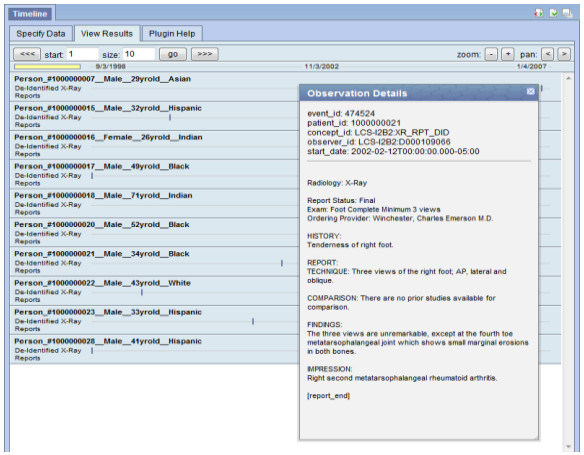
Emily Alsentzer et al
Zero-shot Interpretable Phenotyping of Postpartum Hemorrhage Using Large Language Models
medRxiv preprint doi:
https://doi.org/10.1101/2023.05.31.23290753

Data Integration in Big Data Commons

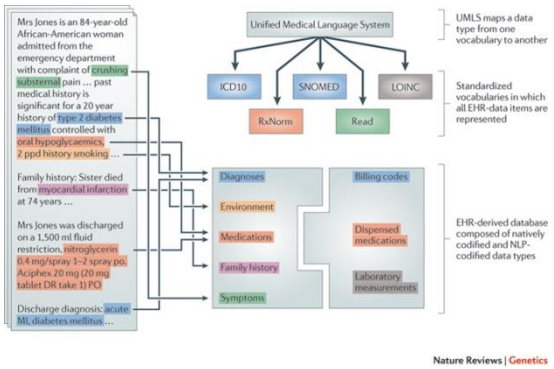


Curating a Disease Algorithm

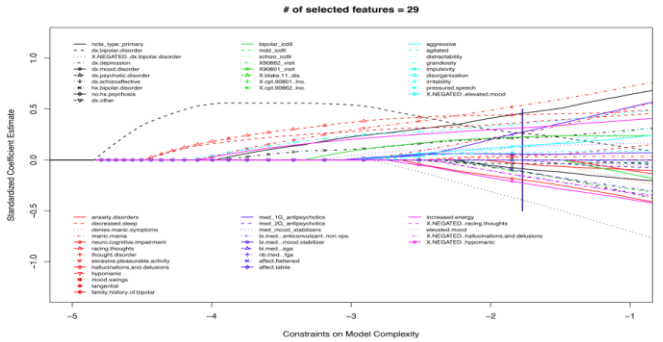
1. Create a gold standard training set.



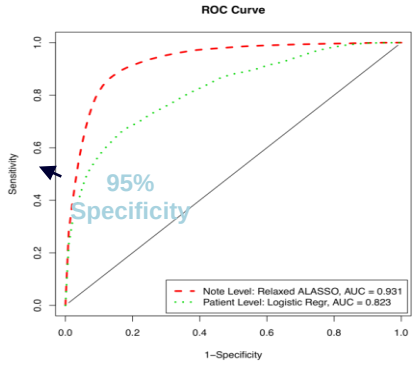
2. Create a comprehensive list of features from patient's electronic data that describe the disease of interest



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



Biobank Portal | Curated Diseases

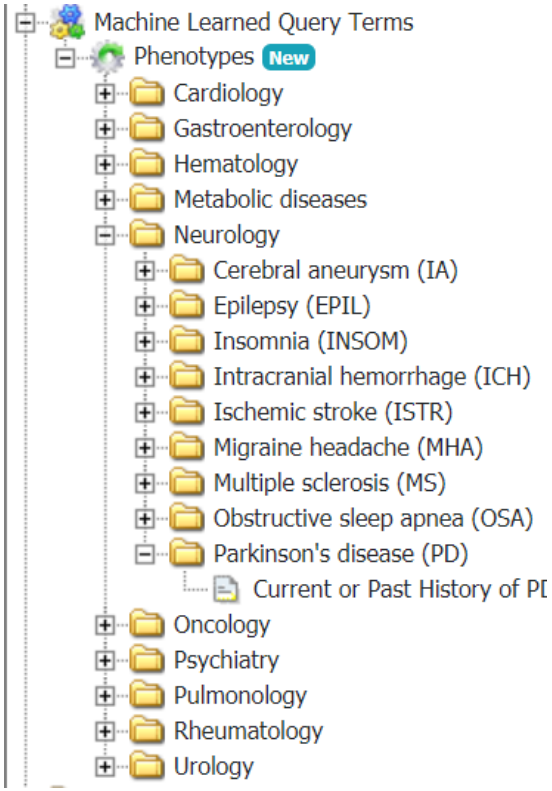
Validated Phenotype	Count*	Predictive Positive Value
Bipolar Disease	71	89%
Congestive Heart Failure	387	90%
Coronary Artery Disease	2,420	97%
Crohn's Disease	453	90%
Multiple Sclerosis	94	90%
Rheumatoid Arthritis	550	90%
Type 2 Diabetes Mellitus	1,887	97%
Ulcerative Colitis	330	90%

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

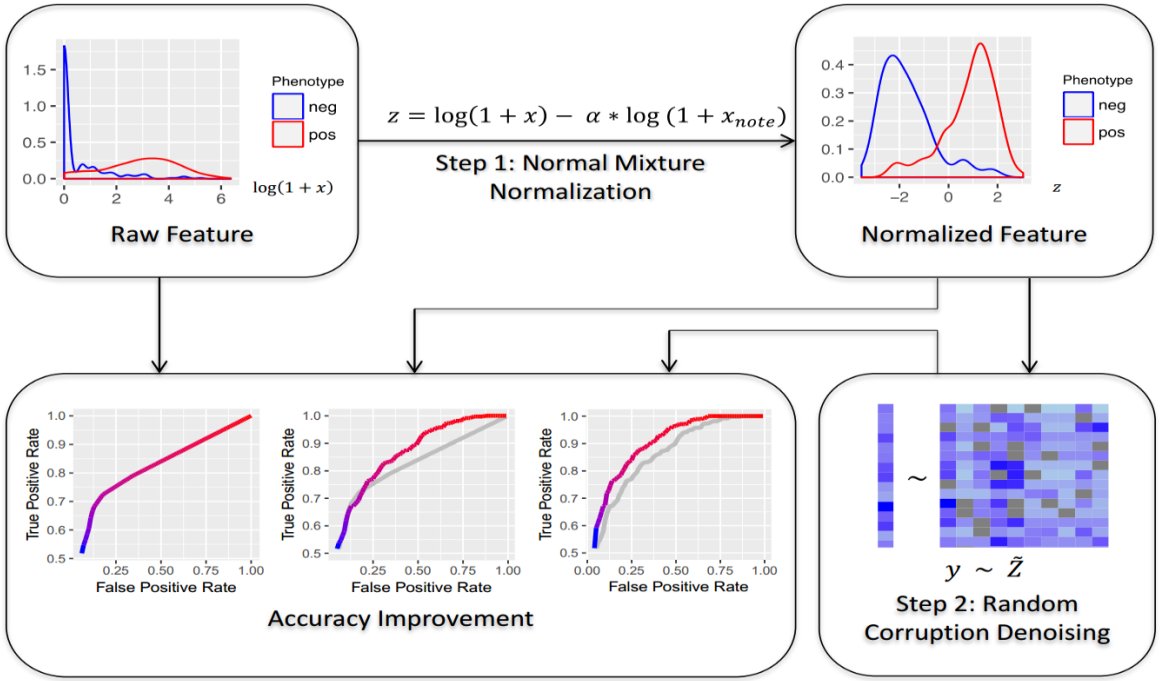
Automated Learning Algorithms enabled in RPDR such as PheNorm Algorithm



J Am Med Inform Assoc. 2018 Jan 1;25(1):54-60. doi: 10.1093/jamia/ocx111.

Enabling phenotypic big data with PheNorm.

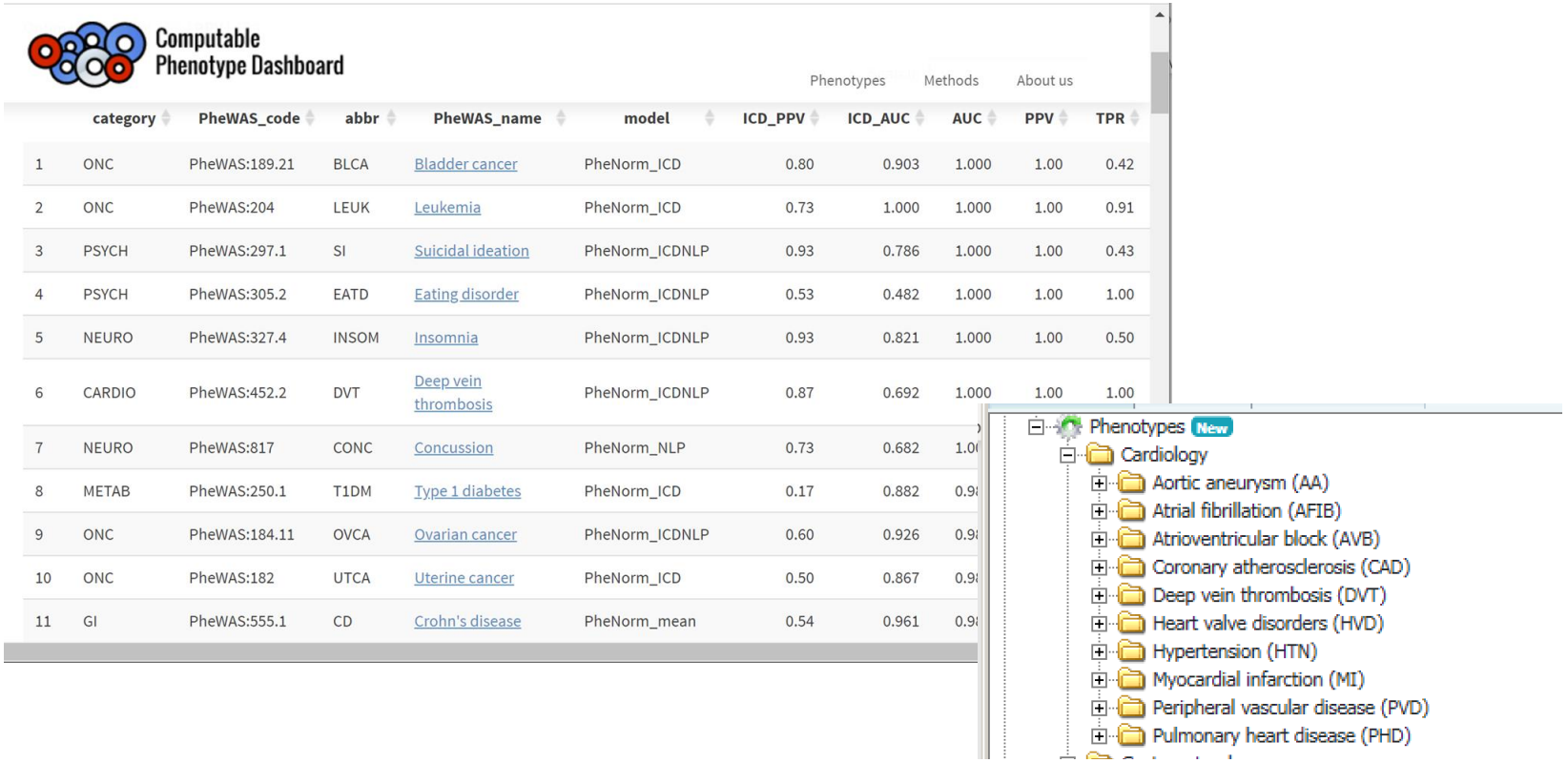
Yu S[1,2], Ma Y[3], Gronsbell J[4], Cai T[5], Ananthakrishnan AN[6], Gainer VS[7], Churchill SE[8], Szolovits P[9], Murphy SN[7,10], Kohane IS[8], Liao KP[11], Cai T[4].



Machine Learned Phenotypes

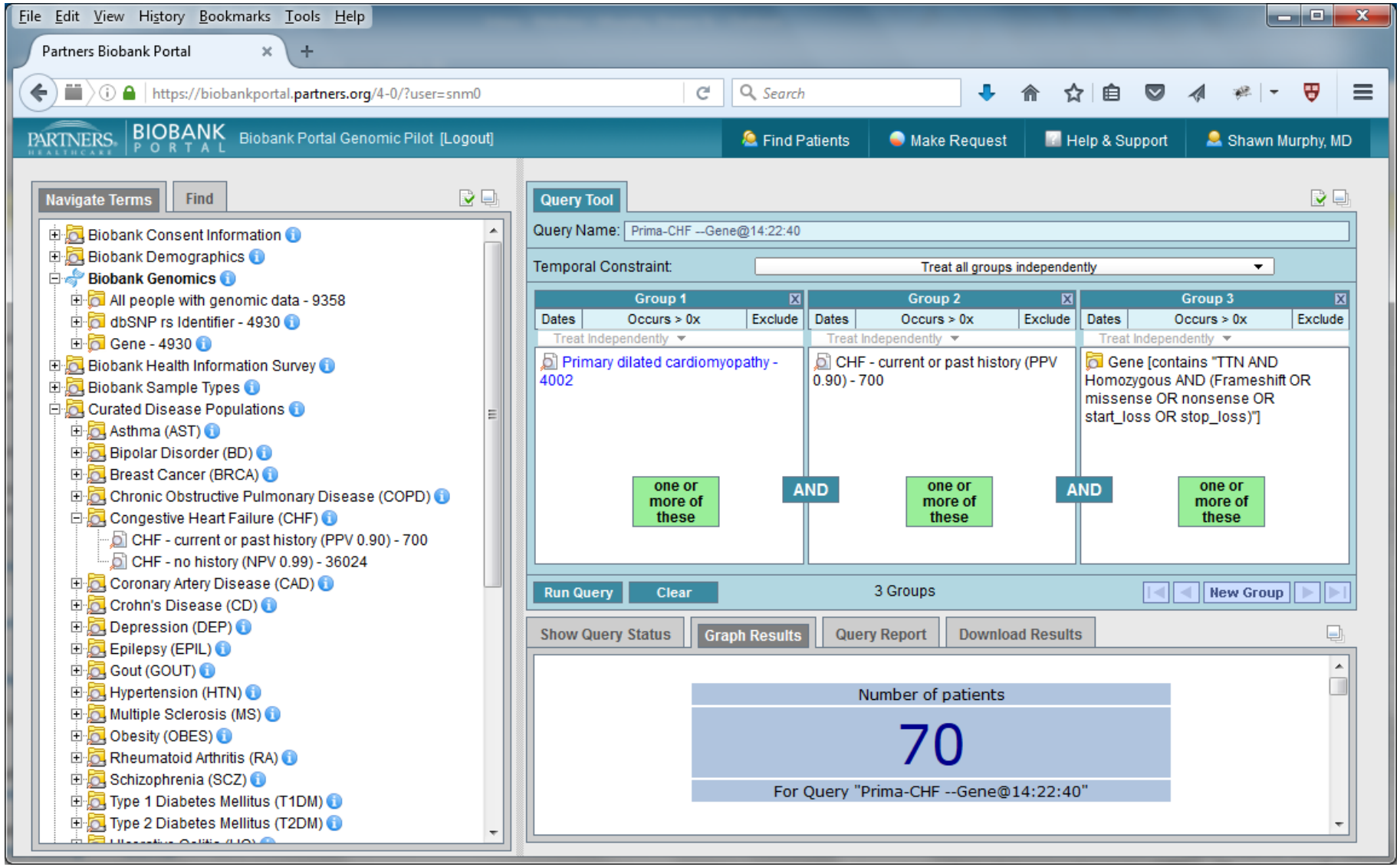
- Abdominal hernia
- Acute bronchitis and bronchiolitis
- Acute pancreatitis
- Alcoholism
- Alzheimer's disease
- Aortic aneurysm
- Aplastic anemia
- Atrial fibrillation
- Atrioventricular block
- Autism spectrum disorders
- Basal cell carcinoma
- Bipolar Disease
- Bladder cancer
- Brain cancer
- Breast cancer
- Cerebral aneurysm
- Cholelithiasis
- Chronic pancreatitis
- Chronic sinusitis
- Coronary atherosclerosis
- Crohn's disease
- Deep vein thrombosis
- Depression
- Diverticulosis and diverticulitis
- Eating disorder
- Epilepsy
- Gastroesophageal reflux disease
- Gout
- Heart valve disorders
- Hyperlipidemia
- Hyperparathyroidism
- Hypertension
- Hypothyroidism
- Insomnia
- Intracranial hemorrhage
- Ischemic stroke
- Leukemia
- Lung cancer
- Melanoma
- Migraine headache
- Multiple sclerosis
- Myocardial infarction
- Neutropenia
- Non-Hodgkin lymphoma
- Obesity
- Obsessive compulsive disorder
- Obstructive sleep apnea
- Ovarian cancer
- Pancreatic cancer
- Parkinson's disease
- Peripheral vascular disease
- Pneumonia
- Polycystic ovaries
- Prostate cancer
- Pulmonary heart disease
- Renal cancer
- Renal failure
- Schizophrenia
- Substance addiction
- Suicidal ideation
- Suicide attempt or self-inflicted injury
- Thyroid cancer
- Tobacco use disorder
- Type 1 diabetes
- Type 2 diabetes
- Ulcerative colitis
- Urinary calculus
- Uterine cancer

Phenotype Automation: Phenotype Quality Dashboard

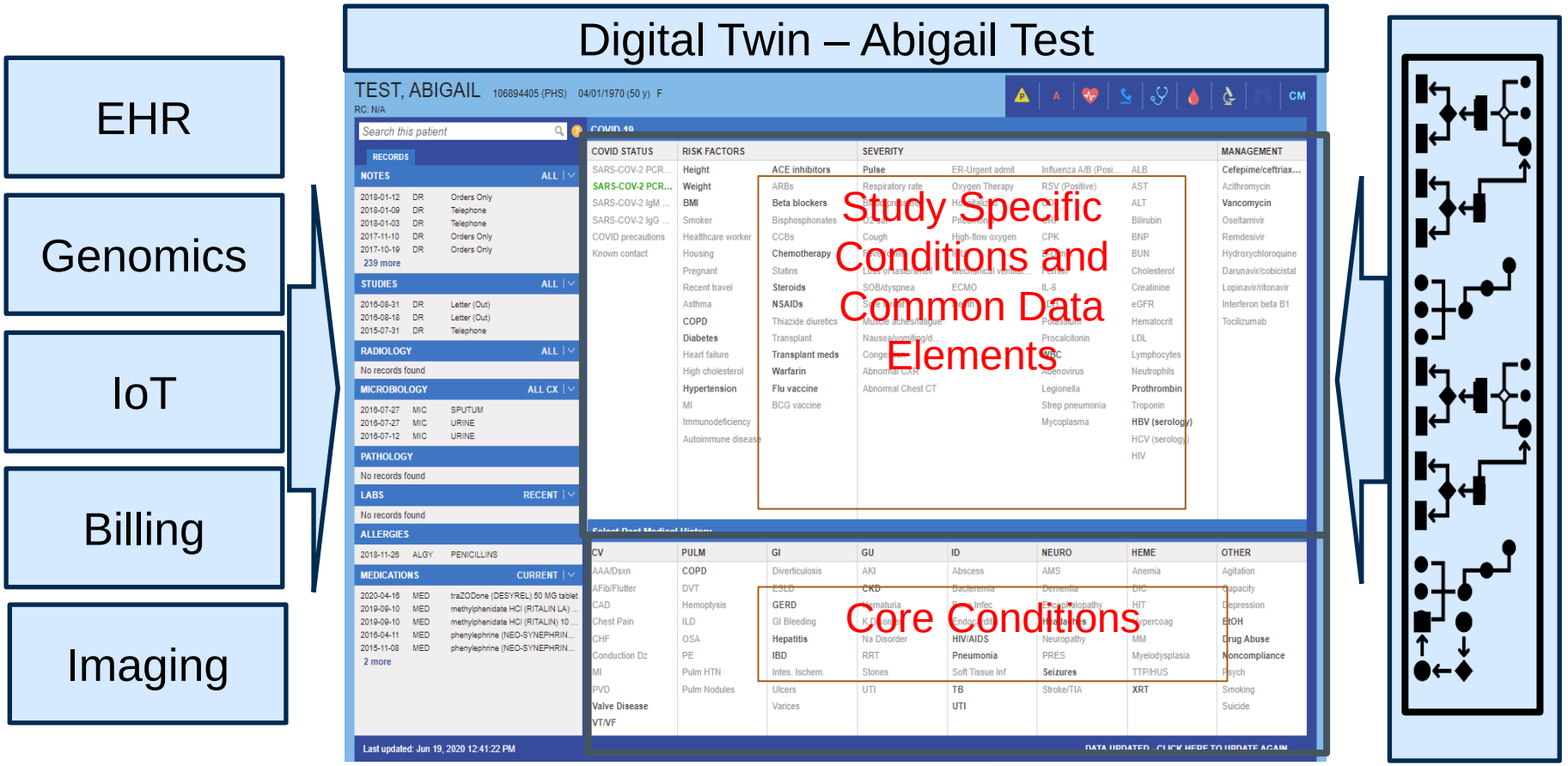


	category	PheWAS_code	abbr	PheWAS_name	model	ICD_PPV	ICD_AUC	AUC	PPV	TPR
1	ONC	PheWAS:189.21	BLCA	Bladder cancer	PheNorm_ICD	0.80	0.903	1.000	1.00	0.42
2	ONC	PheWAS:204	LEUK	Leukemia	PheNorm_ICD	0.73	1.000	1.000	1.00	0.91
3	PSYCH	PheWAS:297.1	SI	Suicidal ideation	PheNorm_ICDNLP	0.93	0.786	1.000	1.00	0.43
4	PSYCH	PheWAS:305.2	EATD	Eating disorder	PheNorm_ICDNLP	0.53	0.482	1.000	1.00	1.00
5	NEURO	PheWAS:327.4	INSOM	Insomnia	PheNorm_ICDNLP	0.93	0.821	1.000	1.00	0.50
6	CARDIO	PheWAS:452.2	DVT	Deep vein thrombosis	PheNorm_ICDNLP	0.87	0.692	1.000	1.00	1.00
7	NEURO	PheWAS:817	CONC	Concussion	PheNorm_NLP	0.73	0.682	1.0		
8	METAB	PheWAS:250.1	T1DM	Type 1 diabetes	PheNorm_ICD	0.17	0.882	0.9		
9	ONC	PheWAS:184.11	OVCA	Ovarian cancer	PheNorm_ICDNLP	0.60	0.926	0.9		
10	ONC	PheWAS:182	UTCA	Uterine cancer	PheNorm_ICD	0.50	0.867	0.9		
11	GI	PheWAS:555.1	CD	Crohn's disease	PheNorm_mean	0.54	0.961	0.9		

High Quality Phenotypes for Research Studies



Combined with Generative AI can produce Digital Twin of Patient

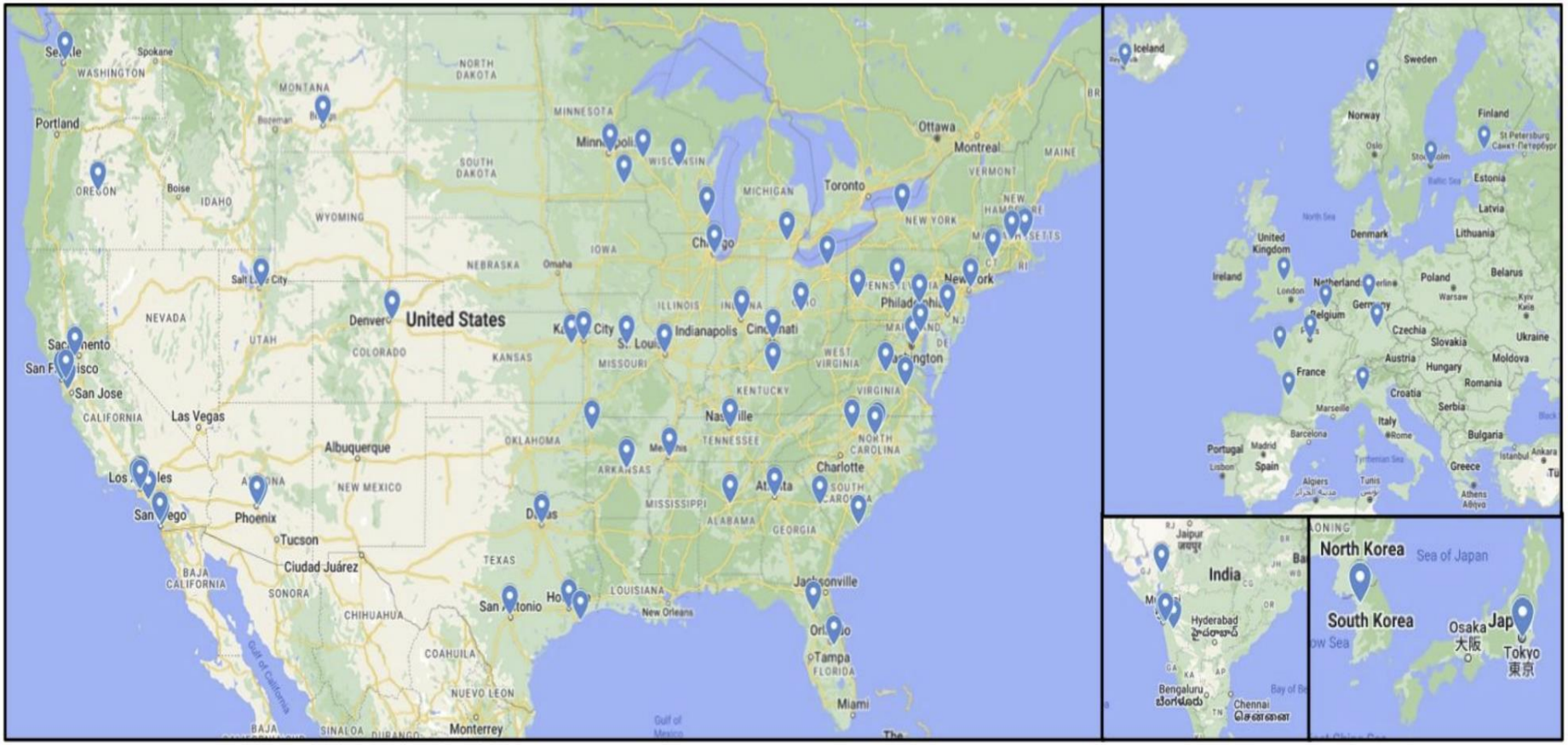


High Throughput Methods for supporting Translational Research

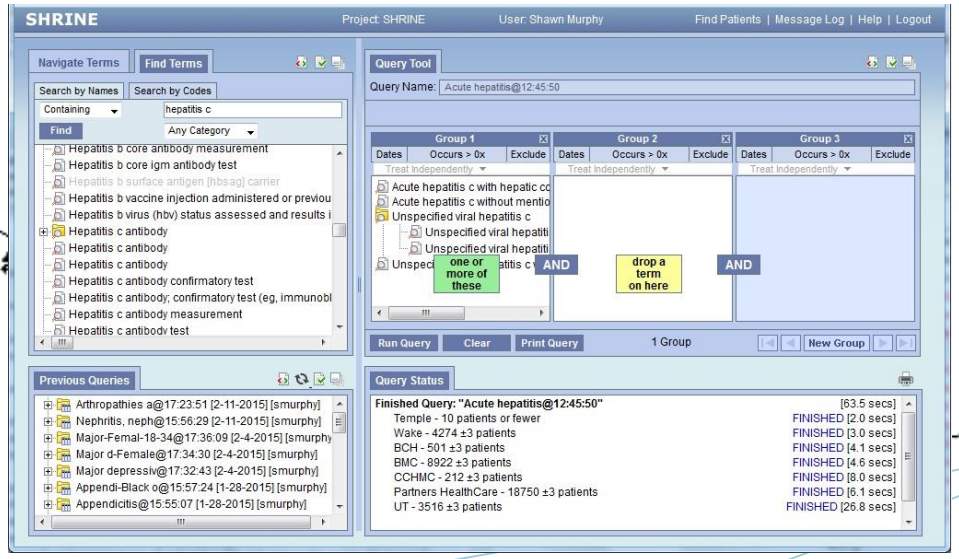
- Set of patients is selected from medical record data in a high throughput fashion
- Investigators explore phenotypes of these patients using Machine Learning tools and a translational team developed to work specifically with medical record data
- Distributed networks cross institutional boundaries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

I2b2 Implementations

>250 across the USA and Internationally, some illustrated below:



Federated Queries



Mass General Brigham

Boston Children's Hospital

BIDMC

Boston Health Net (BMC and Community Health Centers)

Columbia U. Medical Center and New York Presbyterian Hospital

University of California, Davis

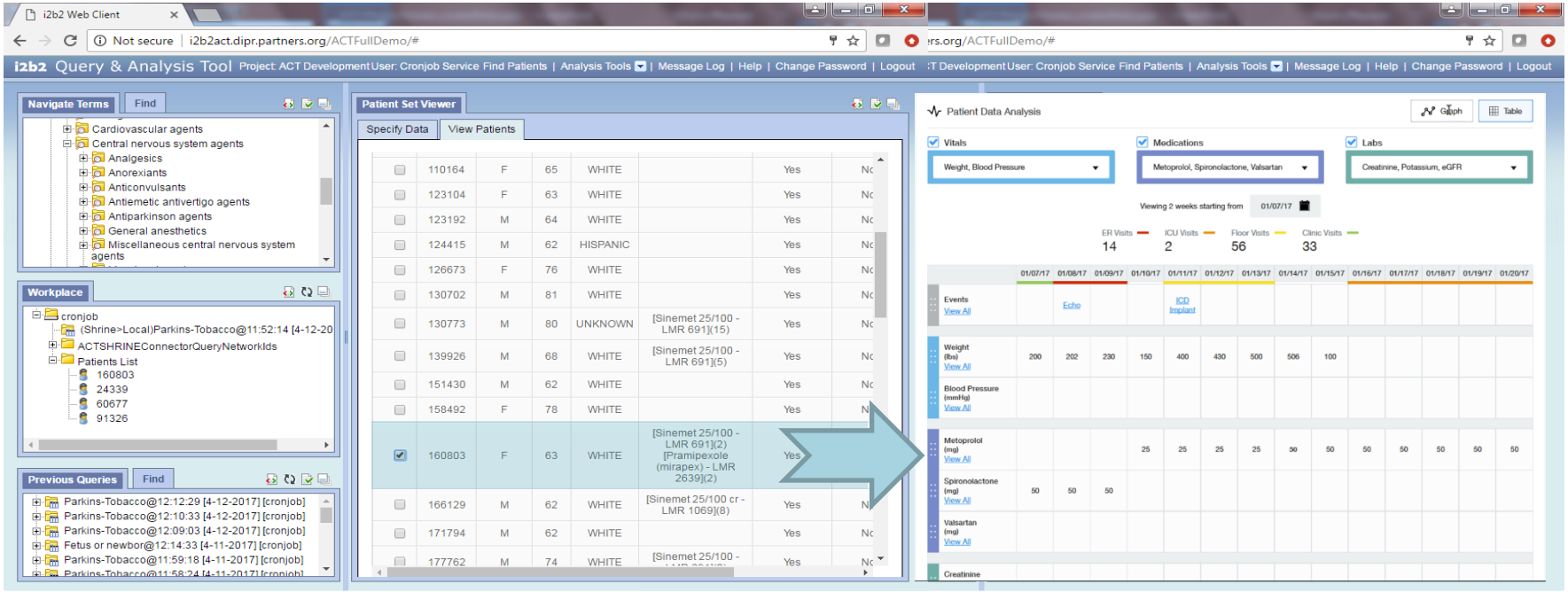
Washington University in St. Louis

Wake Forest Baptist Medical Center

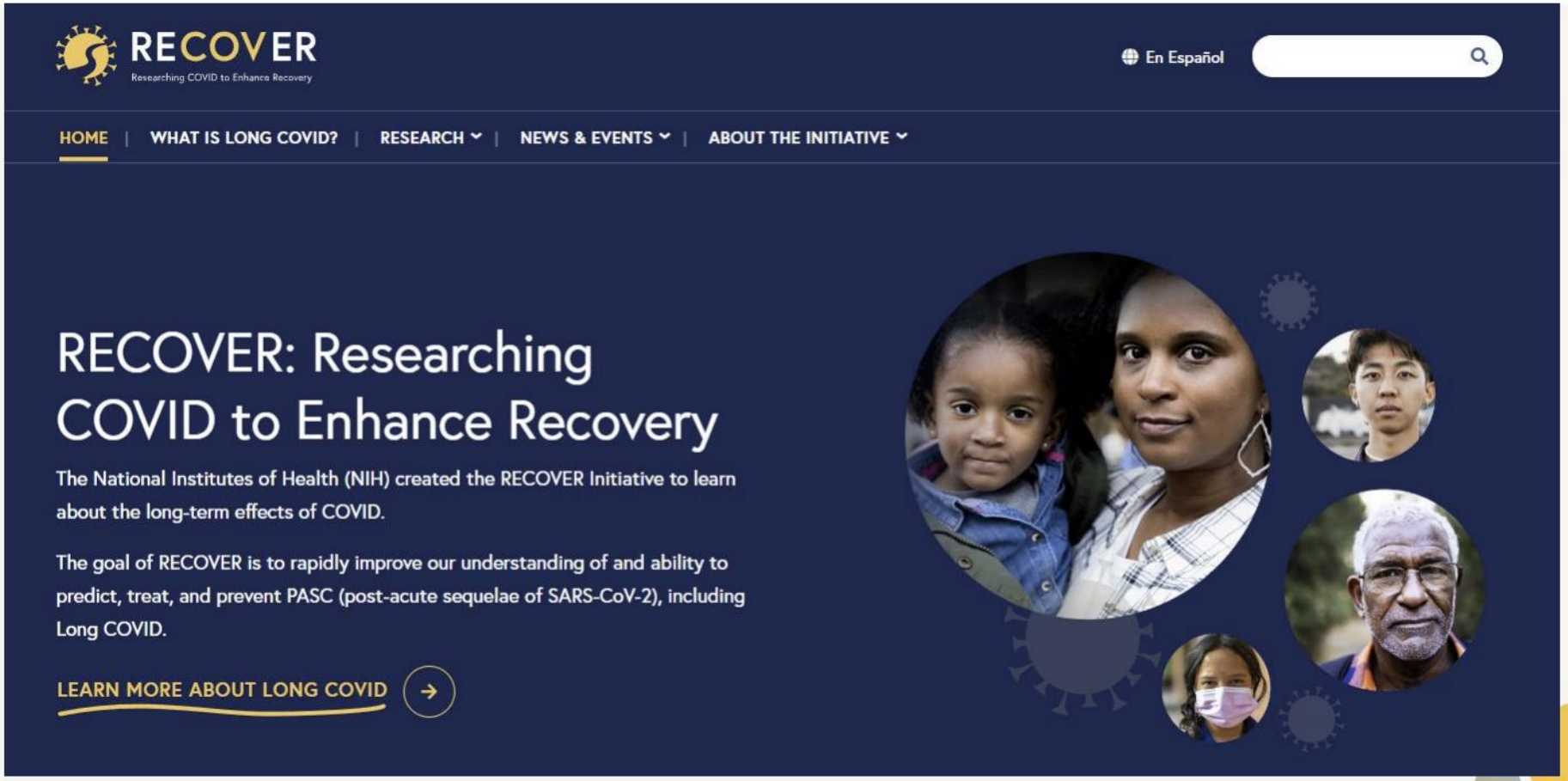
Morehouse/Grady/RCMI

U Texas Health Science Center/Houston

Drive Pragmatic Clinical Studies



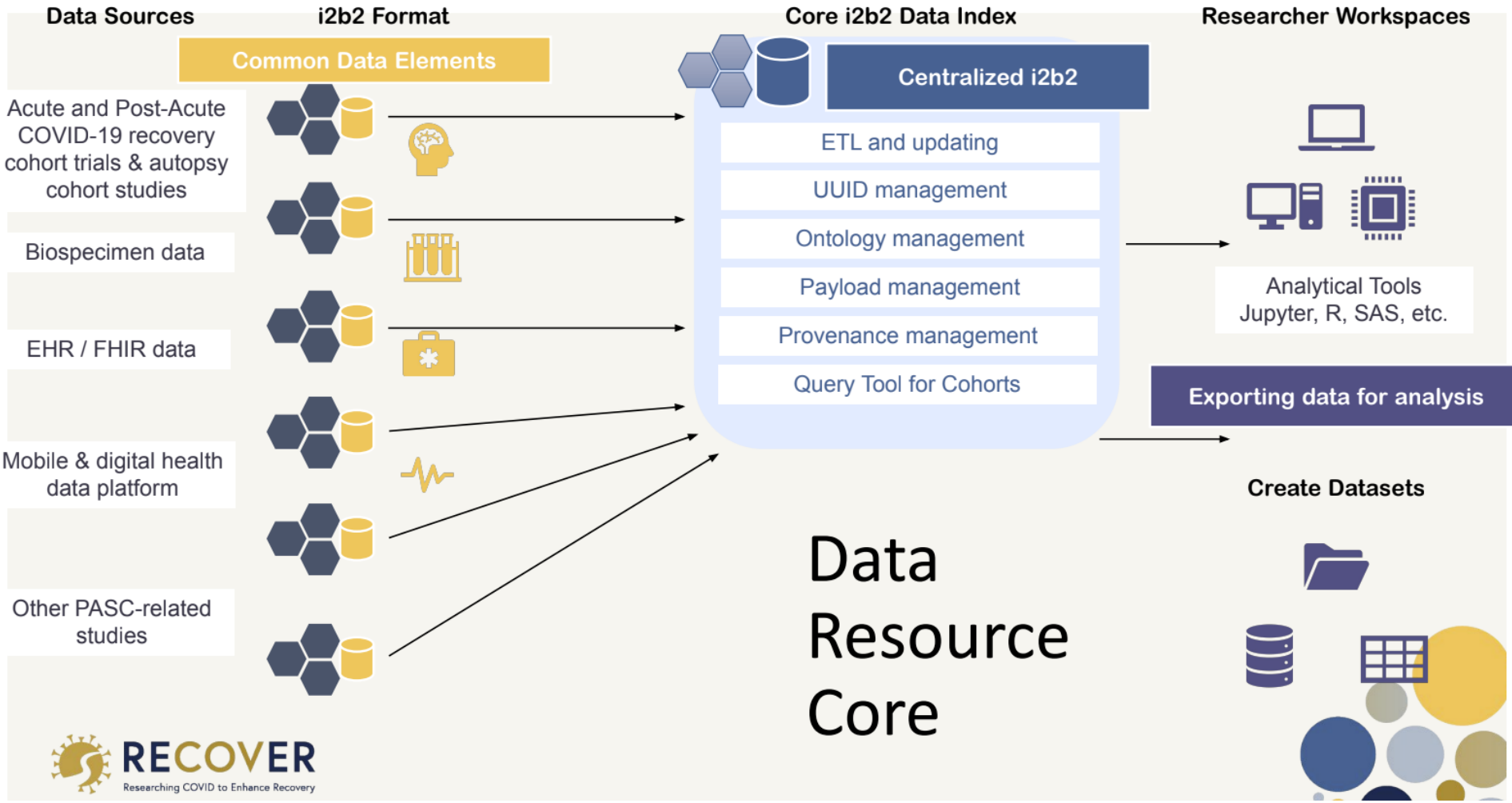
RECOVER Study Data Harmonization



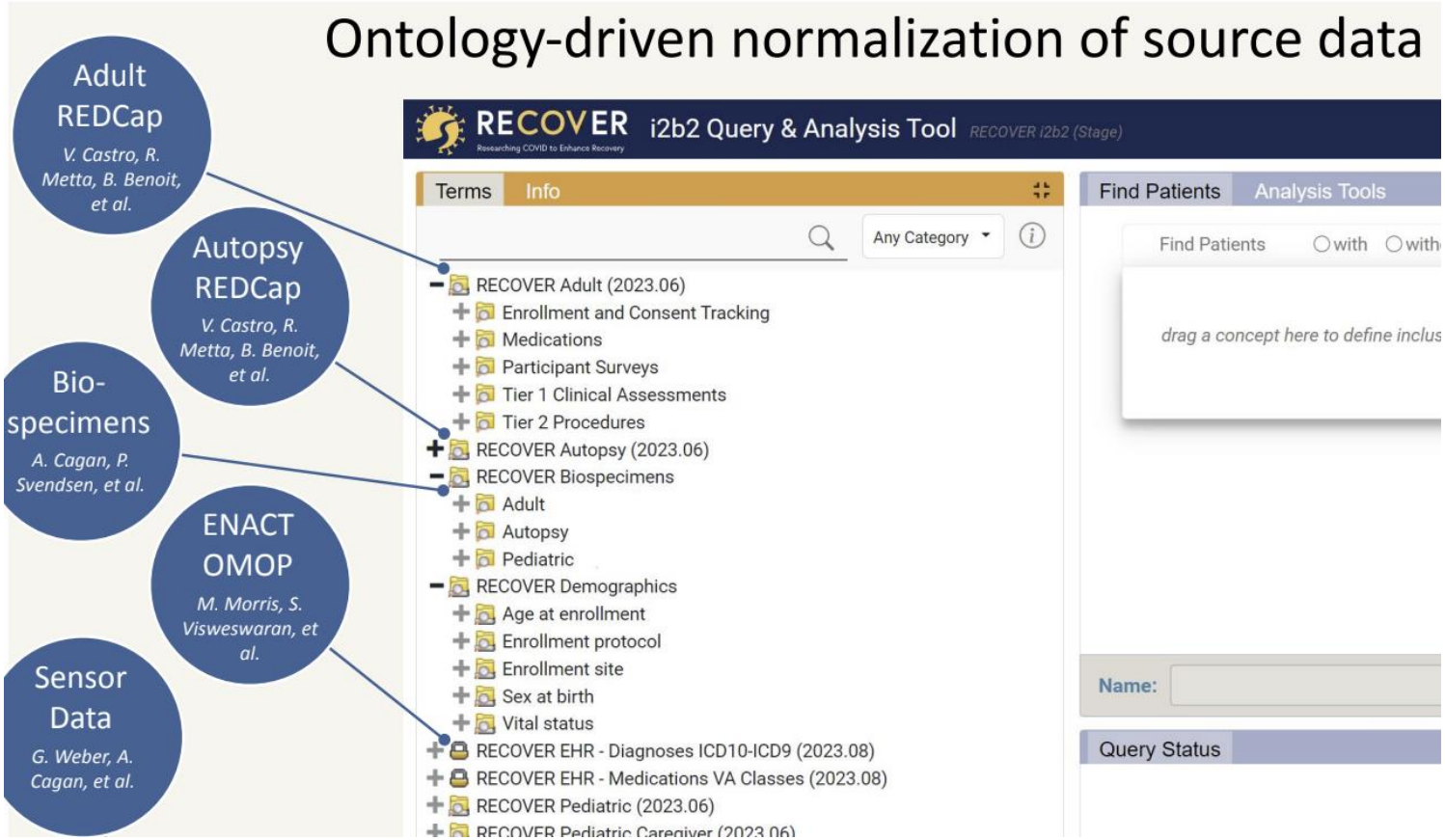
RECOVER
Researching COVID to Enhance Recovery

https://recovercovid.org

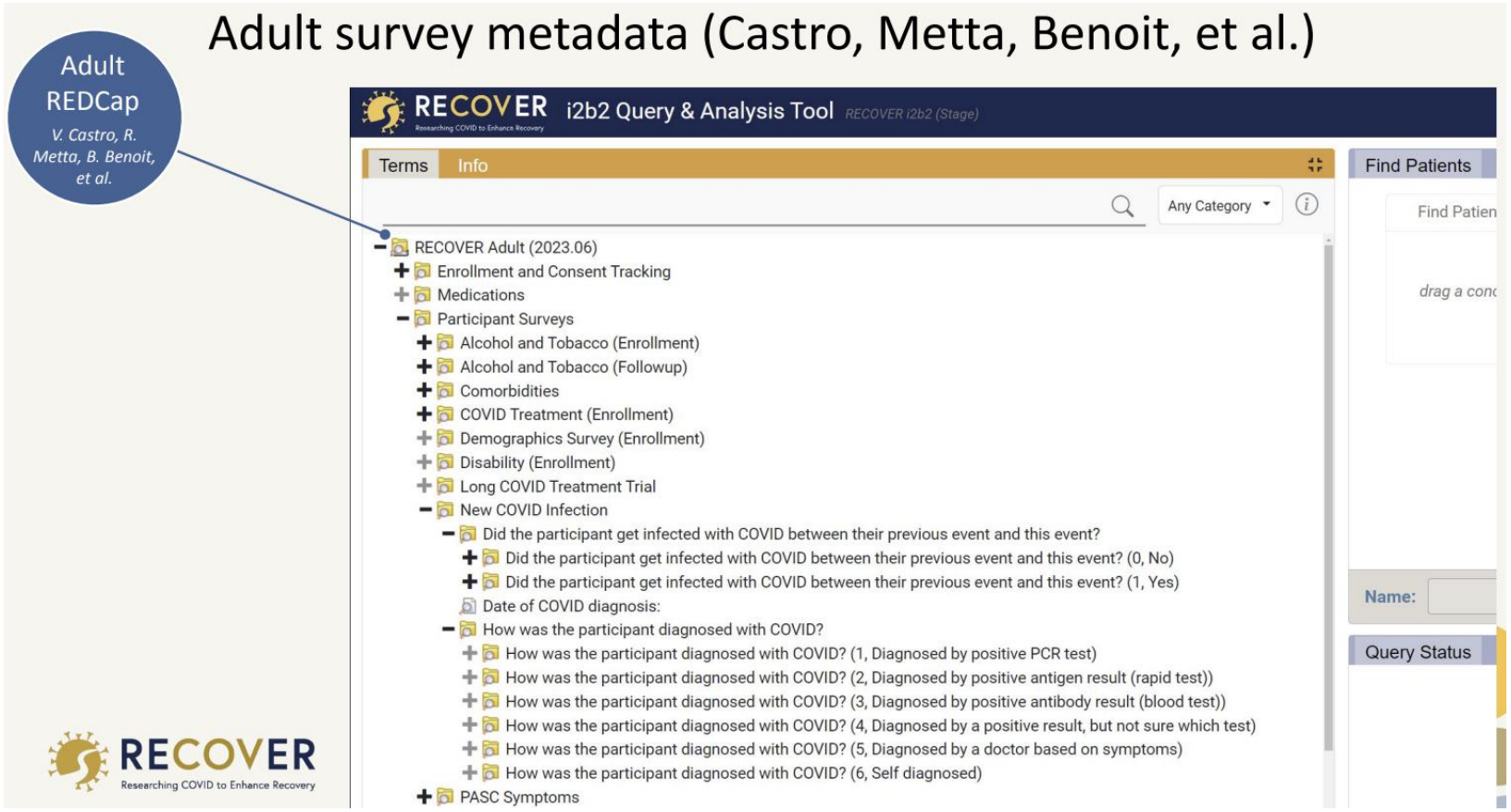
Data harmonized within i2b2 star schema



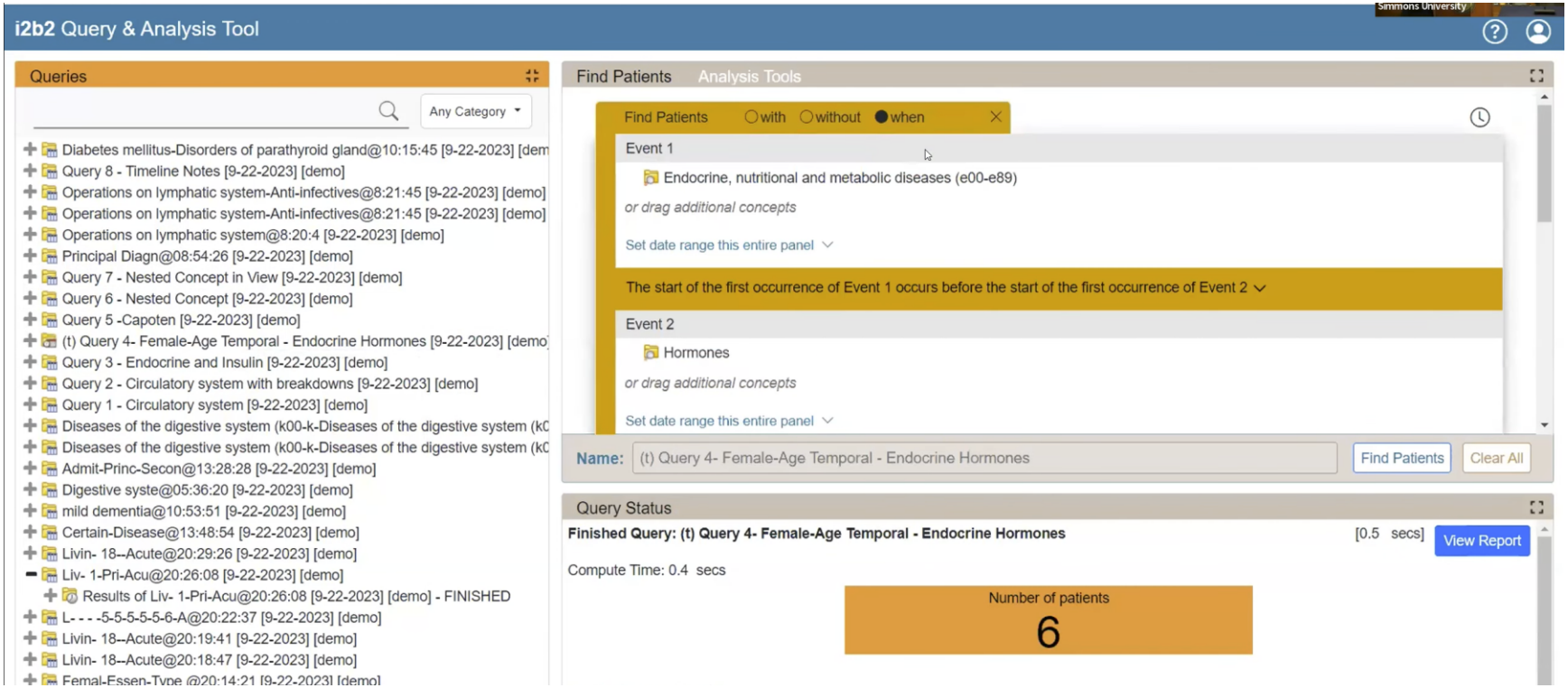
Concepts in database available in harmonized ontology



Includes study participant survey data



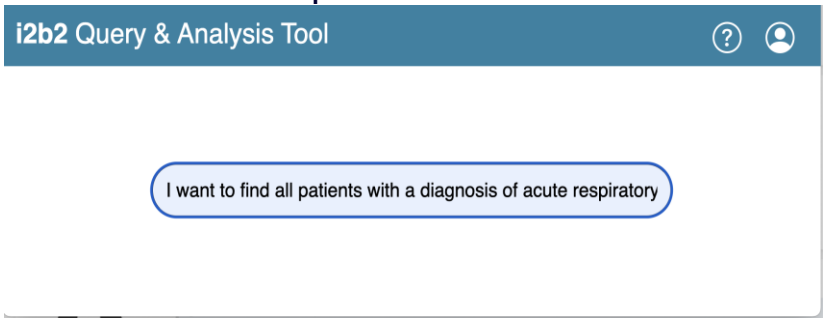
New i2b2 Query Tool to be released:



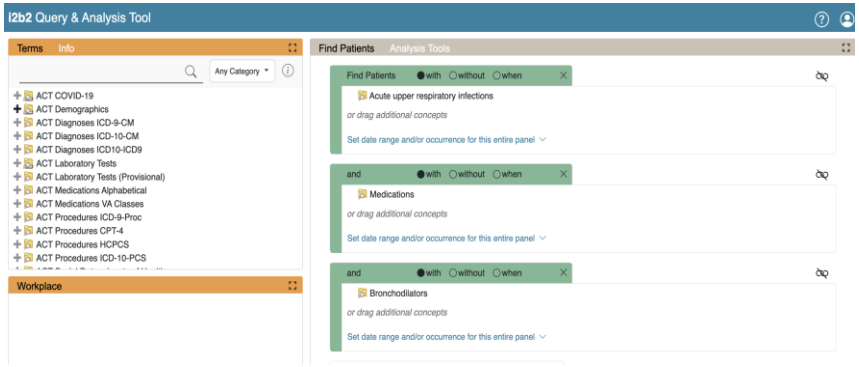
https://i2b2transmart.org/2023-i2b2-symposium/2023-symposium-recordings-slides/

I2B2 AI

User asks a question



Result rendered in web client



AI returns response in i2b2 format

I want to find all patients with a diagnosis of acute respiratory infections who have also been prescribed bronchodilators.

```
<query_definition>
<query_name>Acute respiratory i@19:45:36</query_name>
<query_timing>ANY</query_timing>
<specificity_scale>0</specificity_scale>
<panel>
<panel_number>1</panel_number>
<panel_timing>ANY</panel_timing>
<panel_accuracy_scale>100</panel_accuracy_scale>
<invert>0</invert>
<total_item_occurrences>1</total_item_occurrences>
<item>
  <hlevel>3</hlevel>
  <item_name>Acute respiratory infections</item_name>
  <item_key>\\iSyph\iSyph\Diagnoses\Respiratory system (460-519)\Acute respiratory infections (460-466)\</item_key>
  <item_icon>FA</item_icon>
  <tooltip>Diagnoses \ Respiratory system \ Acute respiratory infections</tooltip>
  <class>ENC</class>
  <constrain_by_date>
    <date_from/>
  </constrain_by_date>
  <item_is_synonym>false</item_is_synonym>
</item>
</panel>
```

High Throughput Methods for supporting Translational Research

- Set of patients is selected from medical record data in a high throughput fashion
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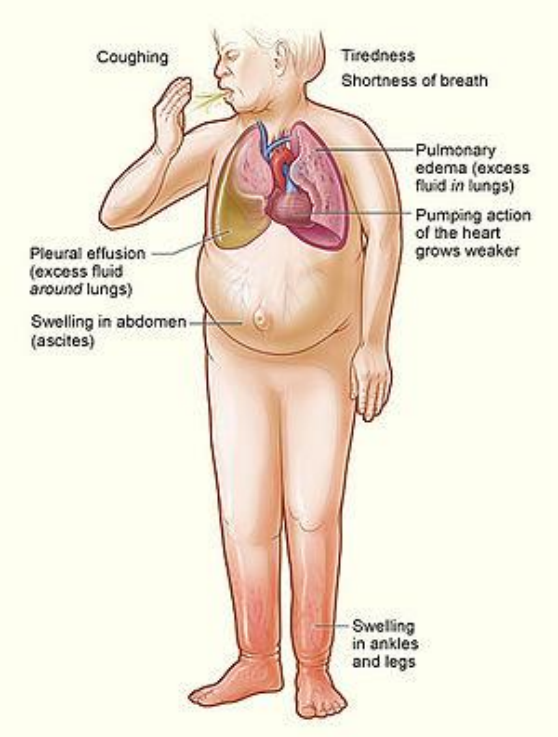
Congestive Heart Failure



- Affects 2% of the adult population
- Risk of death first year after diagnosis: 35%
- In patient hospital costs in 2011: $10.5B which is a small fraction of all heart failure related care

Early Detection of Worsening or Improving Anemia

Background and Methods

- Anemia is one of the strongest predictors of morbidity and mortality in CHF.
- Increasing or decreasing HGB is a further strong predictor, but there is no good way to determine whether a patient's HGB is on its way up or down (*Circulation. 2005;112:1121-1127*)

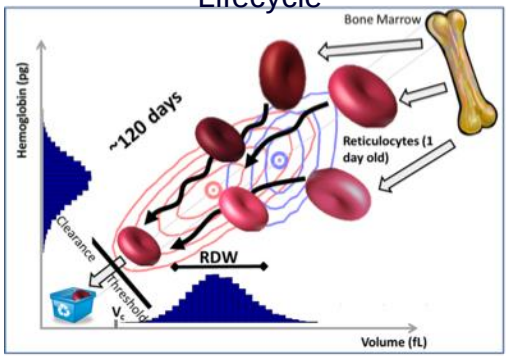
Results and Conclusions

- A novel mathematical model of the RBC lifecycle enables estimation of patient-specific rates of RBC maturation and turnover from a routine CBC.

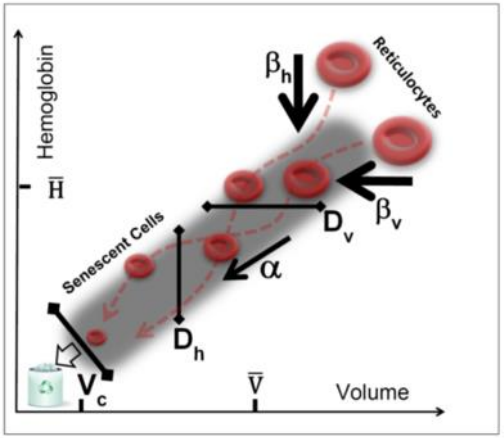
Applications

1. CHF patients most likely to have decreasing HGB may benefit from altered treatment or longer hospitalization to avoid readmission.
2. CHF patients most likely to have increasing HGB may be responding well to treatment and benefit from earlier discharge or maintenance of current therapy.

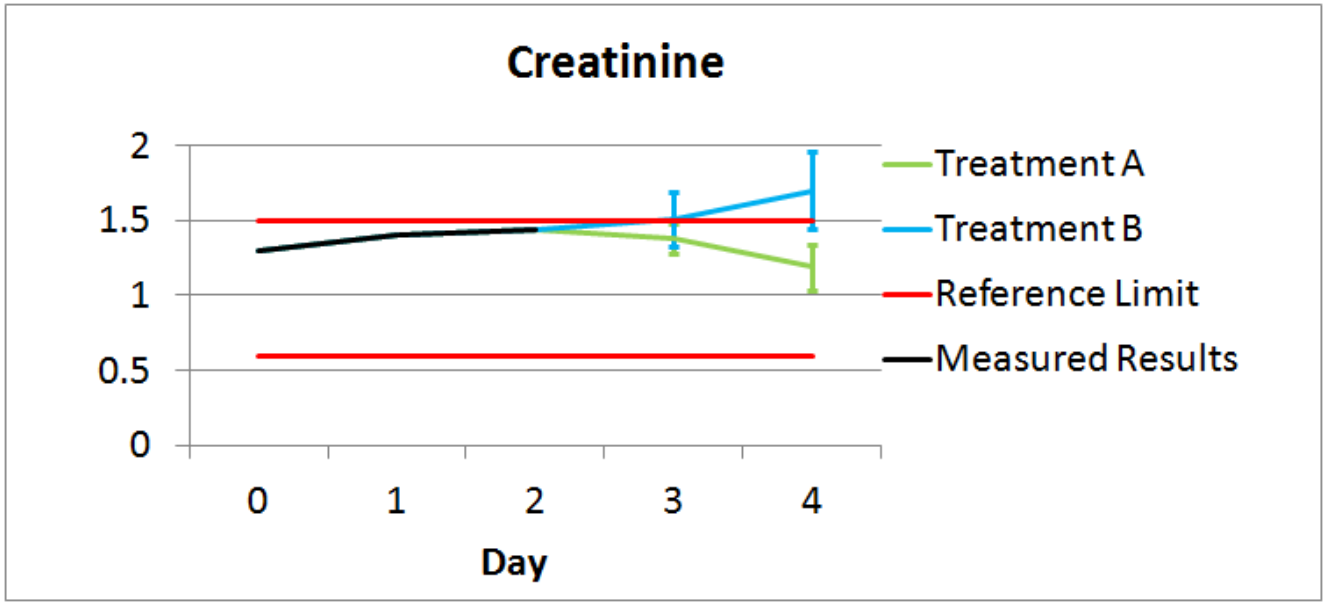
Dynamic Model of the RBC Lifecycle



Quantify Maturation and Clearance Rates

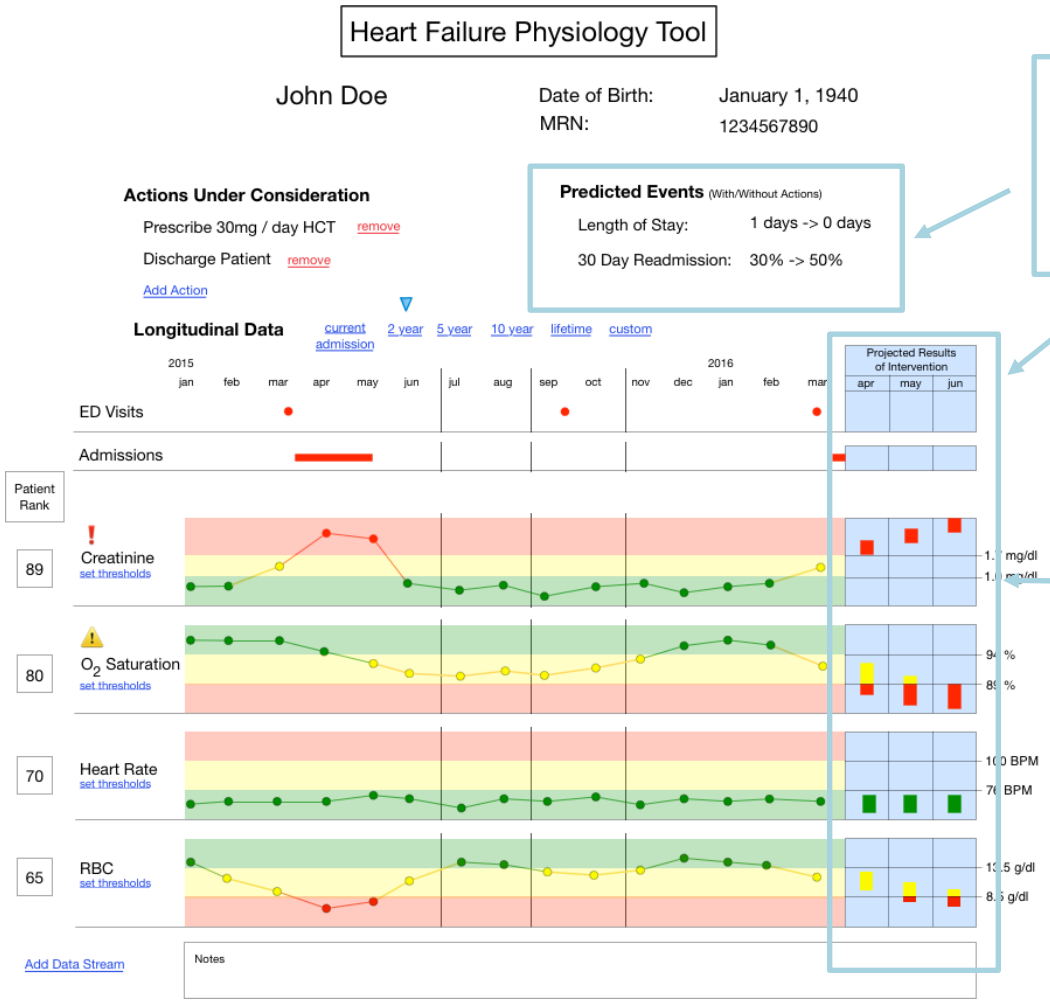


Creatinine Prediction: Hypothetical Application



•Hypothetical analysis of creatinine times series where possible treatments are introduced into the model

•The model hypothetically provide a future trajectory conditioned on each treatment

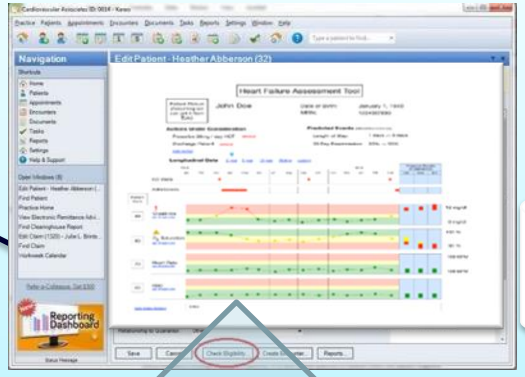


Population Based Predictive Analytics to Support Improved Decision Making

Exploring Integration of MGH Path renal predictive model

Bringing Big Data into Clinical Care with Open App Development

Clinician



SMART App embedded in Epic

Epic Data Repository

DATA

GeneInsight, mHealth, ePath, Medical Images, 25 years of Legacy electronic data, and Other External Systems

Analytic Calculation Engine

Analytics have direct access to repository

Core Integration Database

FHIR interface for real time updates

SMART App in Lab

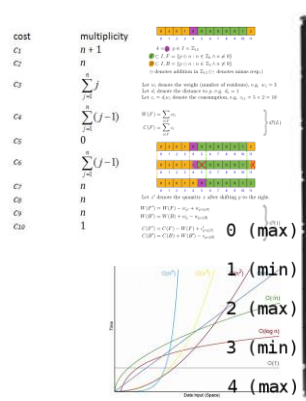
Non-EHR Users View Standalone App

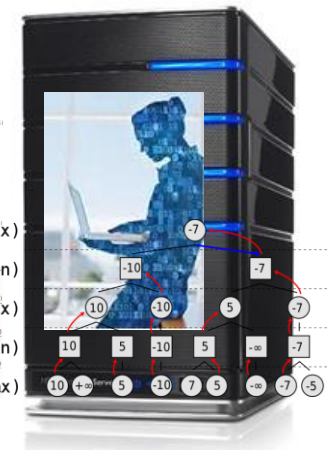
Laboratory Personnel

Transforming Care in the Digital Age

Digital and IoT devices continuously output Patient Data

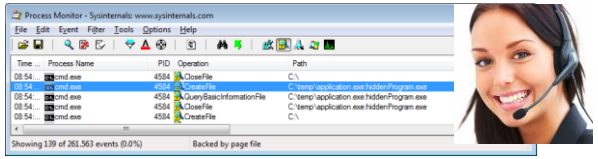
```
1. for ( i = 1; i ≤ a1.length; i++ )
   1.1. j = i
   1.2. while ( a1[i] != a2[j] )
                if ( j ≥ a1.length)
                  1. return false
                  1.2. j++
   1.3. tmp = a2[j]
   1.4. a2[j] = a2[i]
   1.5. a2[i] = tmp
2. return true
```



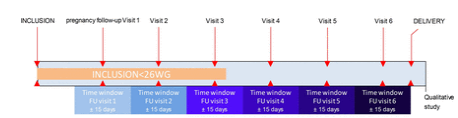


Digital Twin of patient enables continuous assessment of patient with Real Time Algorithms

PATIENT

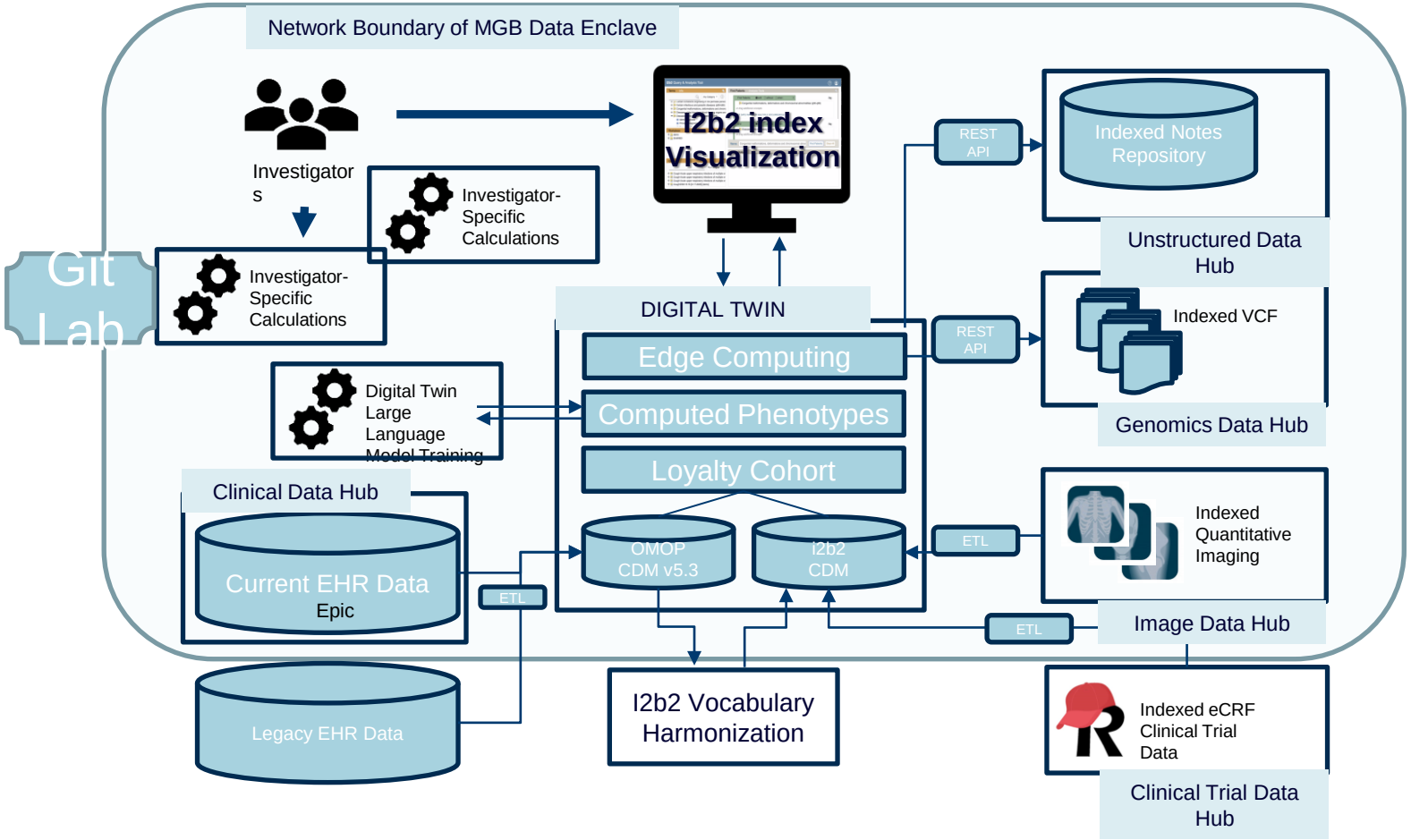


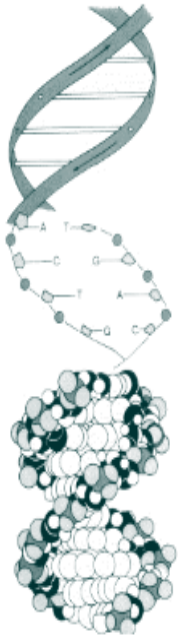
Navigator Model dramatically increases Frequency and Convenience for Patient Communication



System drives Pragmatic Clinical Trials Leading to Continuous Process Improvement

MGB Data Enclave Overview





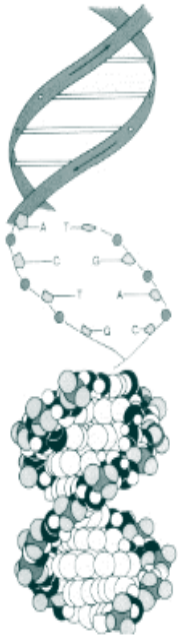
I2b2 tranSMART Software

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

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

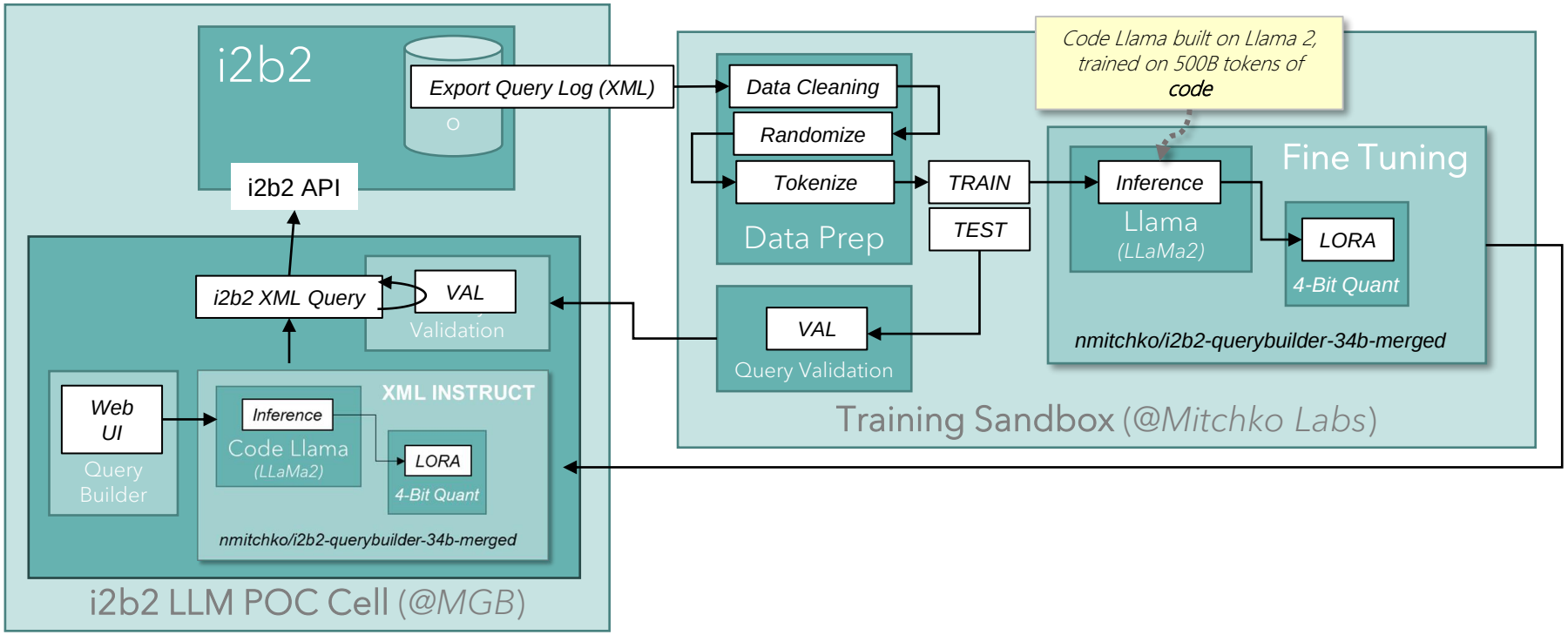
i2b2 Community Site (https://community.i2b2.org)

https://i2b2transmart.org/2023-i2b2-symposium/2023-symposium-recordings-slides/



APPENDIX

AI-ENABLED QUERY BUILDER:
(I.E. INSTRUCTION-TUNED POC)



I2B2 TRAINING ENVIRONMENT

Training Requirements

GPUs (48GB of VRAM or More)
Patience
Cooling

Training Run

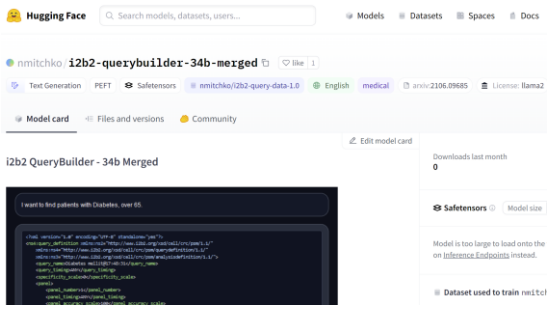
3x Nvidia RTX 6000
3 days time
271 Quadrillion Floating Point Operations
10.05 epochs (runs through the dataset)

Software

Qlora – State of the art mixed precision training library
Transformers, Pytorch, Accelerate – ML Libraries

All Open source

Found at
https://huggingface.co/nmitchko



Experience:

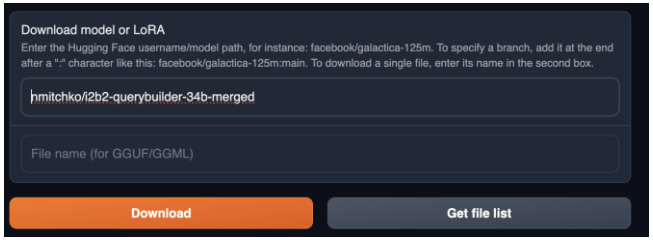
Nicholai Mitchko background in ML and other model finetunes

I2B2 AI DEVELOPMENT SANDBOX

WebUI oobabooga

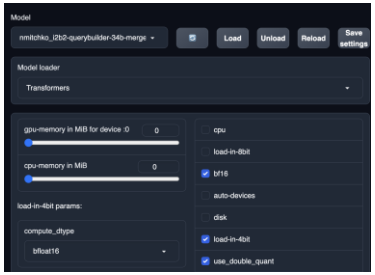
https://github.com/oobabooga/text-generation-webui

Download LLM



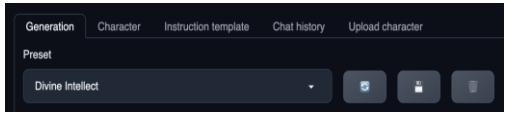
nmitchko/i2b2-querybuilder-34b-merged

Load Model



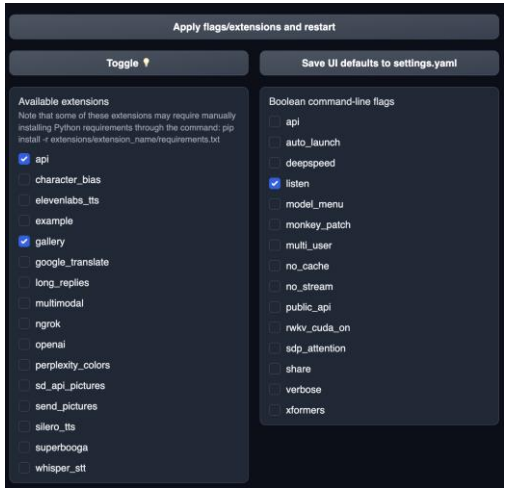
Compute_dtype: bfloat16
Check: bf16
Check: load-in-4bit
Check: use_double_quant

Parameters



Divine Intellect

Enable API



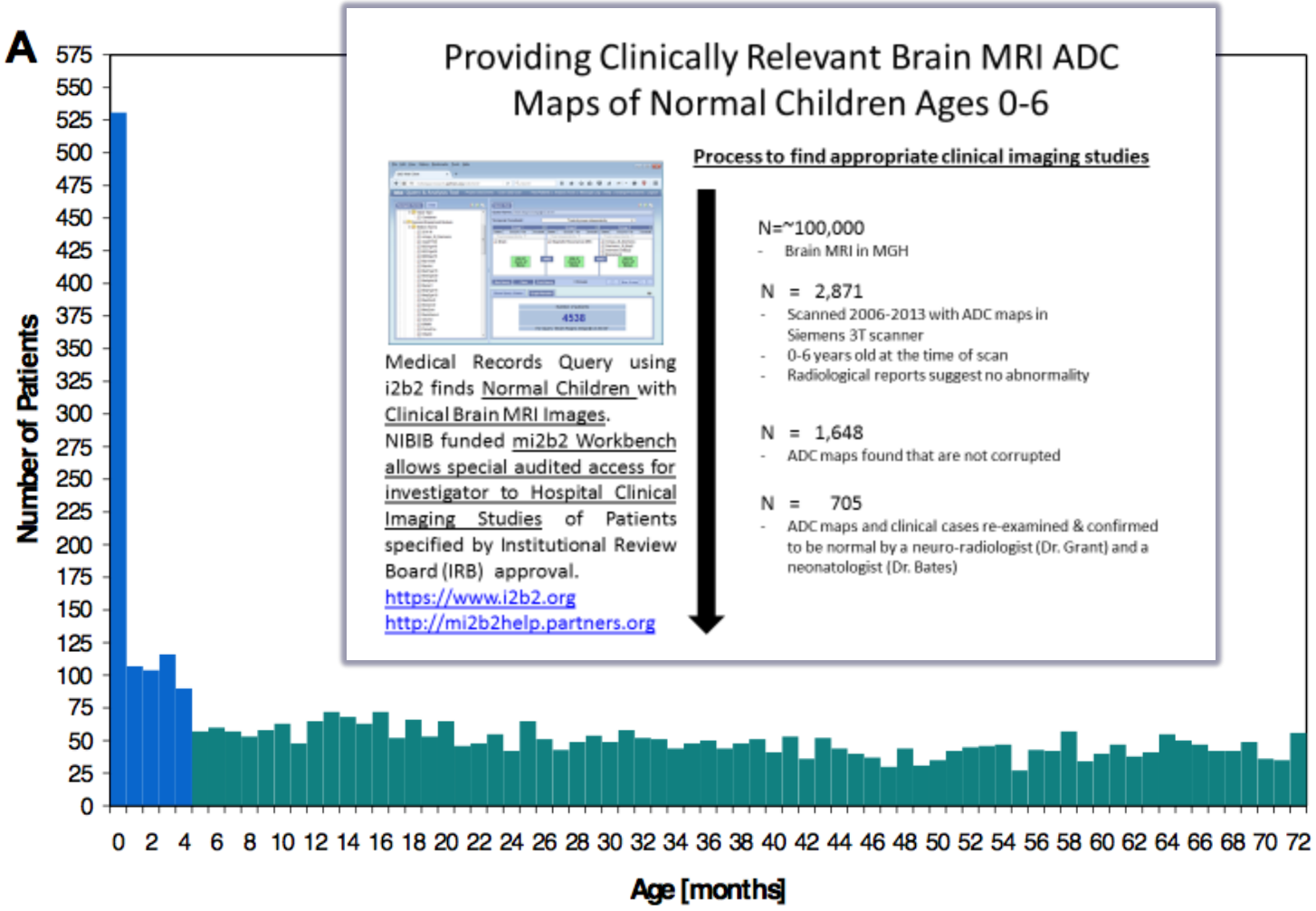
I2b2 AI Cell

https://github.com/i2b2/i2b2-ai

I2b2 Web Client

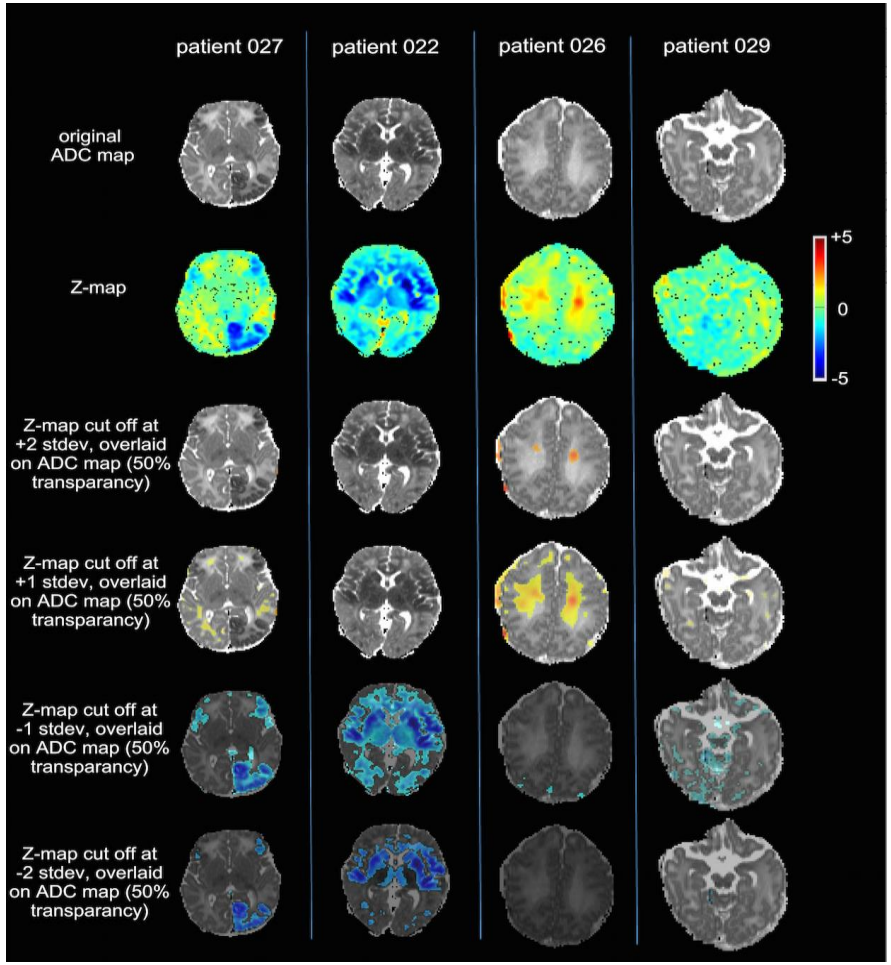
https://github.com/i2b2/i2b2-webclient-prototype/tree/i2b2_ai/

Find Normal Brain MRI's of Children



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)

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