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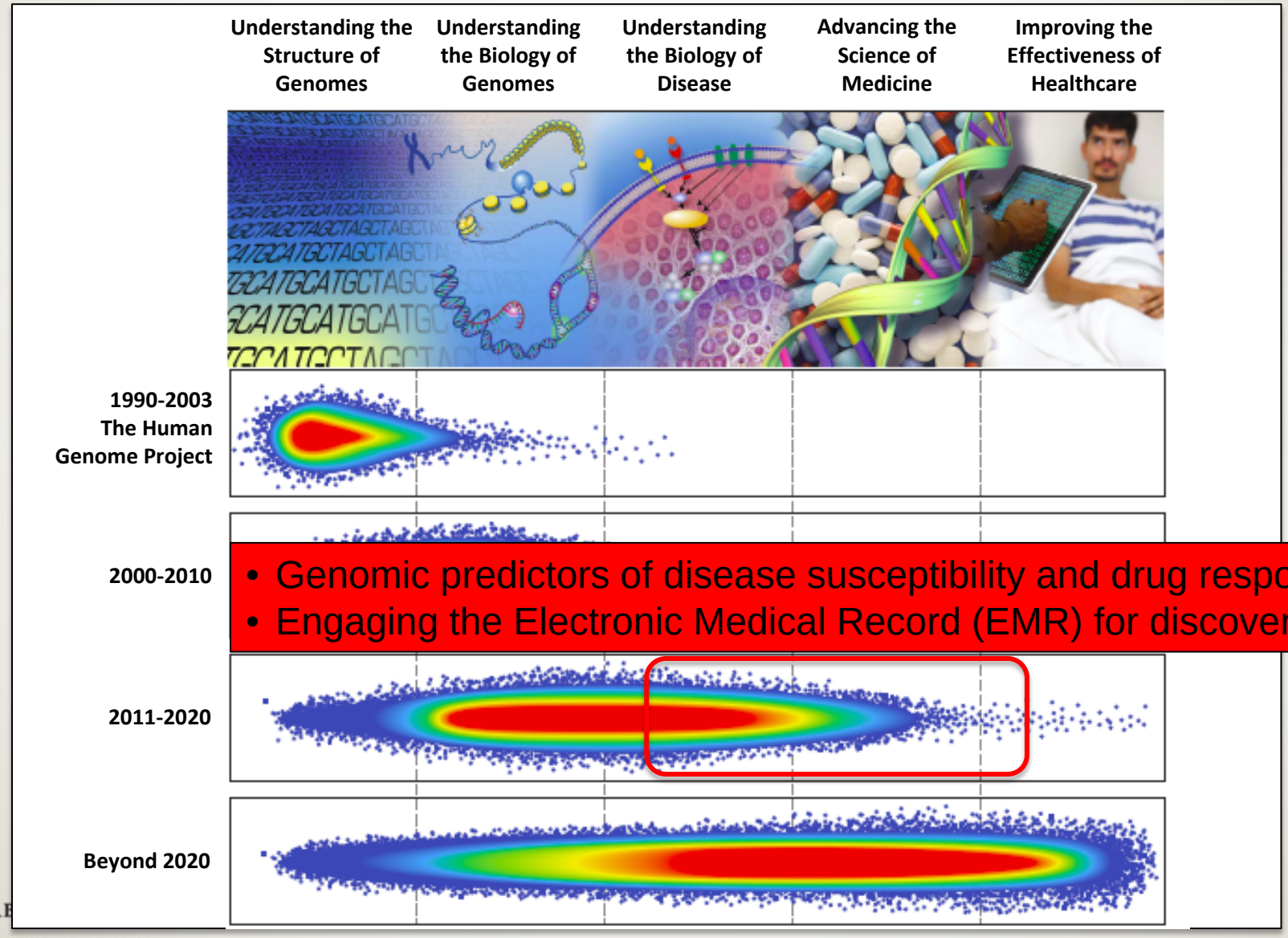
Engineering healthcare systems to deliver genomic medicine

Dan M. Roden, MD
Assistant Vice Chancellor for Personalized Medicine
Vanderbilt University School of Medicine

Domains of genomic research



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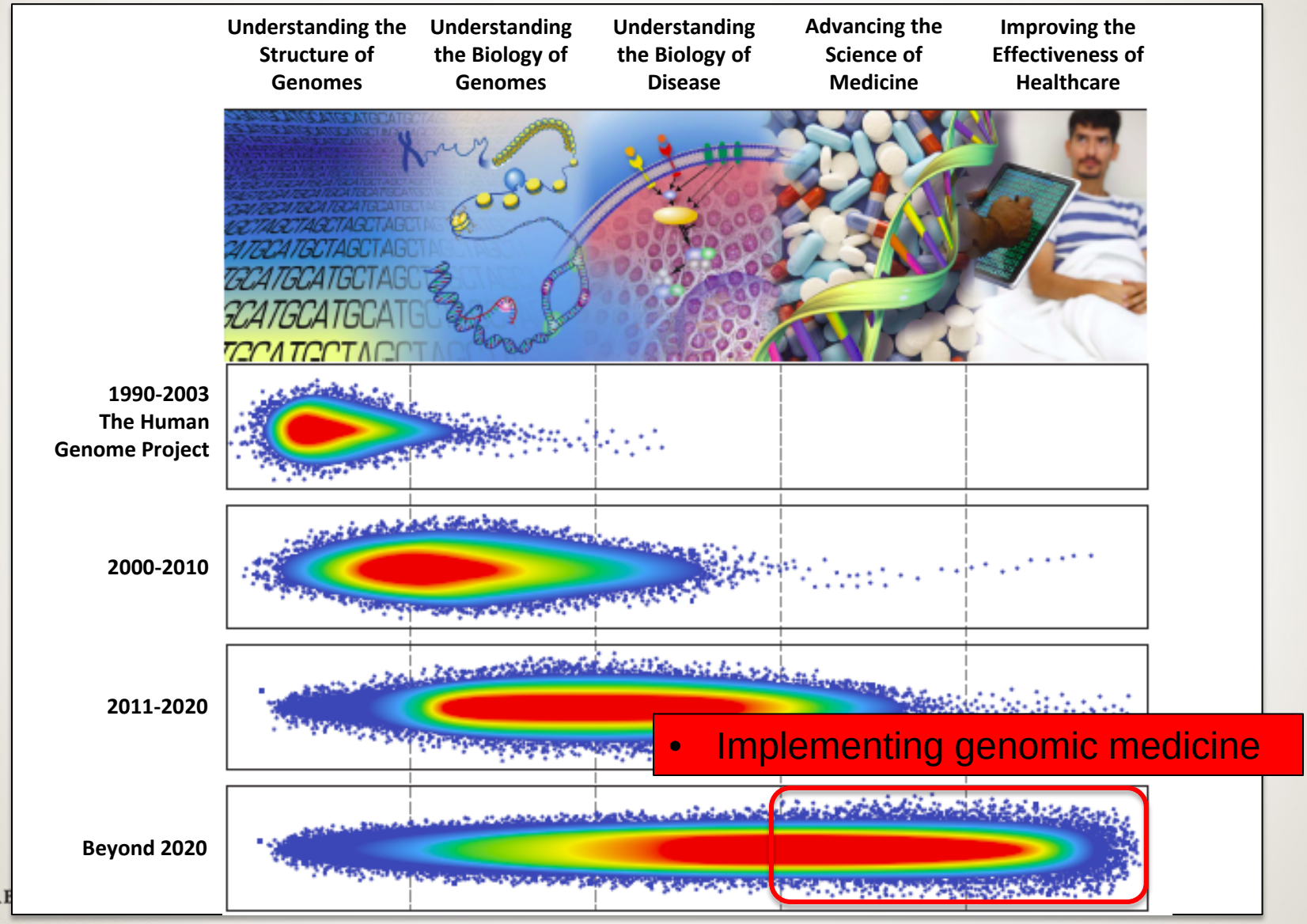
Green ED, Guyer MS. *Nature* 2011; 470:204-13.

Domains of genomic research



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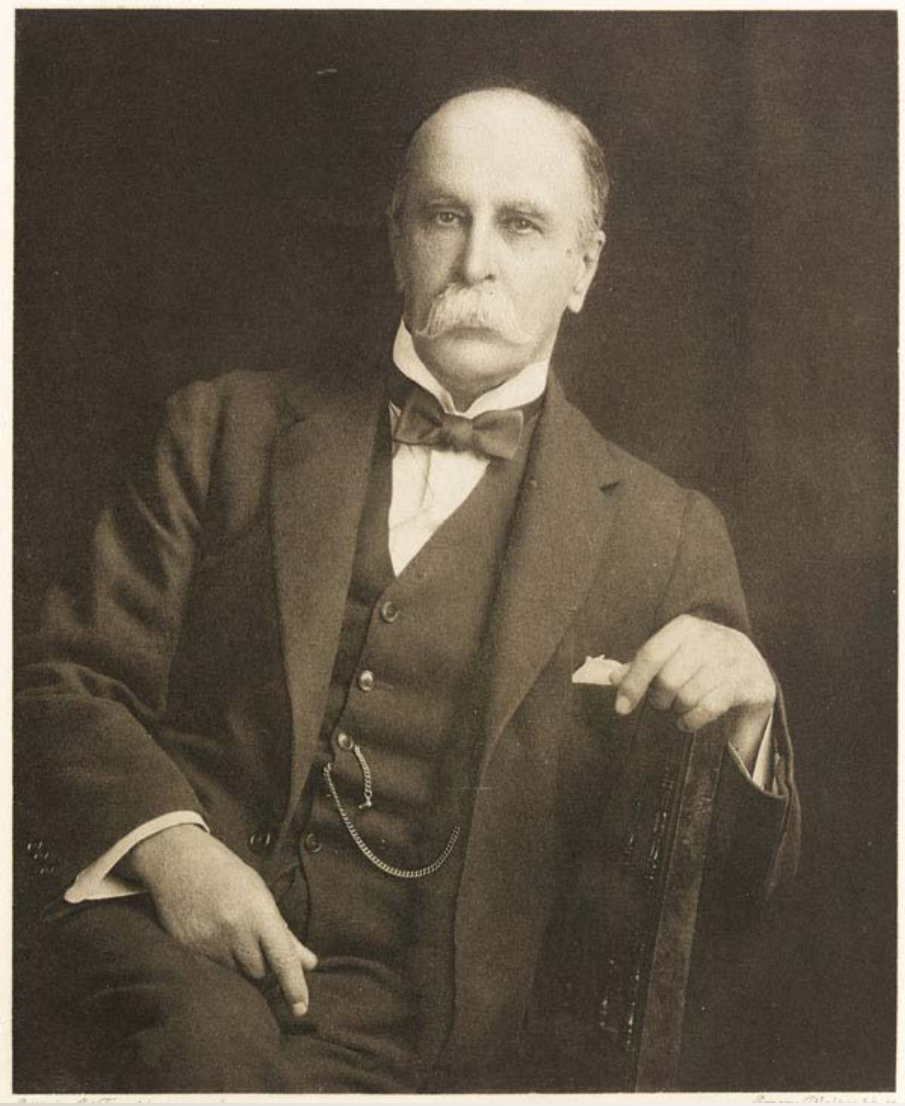
Green ED, Guyer MS. *Nature* 2011; 470:204-13.

One working definition of Genomic Medicine

NHGRI's Genomic Medicine Working Group

- An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision - making) and the other implications of that clinical use.

Personalized medicine – not a new idea



The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler

The vision

"Here's my sequence..."

New Yorker, 2000

Collins: Pharmacogenomics will undoubtedly become a very compelling part of medical practice. The limiting factor right now is that oftentimes, if you are ready to write a prescription, you do not want to wait a week to find out the genotype before you decide whether you've got the right dose and the right drug. But if everybody's DNA sequence is already in their medical record and it is simply a click of the mouse to found out all the information you need, then there is going to be a much lower barrier to beginning to incorporate that information into drug prescribing. If you have the evidence, it will be hard, I think, to say that this is not a good thing. And once you've got the sequence, it's not going to be terribly expensive. And it should improve outcomes and reduce adverse events.

Francis Collins, NEJM 9/16/2009

How will this vision actually start to be tested and become reality?

"Here's my sequence..."

New Yorker, 2000

Excellence in biomedical sciences

Commitment to information technology

Harnessing the healthcare system for discovery

Ability to nimbly adapt a healthcare system to evolving evidence

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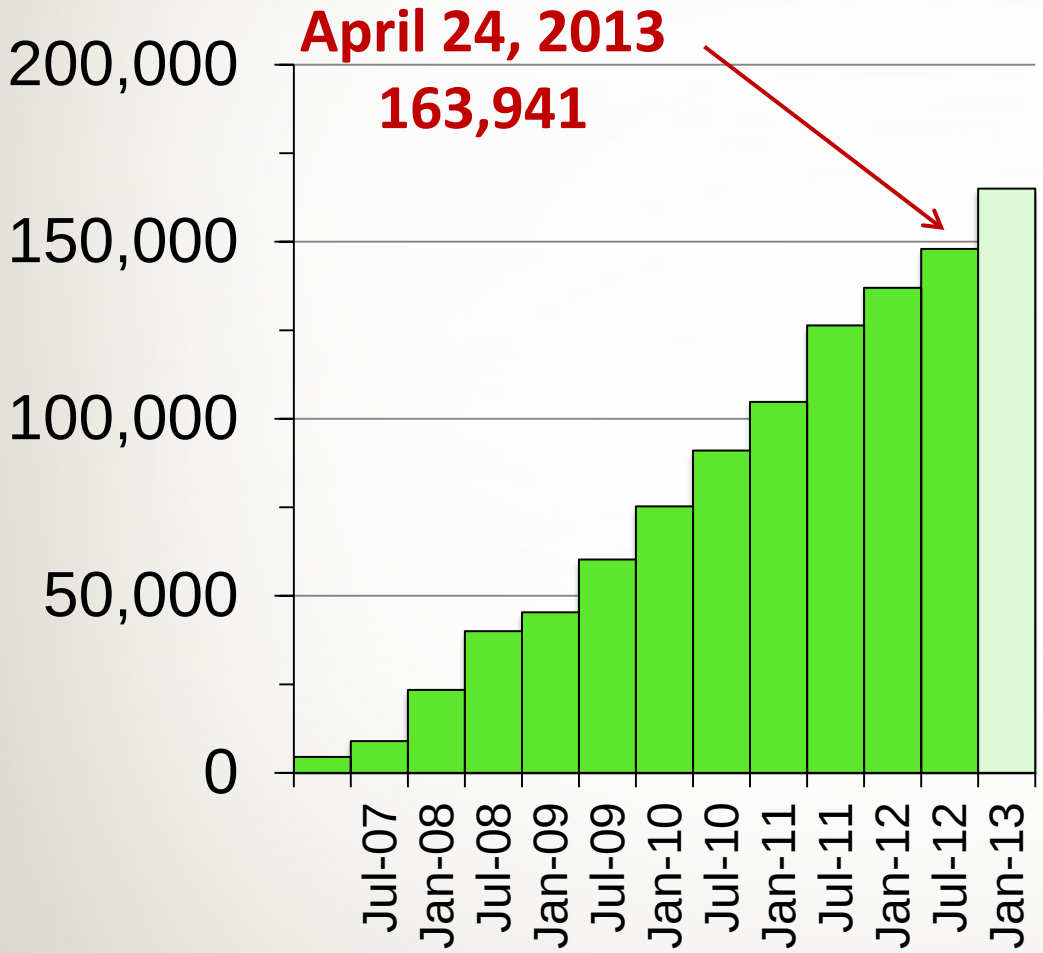
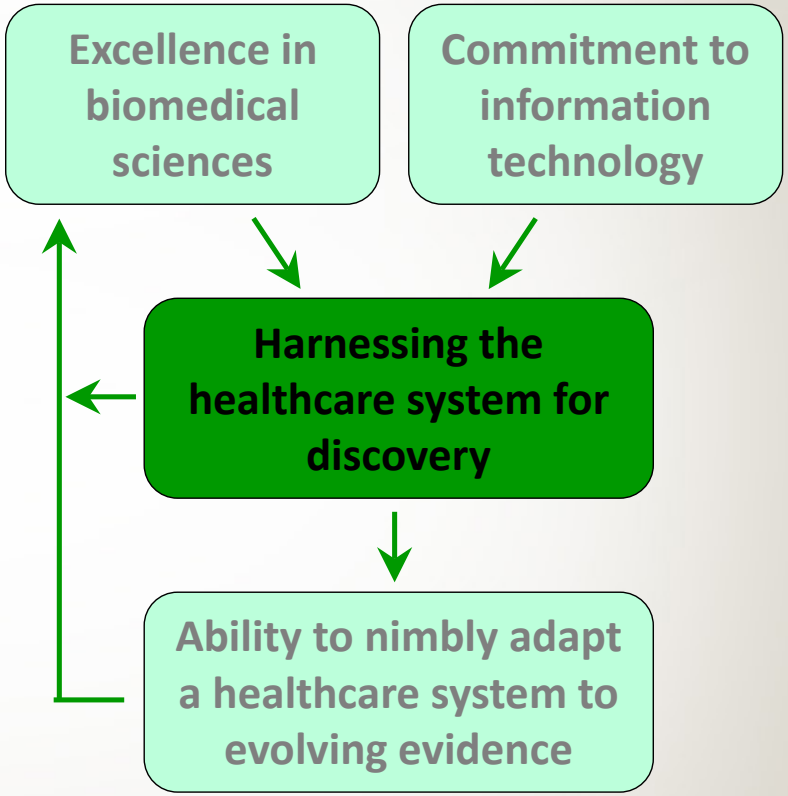
BioVU, the Vanderbilt DNA bank

A clinical laboratory for genomics and pharmacogenomics, linking DNA samples to de-identified electronic medical records





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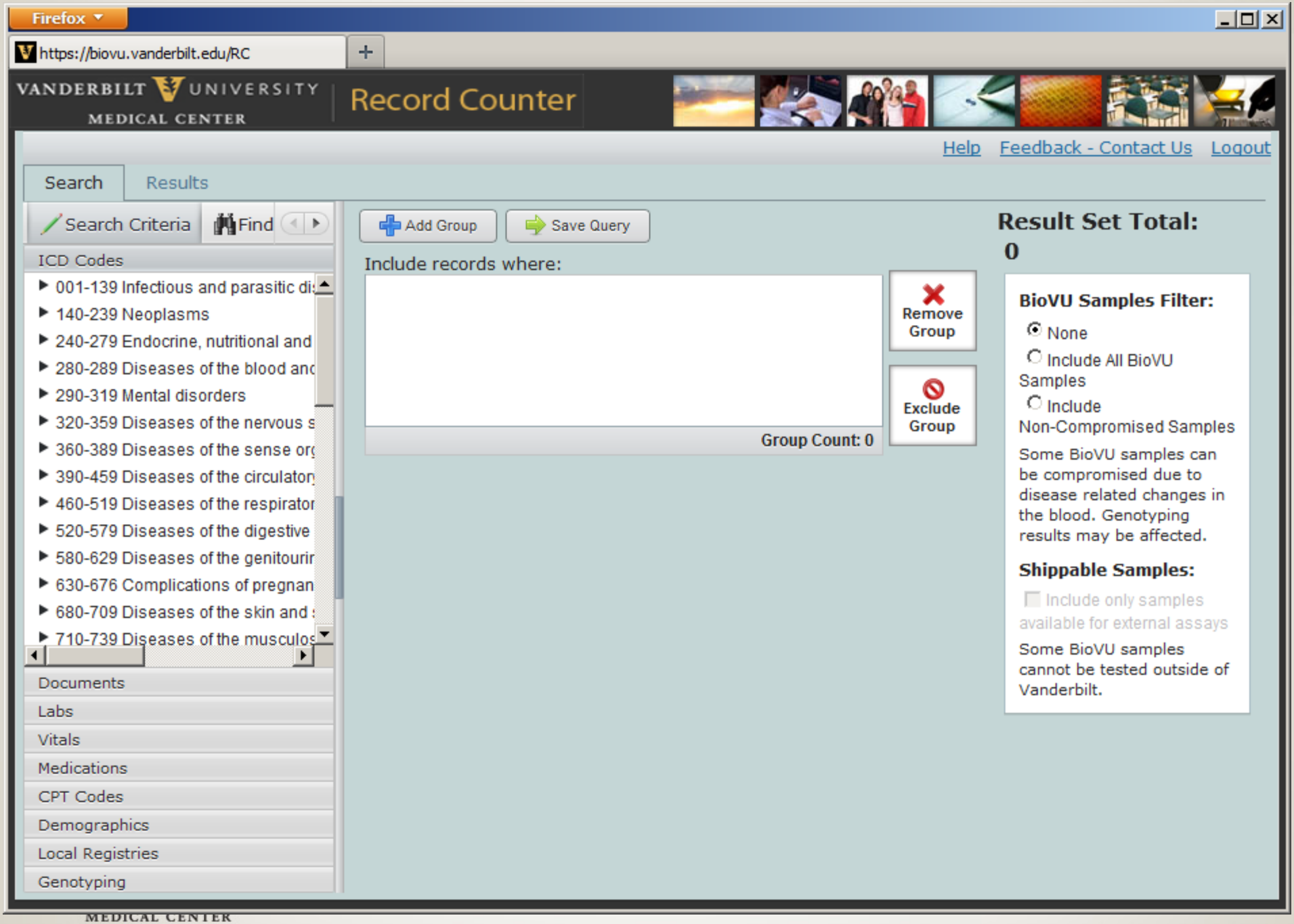
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290-319 Mental disorders
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390-459 Diseases of the circulator
460-519 Diseases of the respirator
520-579 Diseases of the digestive
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630-676 Complications of pregnan
680-709 Diseases of the skin and
710-739 Diseases of the musculos
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BioVU Samples Filter:
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Include All BioVU Samples
Include Non-Compromised Samples
Some BioVU samples can be compromised due to disease related changes in the blood. Genotyping results may be affected.
Shippable Samples:
Include only samples available for external assays
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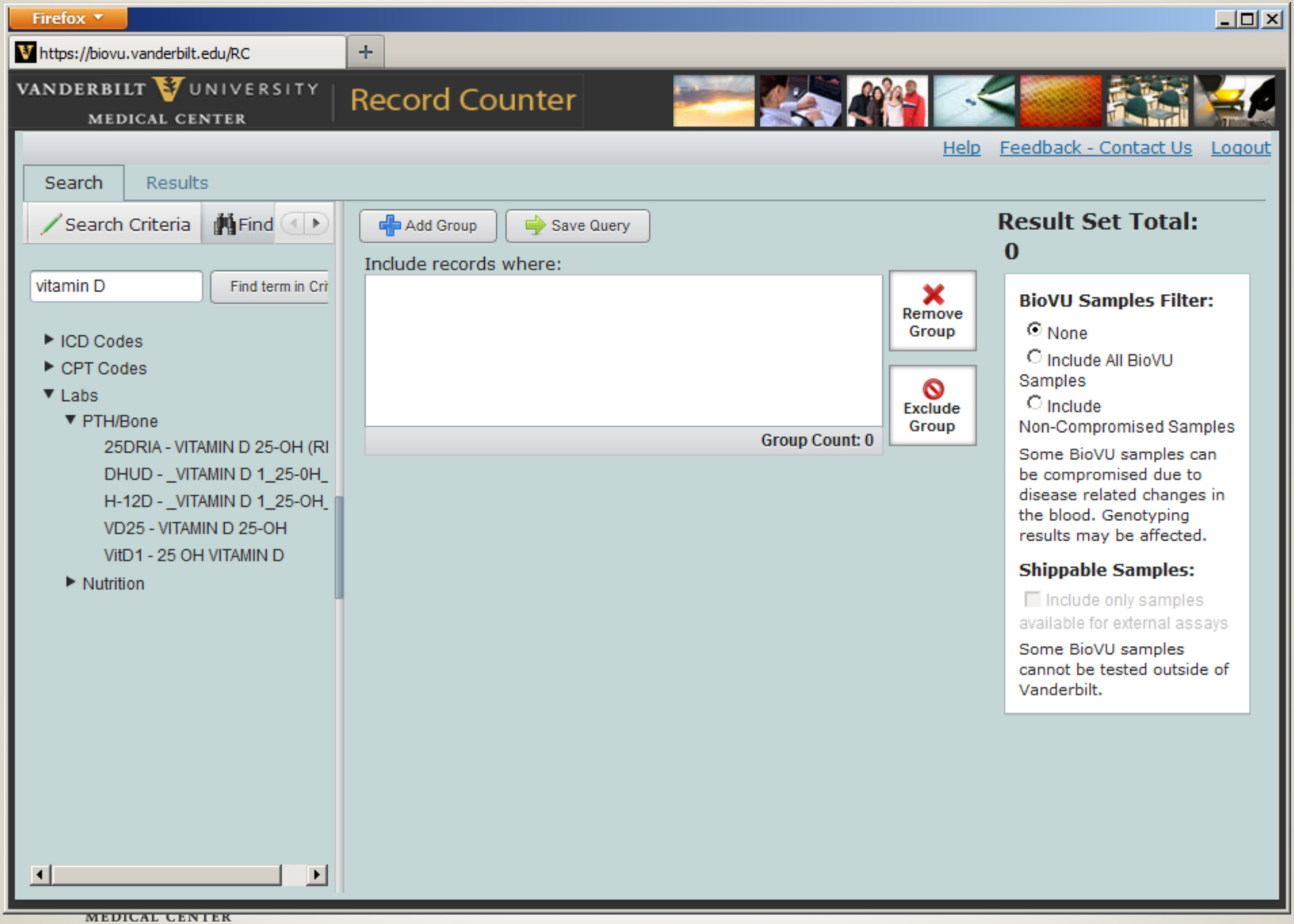
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DHUD - _VITAMIN D 1_25-0H_
H-12D - _VITAMIN D 1_25-OH_
VD25 - VITAMIN D 25-OH
VitD1 - 25 OH VITAMIN D
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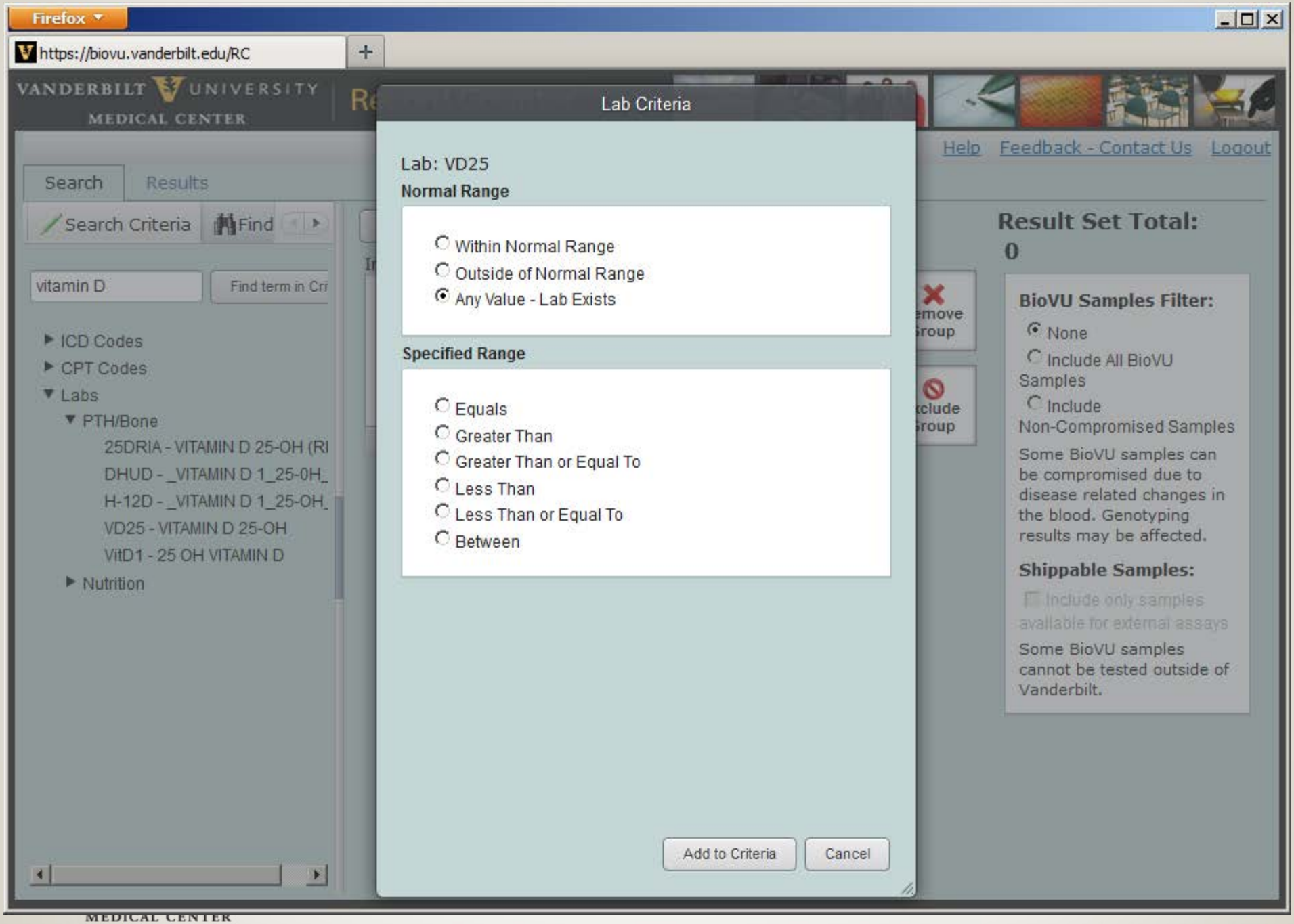
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VitD1 - 25 OH VITAMIN D
Nutrition
Lab Criteria
Lab: VD25
Normal Range
Within Normal Range
Outside of Normal Range
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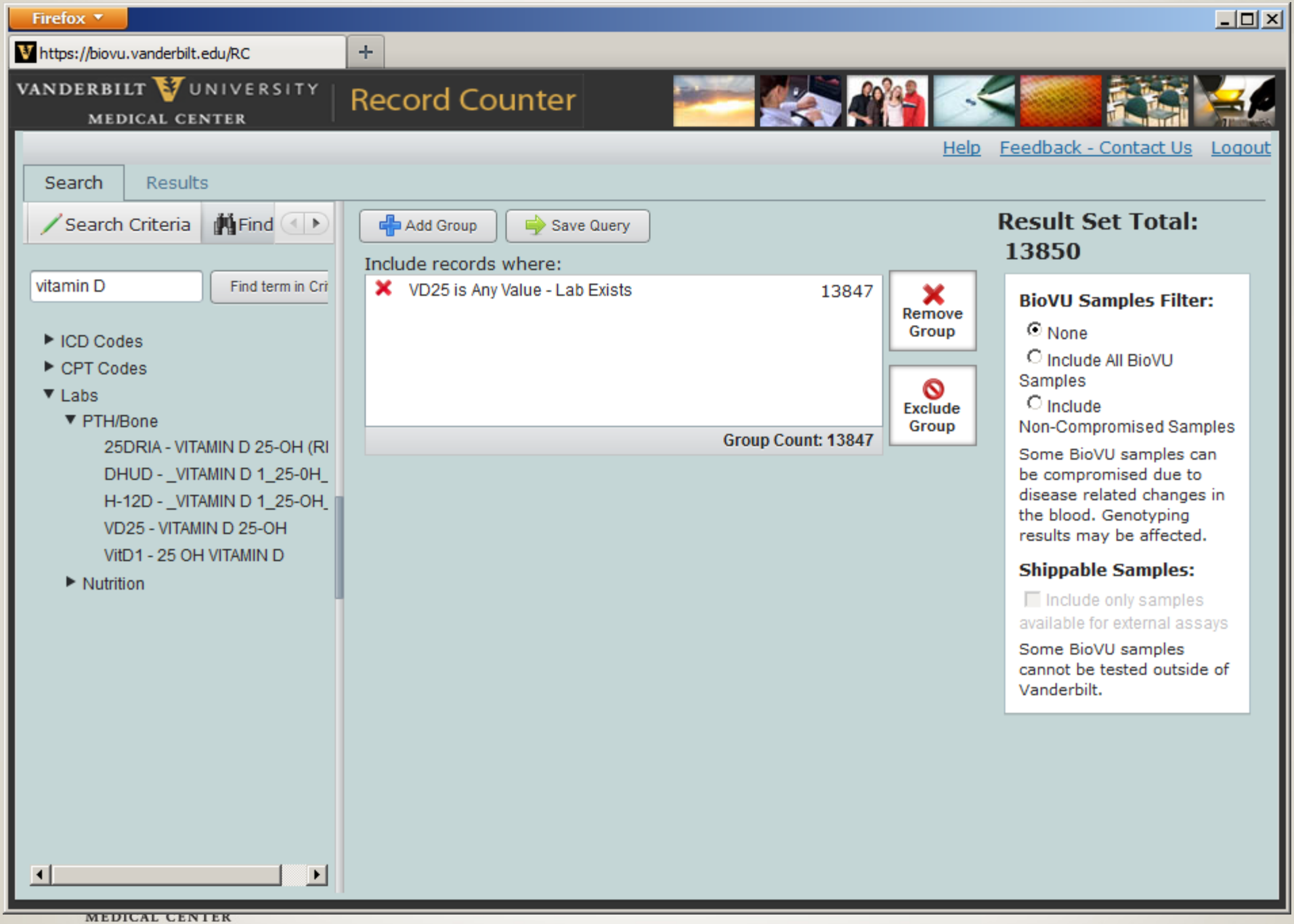
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VitD1 - 25 OH VITAMIN D
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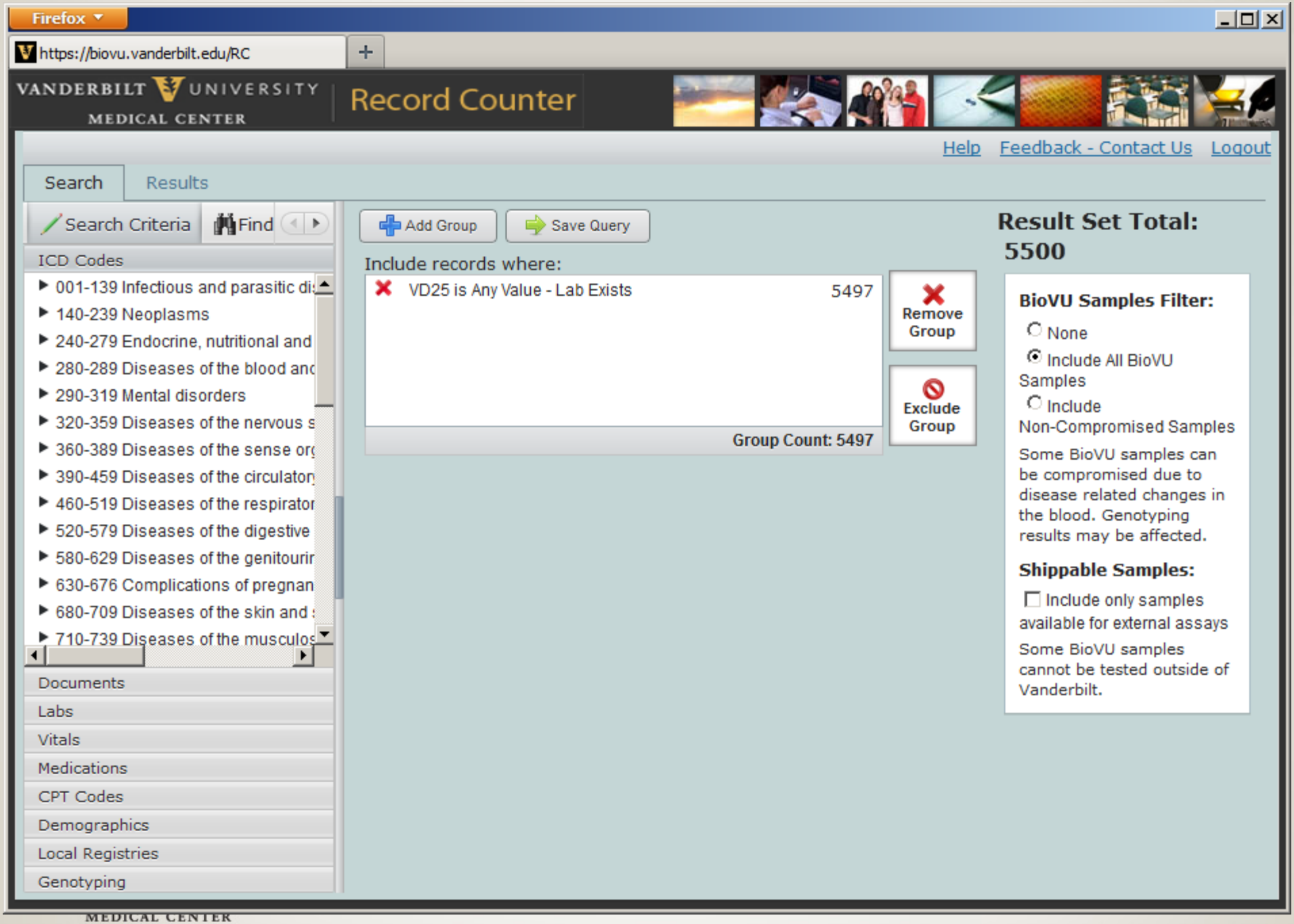
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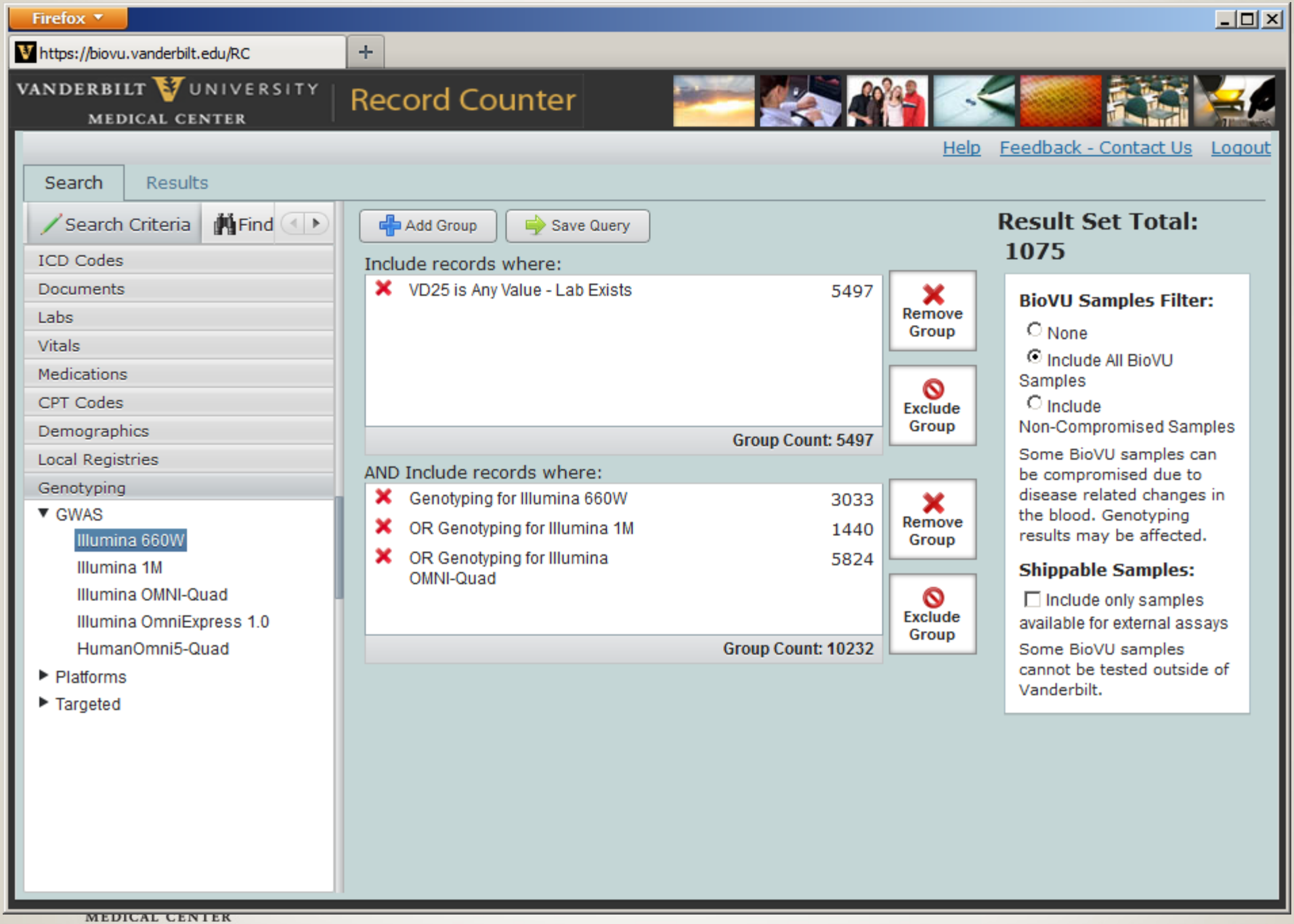

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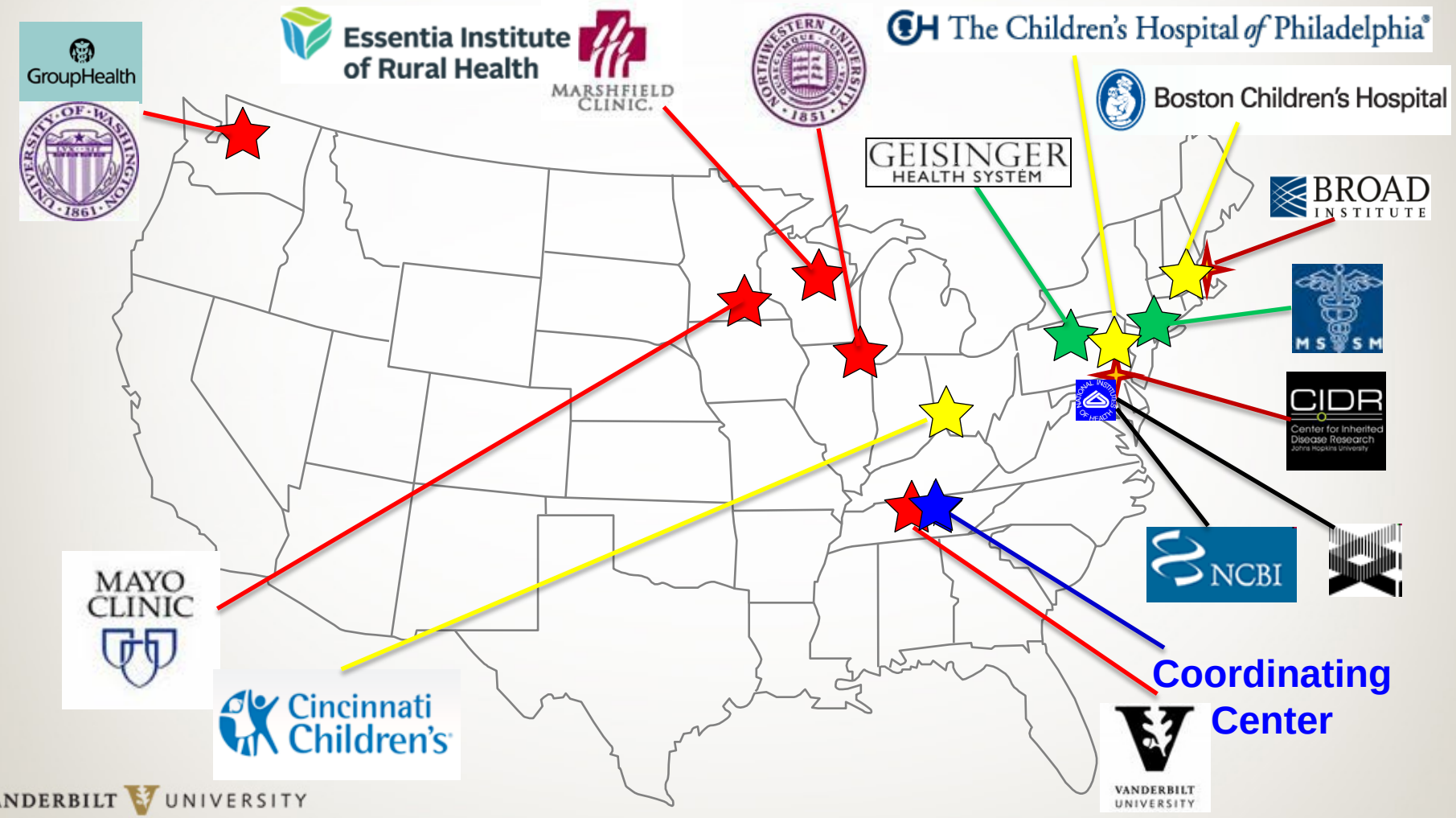
Examples of studies in BioVU

- Searching for genomic variants associated with:
  - Physiologic traits
  - Disease
  - Drug responses
- Searching for phenomic variants associated with
  - DNA polymorphisms (PheWAS)

The *eMERGE* Network

electronic Medical Records & Genomics

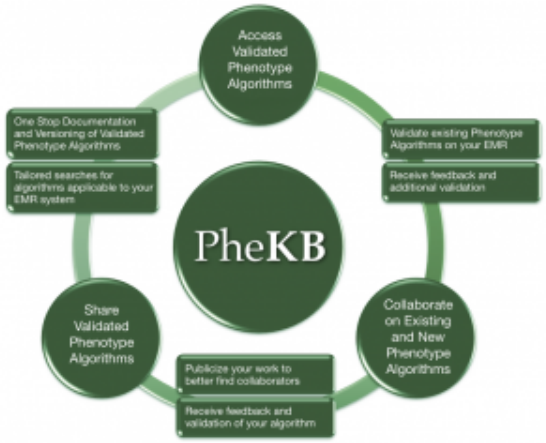
A consortium of biorepositories linked to electronic medical records data for conducting genomic studies



PheKB

a knowledgebase for discovering phenotypes from electronic medical records

What is the Phenotype KnowledgeBase?



The reuse of data from electronic medical records (EMRs) and other clinical data systems holds tremendous promise for improving the efficiency and effectiveness of health research. Clinical data in the EMR is a potential source of rich longitudinal data for research, and the recent government efforts to promote the use of EMRs in the clinical setting may further promote the use of such systems in the US healthcare system. As the use of EMRs expands, the demand for usable data from these systems for research has also expanded.

One such effort by the Electronic Medical Records and Genomics Network (eMERGE) has investigated whether data captured through routine clinical care using EMRs can identify disease phenotypes with sufficient positive and negative predictive values for use in genome-wide association studies (GWAS). Most EMRs captured key information (diagnoses, medications, laboratory tests) used to define phenotypes in a structured format; in addition, natural language processing has also been shown to improve case identification rates.*

PheKB is an outgrowth of that validation effort and provides a collaborative environment of building and

Most Recent Phenotypes

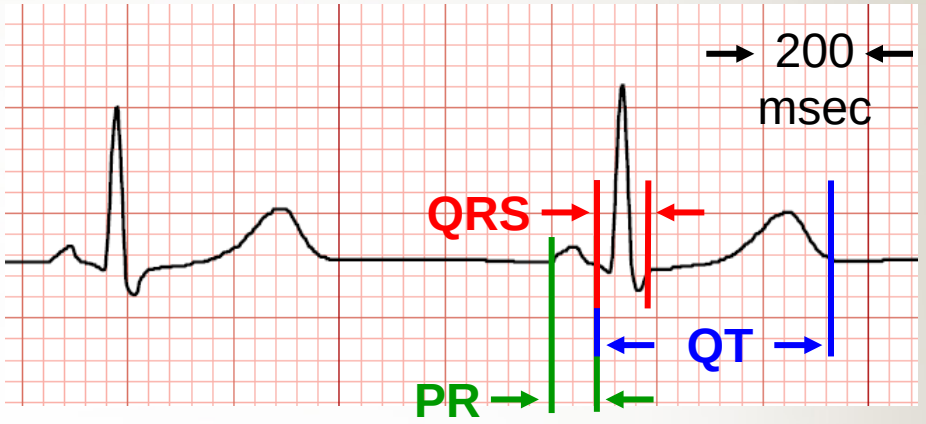
- Clopidogrel Poor Metabolizers
- Atrial Fibrillation - Demonstration Project
- Rhematoid Arthritis - Demonstration Project
- Multiple Sclerosis - Demonstration Project
- Crohn's Disease - Demonstration Project

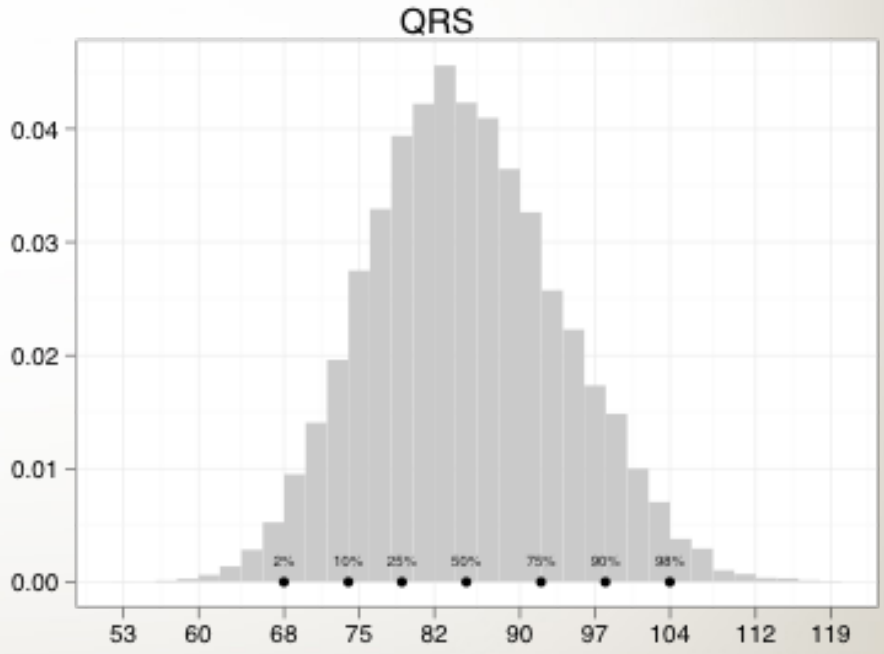
Title	Groups	Institutions	Data and Methods
Atrial Fibrillation - Demonstration Project	Demonstration Project	Vanderbilt University	CPT Codes, ICD 9 Codes, Natural Language Processing
Cardiac Conduction (QRS)	eMERGE Phenotype WG	Vanderbilt University	CPT Codes, ICD 9 Codes, Laboratories, Medications, Natural Language Processing
Cataracts	eMERGE Phenotype WG	Marshfield Clinic Research Foundation	CPT Codes, ICD 9 Codes, Medications, Natural Language Processing
Clopidogrel Poor Metabolizers	Denny's Group at Vandy, VESPA - Vanderbilt Electronic Systems for Pharmacogenomic Assessment		CPT Codes, ICD 9 Codes, Laboratories, Medications, Natural Language Processing
Crohn's Disease - Demonstration Project	Demonstration Project	Vanderbilt University	ICD 9 Codes, Medications, Natural Language Processing
Dementia	eMERGE Phenotype WG	Group Health Cooperative	ICD 9 Codes, Medications
Diabetic Retinopathy	eMERGE Phenotype WG	Marshfield Clinic Research Foundation	CPT Codes, ICD 9 Codes, Medications, Natural Language Processing
Height	eMERGE Phenotype WG	Northwestern University	ICD 9 Codes, Laboratories, Medications
High-Density Lipoproteins (HDL)	eMERGE Phenotype WG	Marshfield Clinic Research Foundation	ICD 9 Codes, Laboratories, Medications, Natural Language Processing
Hypothyroidism	eMERGE Phenotype WG	Vanderbilt University	CPT Codes, ICD 9 Codes, Laboratories, Medications, Natural Language Processing
Lipids	eMERGE Phenotype WG	Northwestern University	ICD 9 Codes, Laboratories, Medications
Multiple Sclerosis - Demonstration Project	Demonstration Project	Vanderbilt University	ICD 9 Codes, Medications, Natural Language Processing
Peripheral Arterial Disease	eMERGE Phenotype WG	Mayo Clinic	CPT Codes, ICD 9 Codes, Laboratories, Medications, Natural Language Processing
Red Blood Cell Indices	eMERGE Phenotype WG	Mayo Clinic	CPT Codes, ICD 9 Codes, Laboratories, Medications, Natural Language Processing

Multiple Sclerosis - Demonstration Project
Crohn's Disease - Demonstration Project
Atrial Fibrillation - Demonstration Project

QRS duration in the normal ECG

- QRS duration is an index of conduction velocity in heart. Longer QRS implies slow conduction. Slow conduction predisposes to arrhythmias.
- Algorithms developed to identify records in which the 1st ECG is normal and
  - no heart disease
  - normal electrolytes
  - no confounding drugs
- Deployed in the entire electronic record → 30,363 subjects



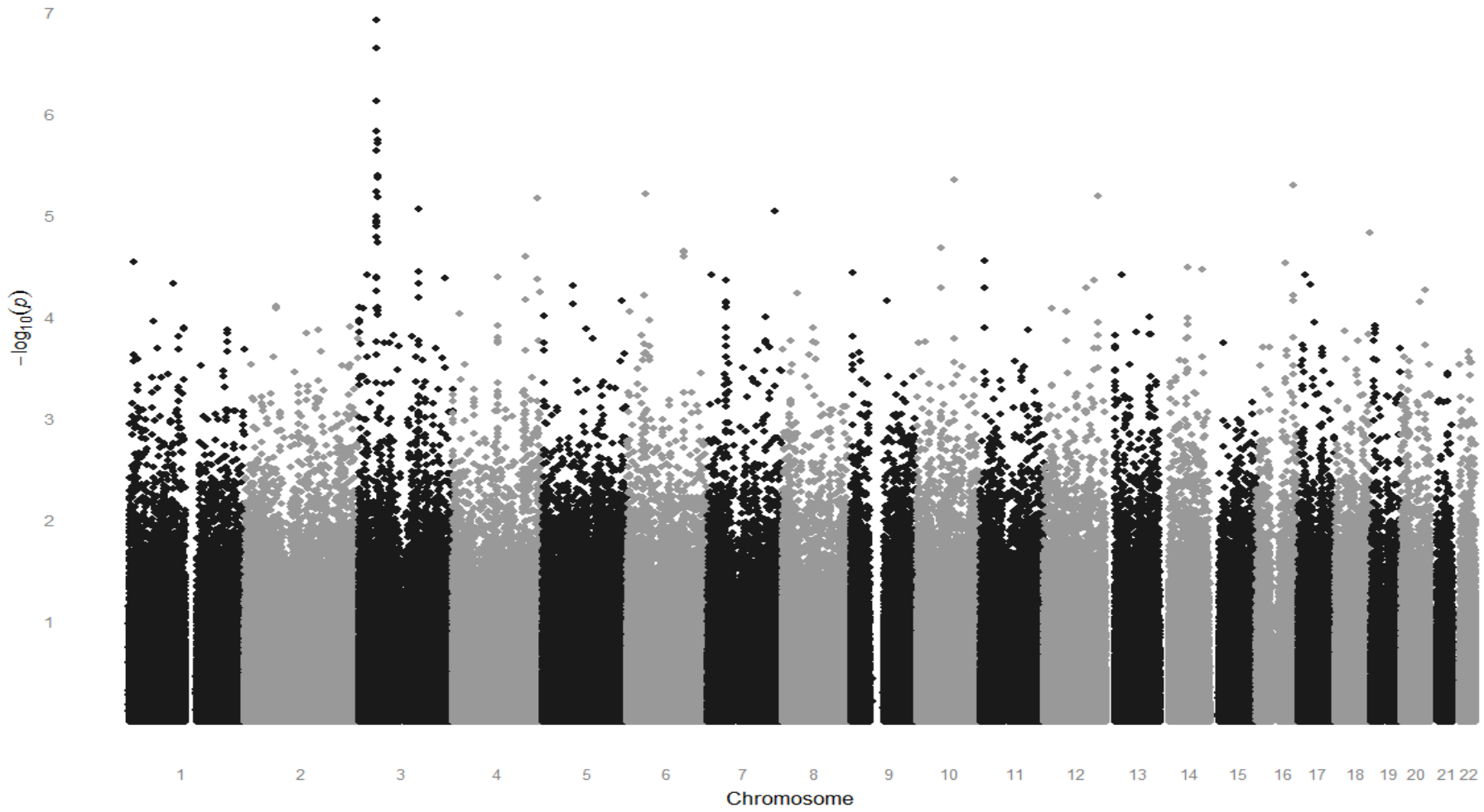


Ramirez et al, 2011

GWAS of QRS Duration

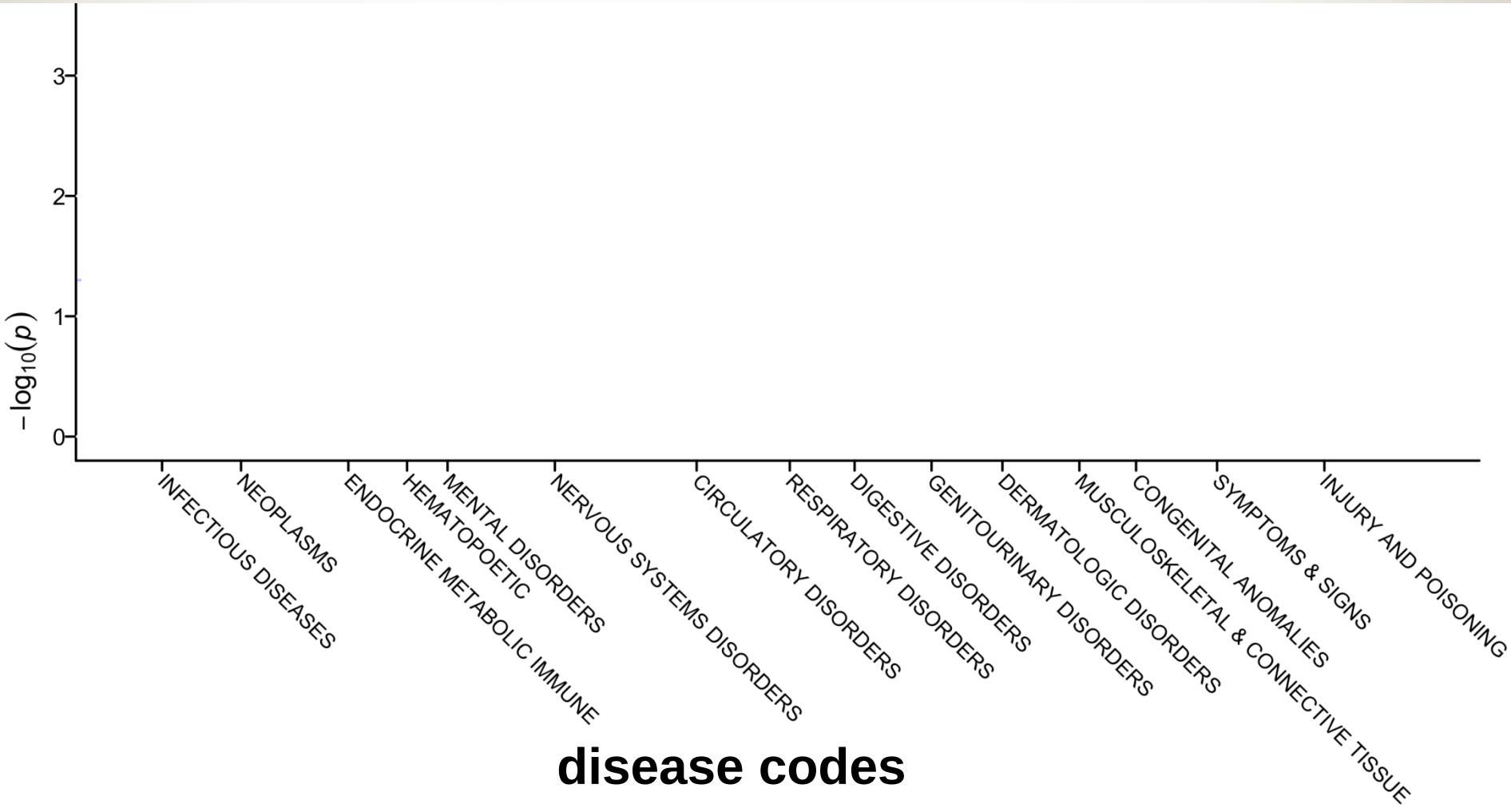
SCN5A/SCN10A

n=5,272



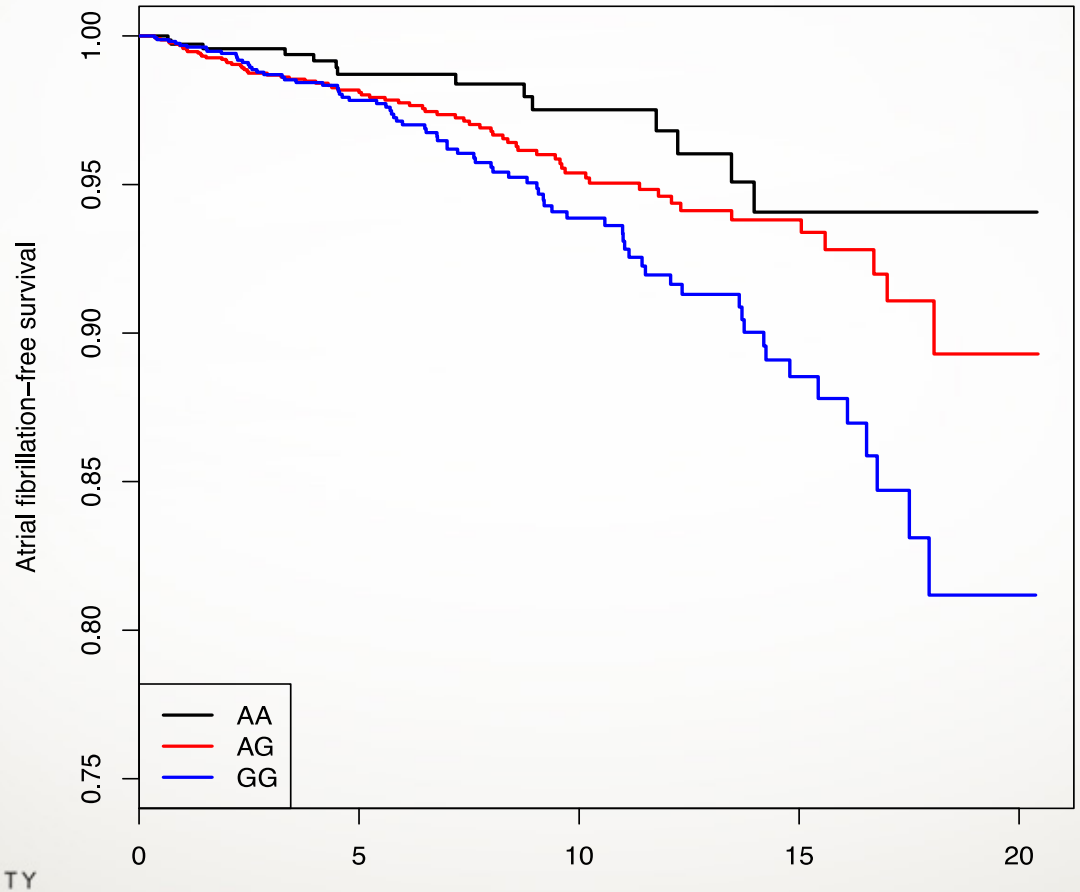
Ritchie, Denny et al., 2013

ΦWAS
PHEnome Wide Association Study



Ritchie, Denny et al., 2013

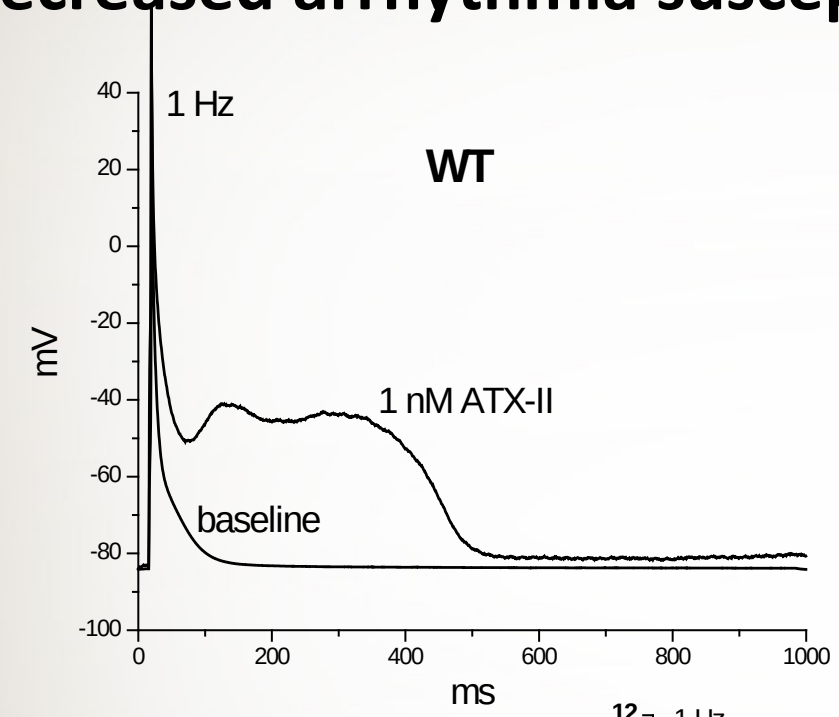
rs6795970 (SCN10A) is associated not only with variability in normal QRS but also with development of atrial fibrillation

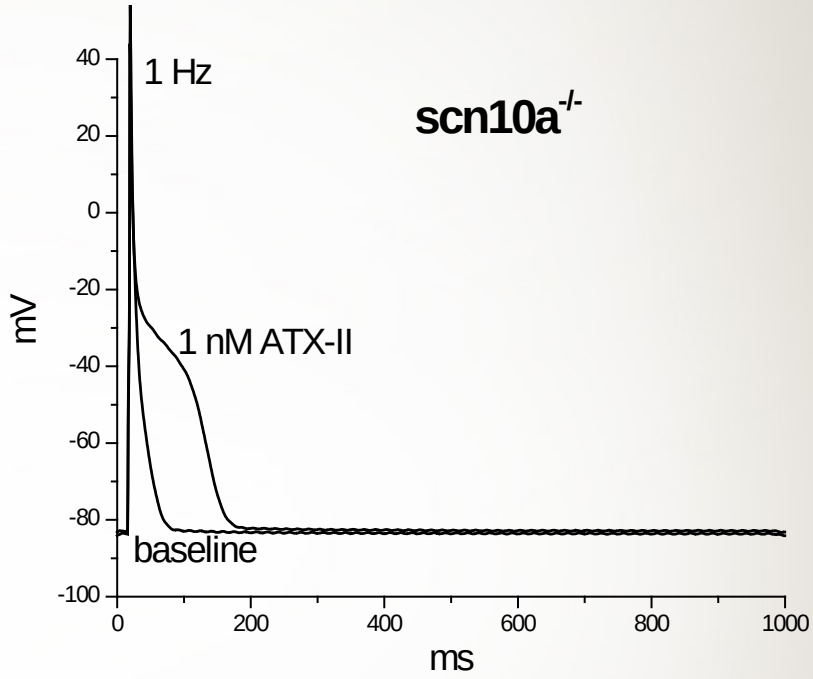


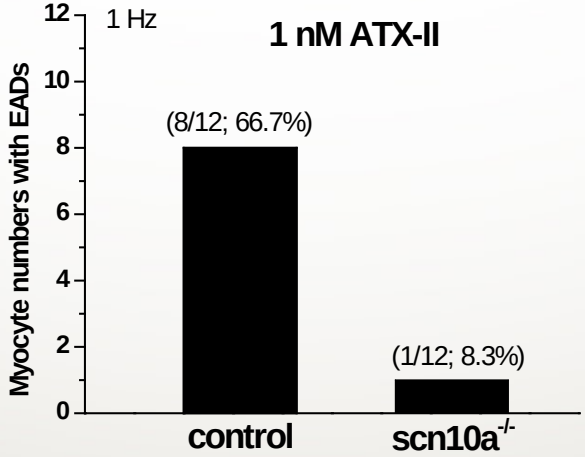
Ritchie, Denny et al., 2013

A not irrelevant digression…

Decreased arrhythmia susceptibility in *scn10a*$^{-/-}$ myocytes







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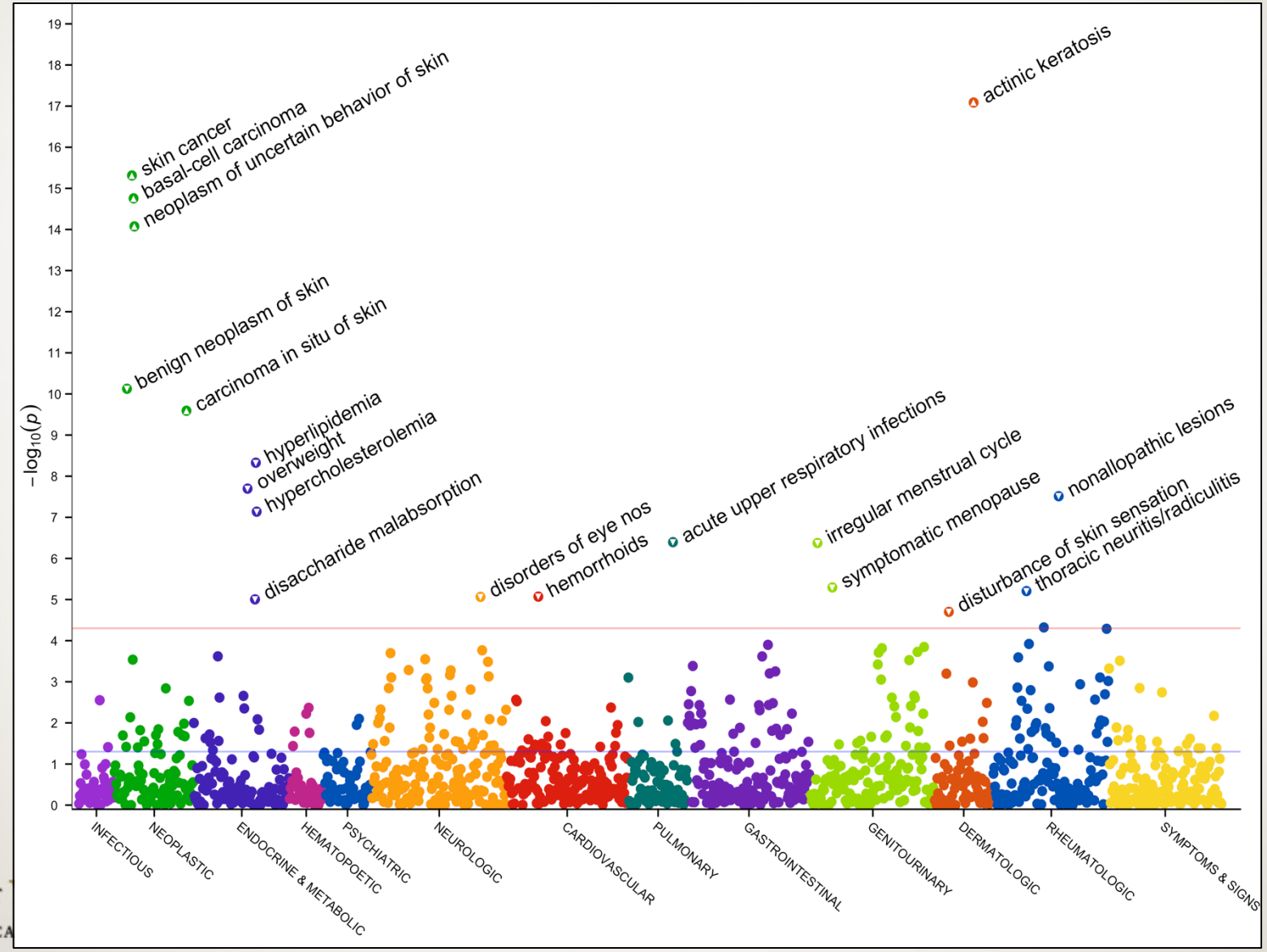
Pleiotropy: PheWAS associations with a skin color SNP

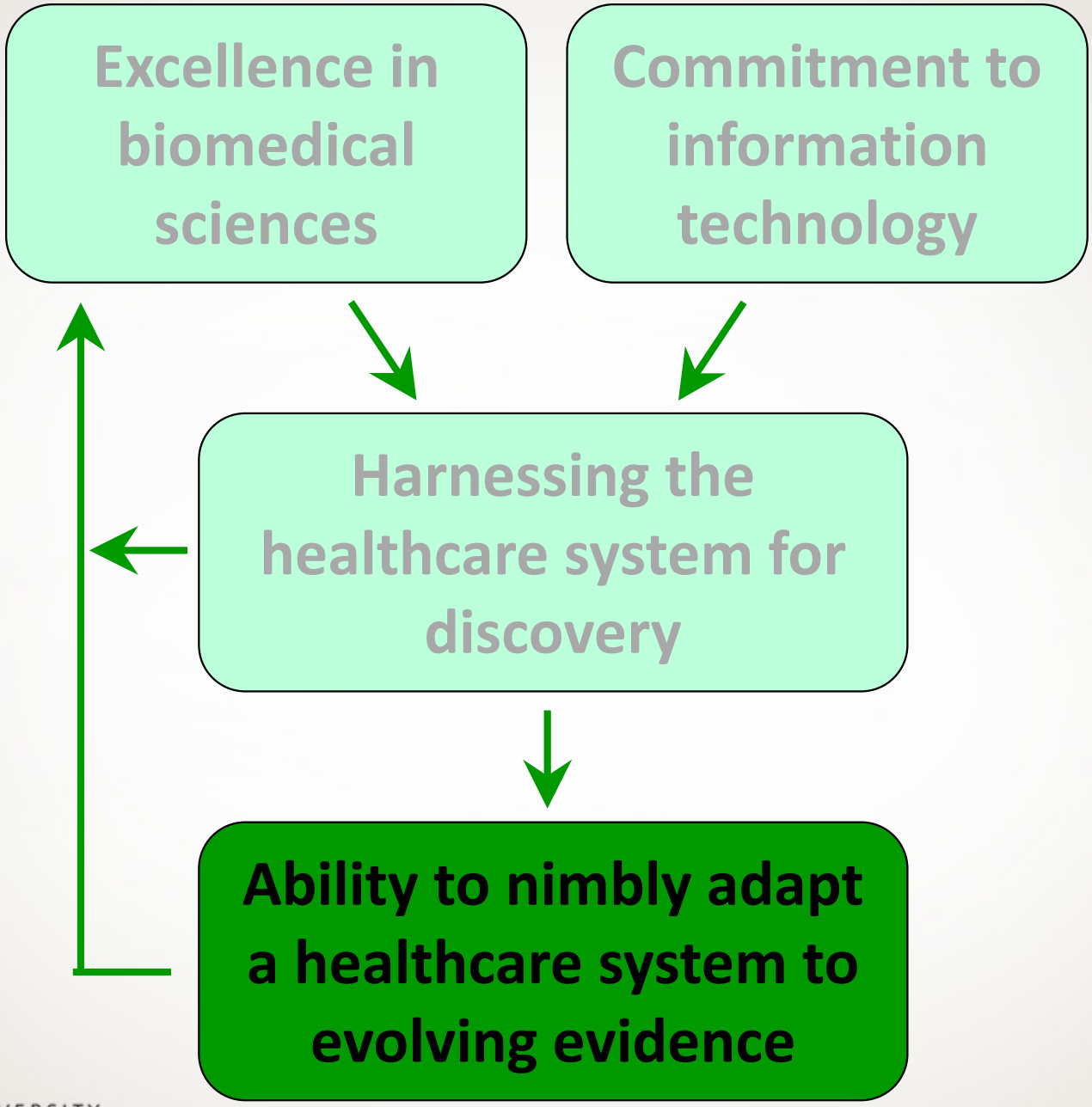


EMR-linked biobanks in eMERGE-II

Site	Participants	(GWAS)-Genotyped Samples
Mt. Sinai	22,000	2,867
CHOP	60,000	22,000
Cincinnati/Boston	10,000	3,000
TOTAL	328,895	75,983

A paradox

Large numbers of patients, of diverse ancestries, are required to develop evidence to "personalize" medicine.



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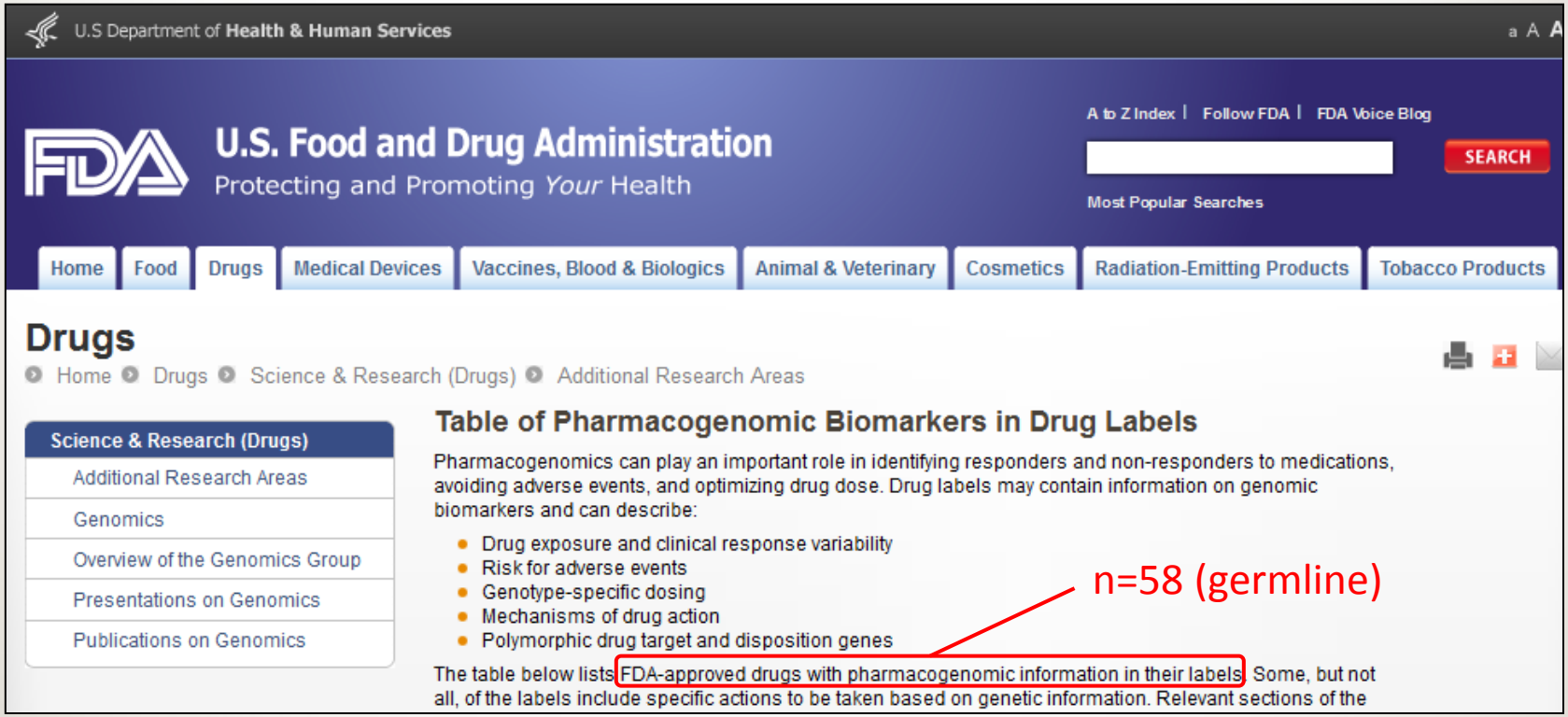
PGRN

Pharmacogenomics Research Network



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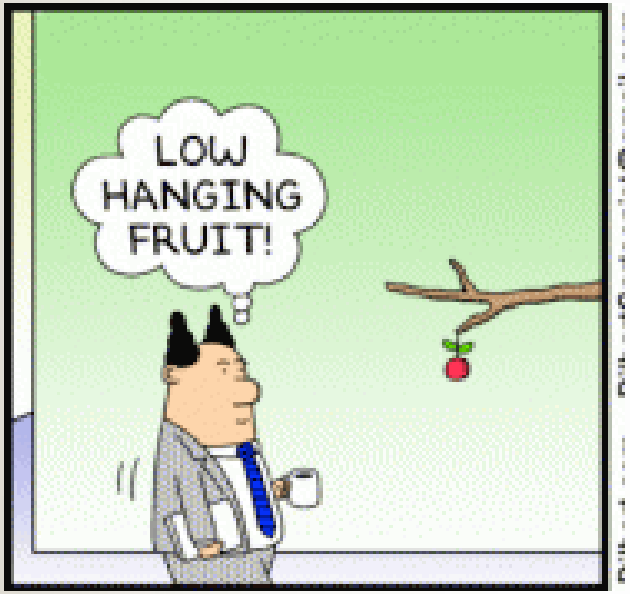
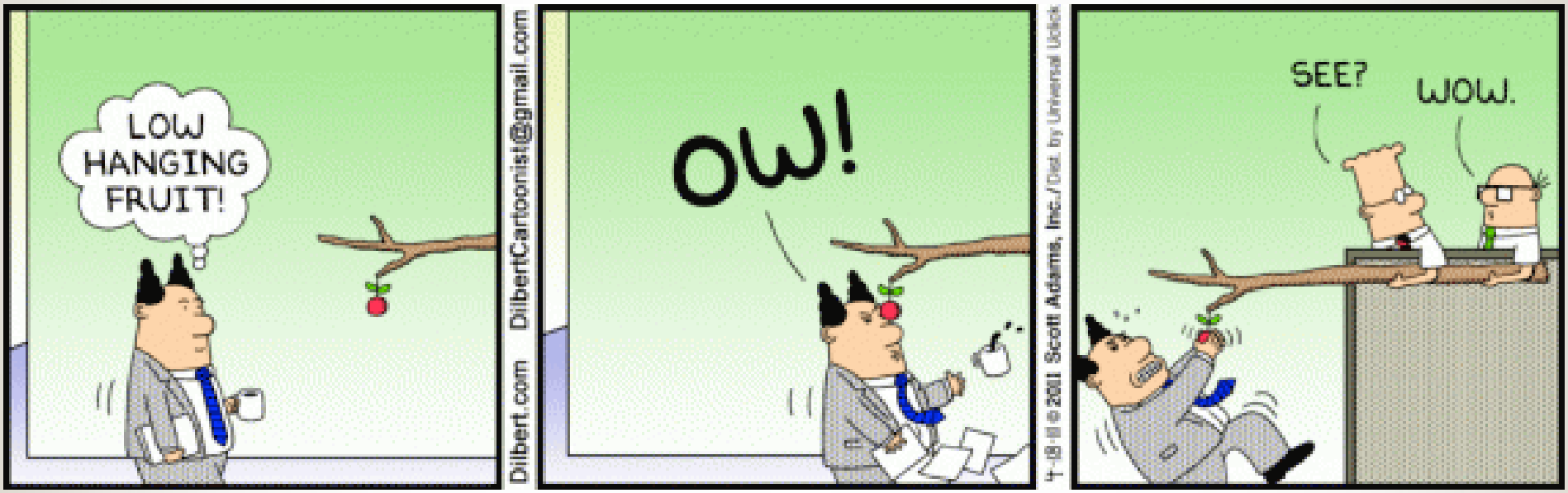
Pharmacogenomics: even low hanging fruit…

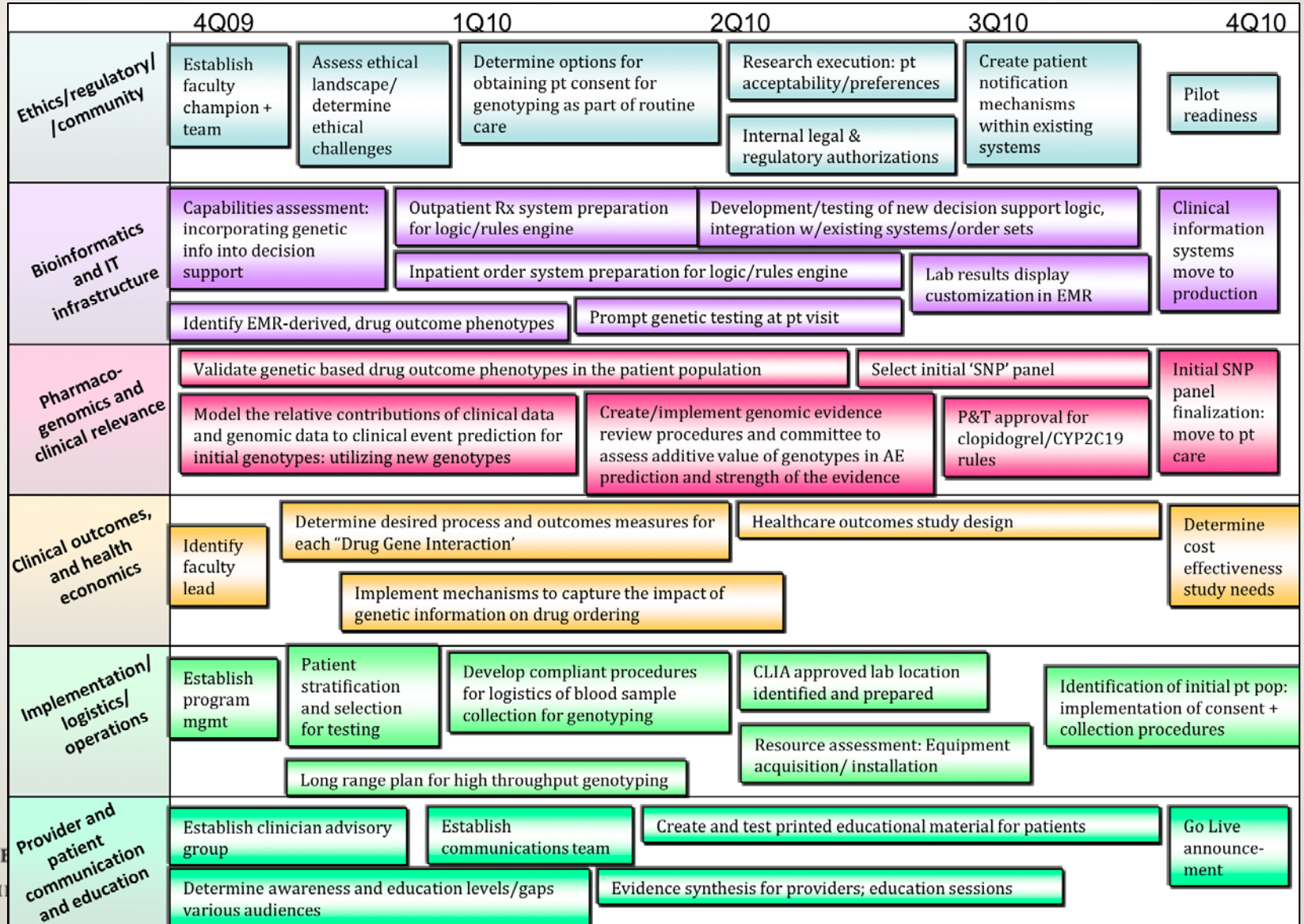


…is not so simple



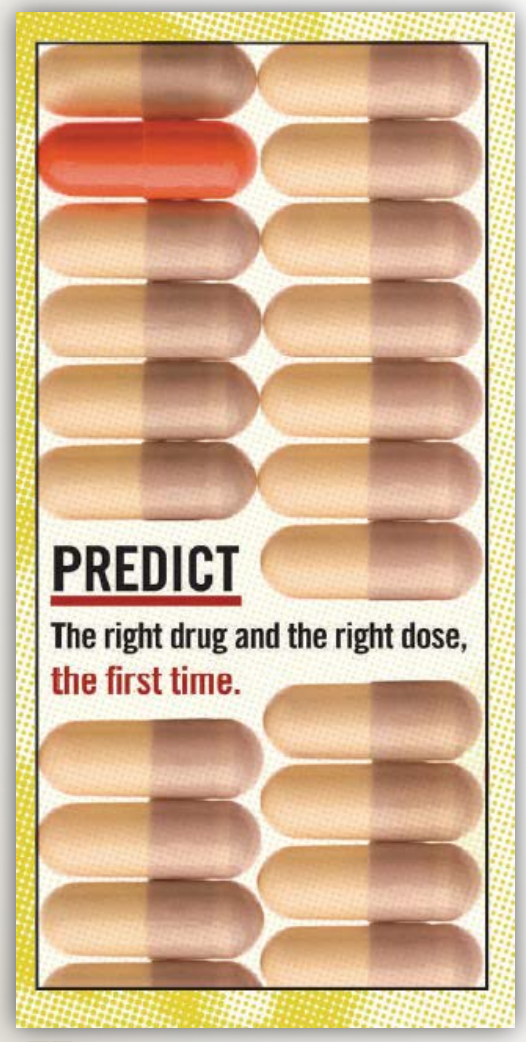
Planning the PREDICT Project

Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment



PREDICT

Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment



1. Select populations of patients who are "**at high risk**" for receiving a drug with an actionable "pharmacogenetic" story.
2. Genotype all of them on a platform that assays genotypes important for variable actions of many drugs preemptively.
3. Store the genotypes, develop the informatics tools to provide point-of-care advice. Track outcomes. The "easy stuff".

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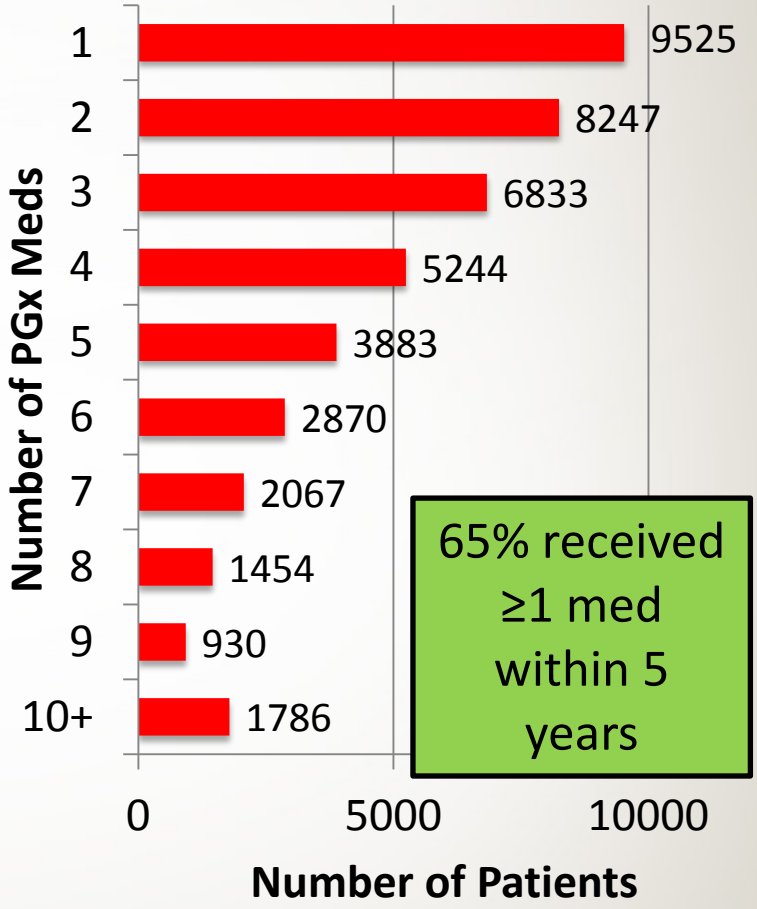
Who is at "high risk"?

A case for preemptive genotyping

In a cohort of 53,196 "Medical Home" patients followed for up to 5 years, how many received drug(s) that have a recognized pharmacogenetic "story"?



Clopidogrel label revision March 2010 identifies another high risk group

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

ation for complete boxed warning.

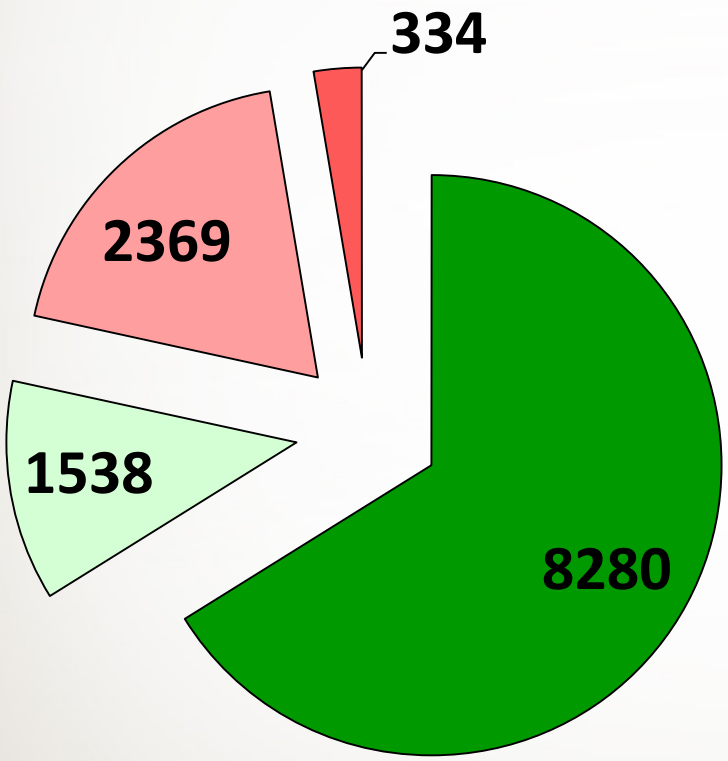
- Effe ds on activation to an active metabolite by t) system, principally CYP2C19. (5.1)
- Poor h Plavix at recommended doses exhibit high ates following acute coronary syndrome (AC ry intervention (PCI) than patients with norm 2.5)
- Test a patient's CYP2C19 genotype and can be u ng therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

In BioVU: Vascular events during clopidogrel (205 cases; 493 controls)

SNP (Gene)	Genotype	Odds Ratio (vs *1/*1)	P
rs4244285 (*CYP2C19*2*)	*1/*2 or *2/*2	1.54	0.003
rs1045642 (*ABCB1*)	3435 C→T	1.28	0.018

Delaney et al., 2012

CYP2C19 genotypes in 12,521 PREDICT patients (9/2010-4/2013)

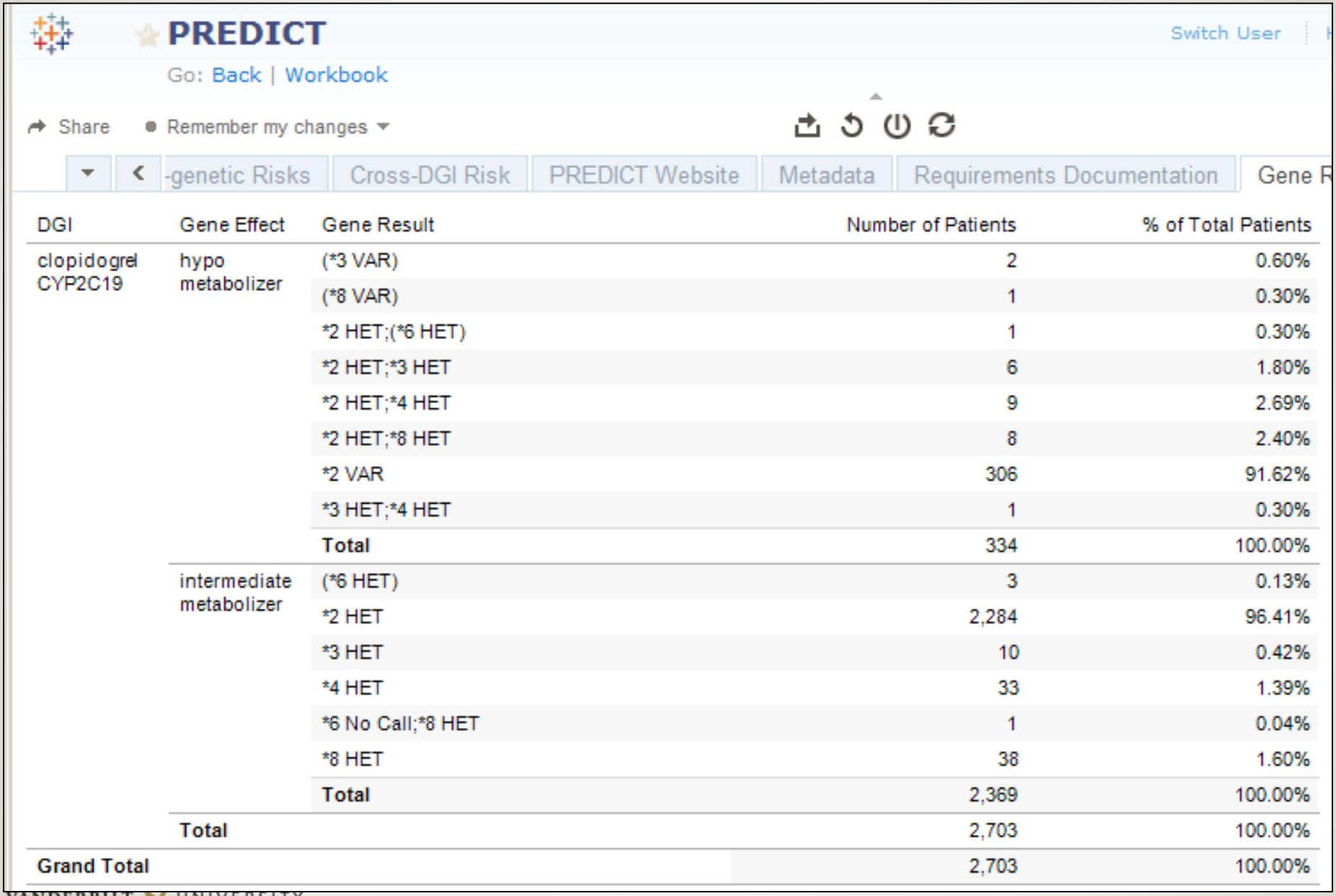


2.7% homozygous

18.9% heterozygous

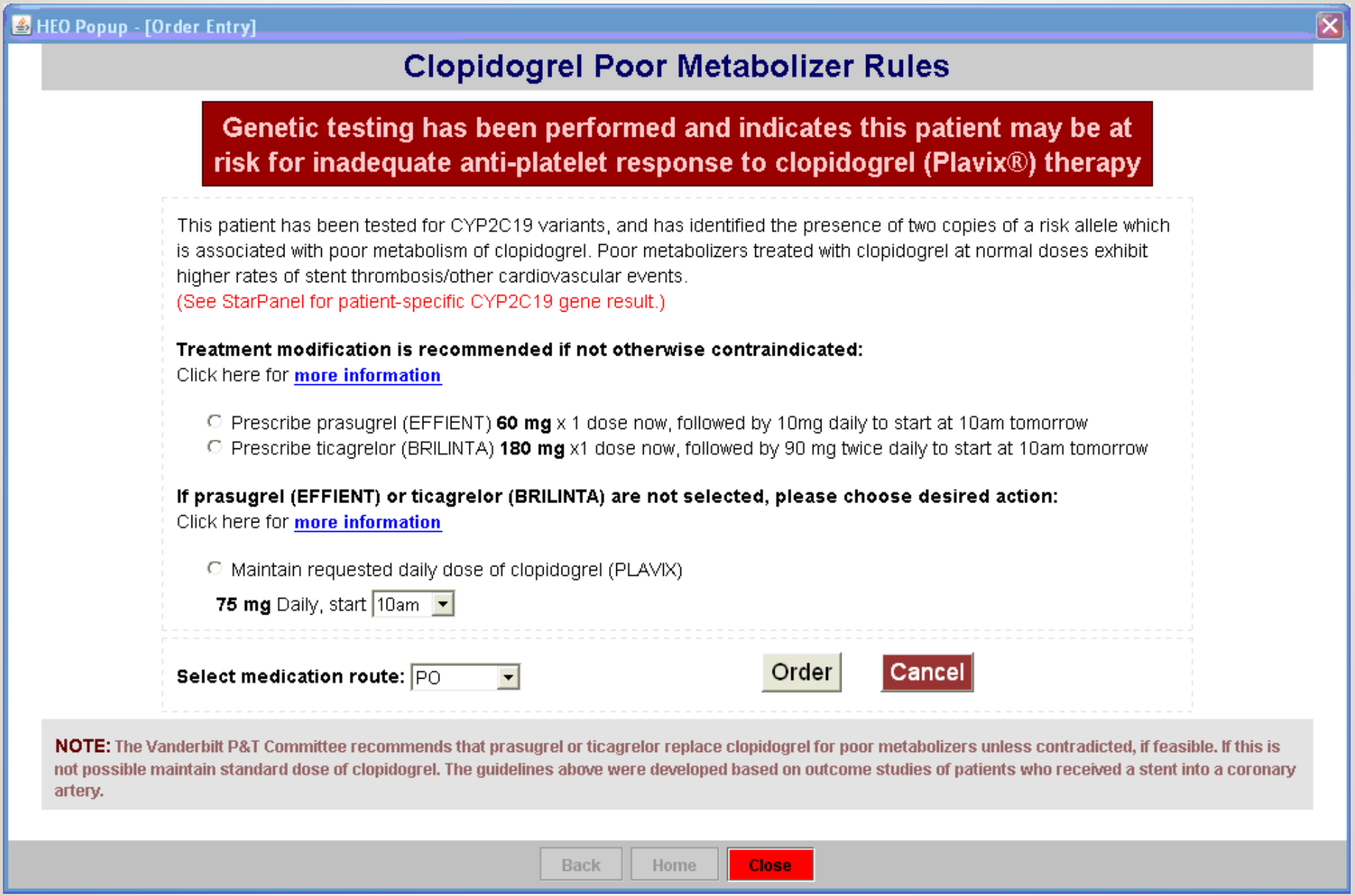
12.2% non-actionable variant

66.1% no common variant



DGI	Gene Effect	Gene Result	Number of Patients	% of Total Patients
clopidogrel CYP2C19	hypo metabolizer	(*3 VAR)	2	0.60%
		(*8 VAR)	1	0.30%
		*2 HET;(*6 HET)	1	0.30%
		*2 HET;*3 HET	6	1.80%
		*2 HET;*4 HET	9	2.69%
		*2 HET;*8 HET	8	2.40%
		*2 VAR	306	91.62%
		*3 HET;*4 HET	1	0.30%
		Total	334	100.00%
	intermediate metabolizer	(*6 HET)	3	0.13%
		*2 HET	2,284	96.41%
		*3 HET	10	0.42%
		*4 HET	33	1.39%
		*6 No Call;*8 HET	1	0.04%
		*8 HET	38	1.60%
		Total	2,369	100.00%
	Total		2,703	100.00%
Grand Total			2,703	100.00%

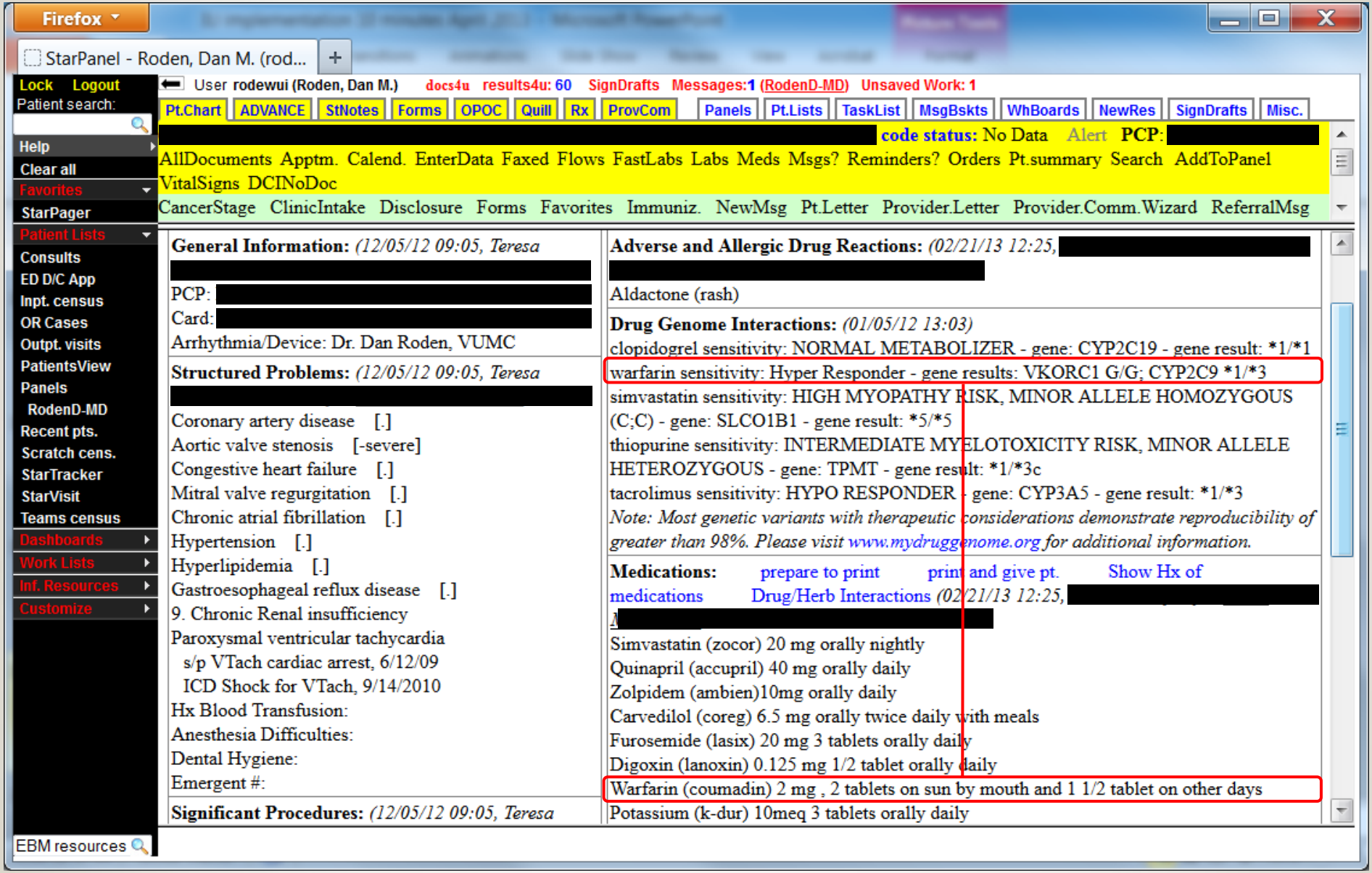
Point of care decision support



Personalizing medicine

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

Sir William Osler


Firefox
StarPanel - Roden, Dan M. (rod...
Lock Logout
Patient search:
Help
Clear all
Favorites
StarPager
Patient Lists
Consults
ED D/C App
Inpt. census
OR Cases
Outpt. visits
PatientsView
Panels
RodenD-MD
Recent pts.
Scratch cens.
StarTracker
StarVisit
Teams census
Dashboards
Work Lists
Inf. Resources
Customize
EBM resources
User rodewui (Roden, Dan M.) docs4u results4u: 60 SignDrafts Messages:1 (RodenD-MD) Unsaved Work: 1
Pt.Chart ADVANCE StNotes Forms OPOC Quill Rx ProvCom Panels Pt.Lists TaskList MsgBskts WhBoards NewRes SignDrafts Misc.
code status: No Data Alert PCP:
AllDocuments Apptm. Calend. EnterData Faxed Flows FastLabs Labs Meds Msgs? Reminders? Orders Pt.summary Search AddToPanel
VitalSigns DCINoDoc
CancerStage ClinicIntake Disclosure Forms Favorites Immuniz. NewMsg Pt.Letter Provider.Letter Provider.Comm.Wizard ReferralMsg
General Information: (12/05/12 09:05, Teresa
PCP:
Card:
Arrhythmia/Device: Dr. Dan Roden, VUMC
Structured Problems: (12/05/12 09:05, Teresa
Coronary artery disease [.]
Aortic valve stenosis [-severe]
Congestive heart failure [.]
Mitral valve regurgitation [.]
Chronic atrial fibrillation [.]
Hypertension [.]
Hyperlipidemia [.]
Gastroesophageal reflux disease [.]
9. Chronic Renal insufficiency
Paroxysmal ventricular tachycardia
s/p VTach cardiac arrest, 6/12/09
ICD Shock for VTach, 9/14/2010
Hx Blood Transfusion:
Anesthesia Difficulties:
Dental Hygiene:
Emergent #:
Significant Procedures: (12/05/12 09:05, Teresa
Adverse and Allergic Drug Reactions: (02/21/13 12:25,
Aldactone (rash)
Drug Genome Interactions: (01/05/12 13:03)
clopidogrel sensitivity: NORMAL METABOLIZER - gene: CYP2C19 - gene result: *1/*1
warfarin sensitivity: Hyper Responder - gene results: VKORC1 G/G; CYP2C9 *1/*3
simvastatin sensitivity: HIGH MYOPATHY RISK, MINOR ALLELE HOMOZYGOUS (C;C) - gene: SLCO1B1 - gene result: *5/*5
thiopurine sensitivity: INTERMEDIATE MYELOTOXICITY RISK, MINOR ALLELE HETEROZYGOUS - gene: TPMT - gene result: *1/*3c
tacrolimus sensitivity: HYPO RESPONDER - gene: CYP3A5 - gene result: *1/*3
Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 98%. Please visit www.mydruggenome.org for additional information.
Medications: prepare to print print and give pt. Show Hx of medications Drug/Herb Interactions (02/21/13 12:25,
Simvastatin (zocor) 20 mg orally nightly
Quinapril (accupril) 40 mg orally daily
Zolpidem (ambien)10mg orally daily
Carvedilol (coreg) 6.5 mg orally twice daily with meals
Furosemide (lasix) 20 mg 3 tablets orally daily
Digoxin (lanoxin) 0.125 mg 1/2 tablet orally daily
Warfarin (coumadin) 2 mg , 2 tablets on sun by mouth and 1 1/2 tablet on other days
Potassium (k-dur) 10meq 3 tablets orally daily

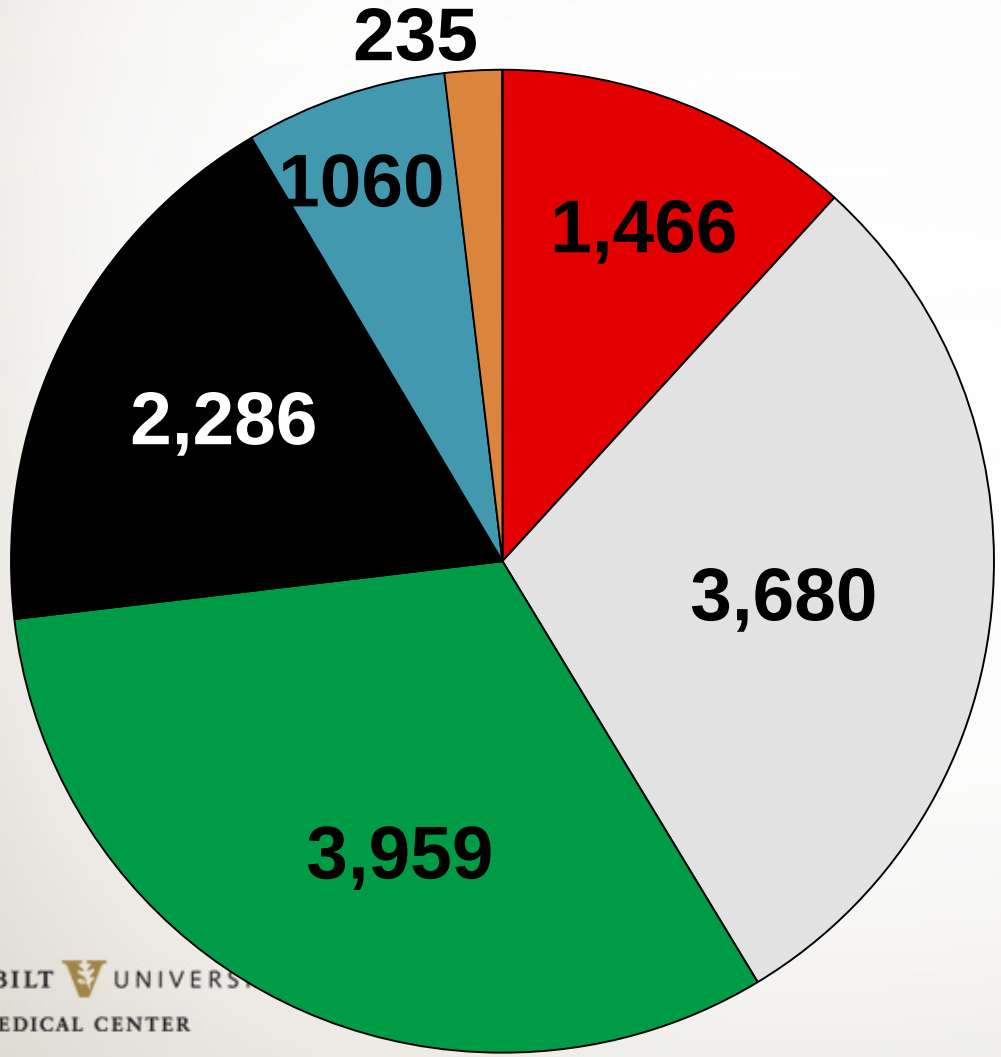
Displaying SNaPshot results for mutation-specific therapy in melanoma in the EMR

MR#	Patient Name	Actions	Tumor Gene Mutations H-SMP	BRAF	CTNNB1	GNA11	GNAQ	KIT	NRAS
03 81	A, B M.	Actions	■	■					
03 56	A, P	Actions	■		■				■
03 35	B, J A	Actions	■						■
01 80	B, S A	Actions							
02 29	E, J E	Actions	■					■	
02 27	F, R M	Actions							
02 77	G, T	Actions							
02 73	H, A	Actions	■			■			
03 64	S, C	Actions	A						
02 79	S, A S	Actions	R						
02 40	W, J E I	Actions							
03 74	W, C L	Actions	■	■					

BRAF c.1798_1799GT>AG (V600R)	Not Detected
BRAF c.1798_1799GT>AA (V600K)	Not Detected
BRAF c.1799T>A (V600E)	Detected
BRAF c.1799_1800TG>AA (V600E)	Not Detected
BRAF c.1798G>A (V600M)	Not Detected
BRAF c.1799T>G (V600G)	Not Detected
BRAF c.1799_1800TG>AT (V600D)	Not Detected

Multiplexed testing for pharmacogenetic variants

(after 5 drug-gene pairs…)



Total n=12,451
(9/10-4/13)

- 0 variants (11.8%)
- 1 variant (29.6%)
- 2 variants (31.8%)
- 3 variants (18.4%)
- 4 variants (6.6%)
- ≥5 variants (1.9%)

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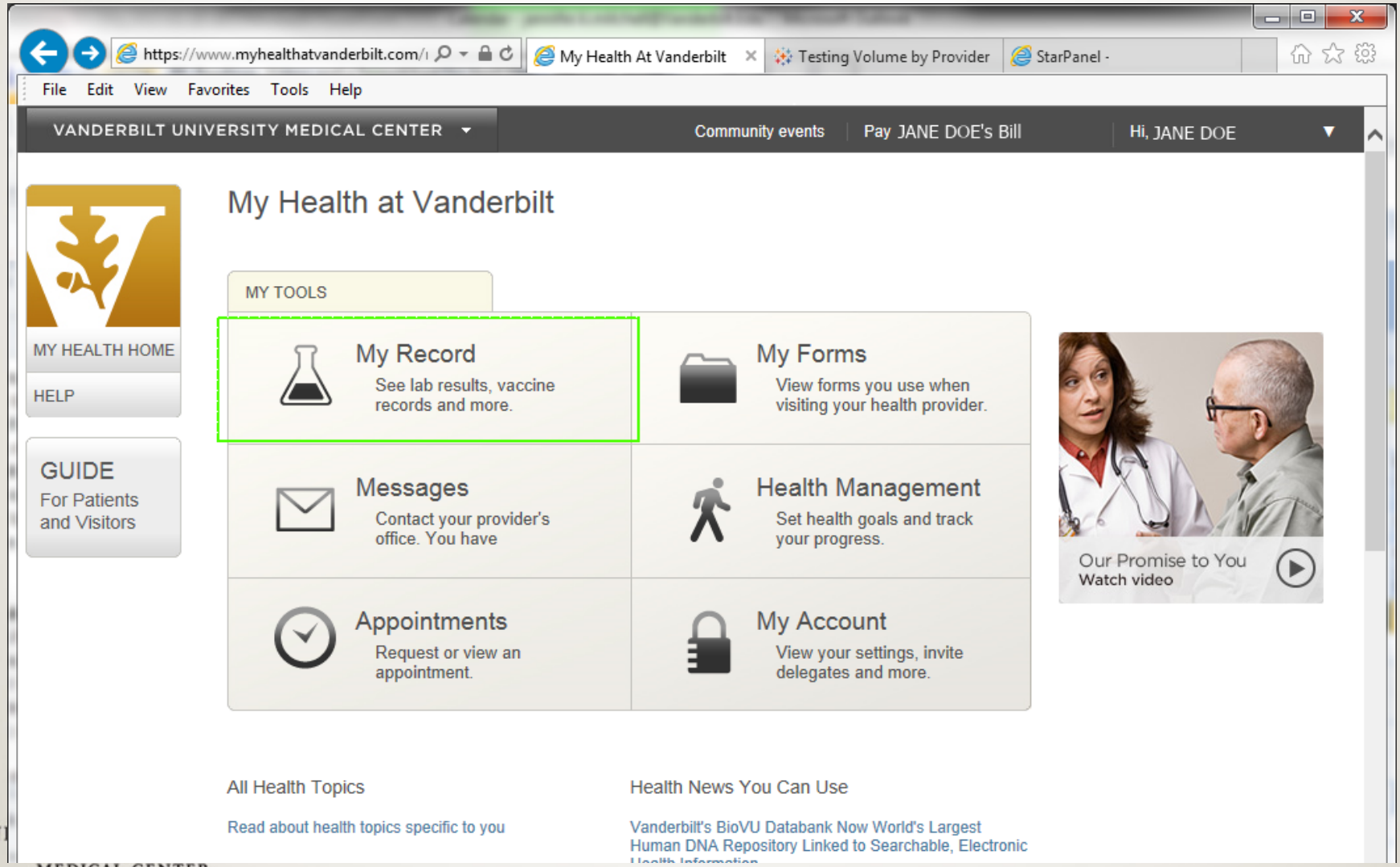
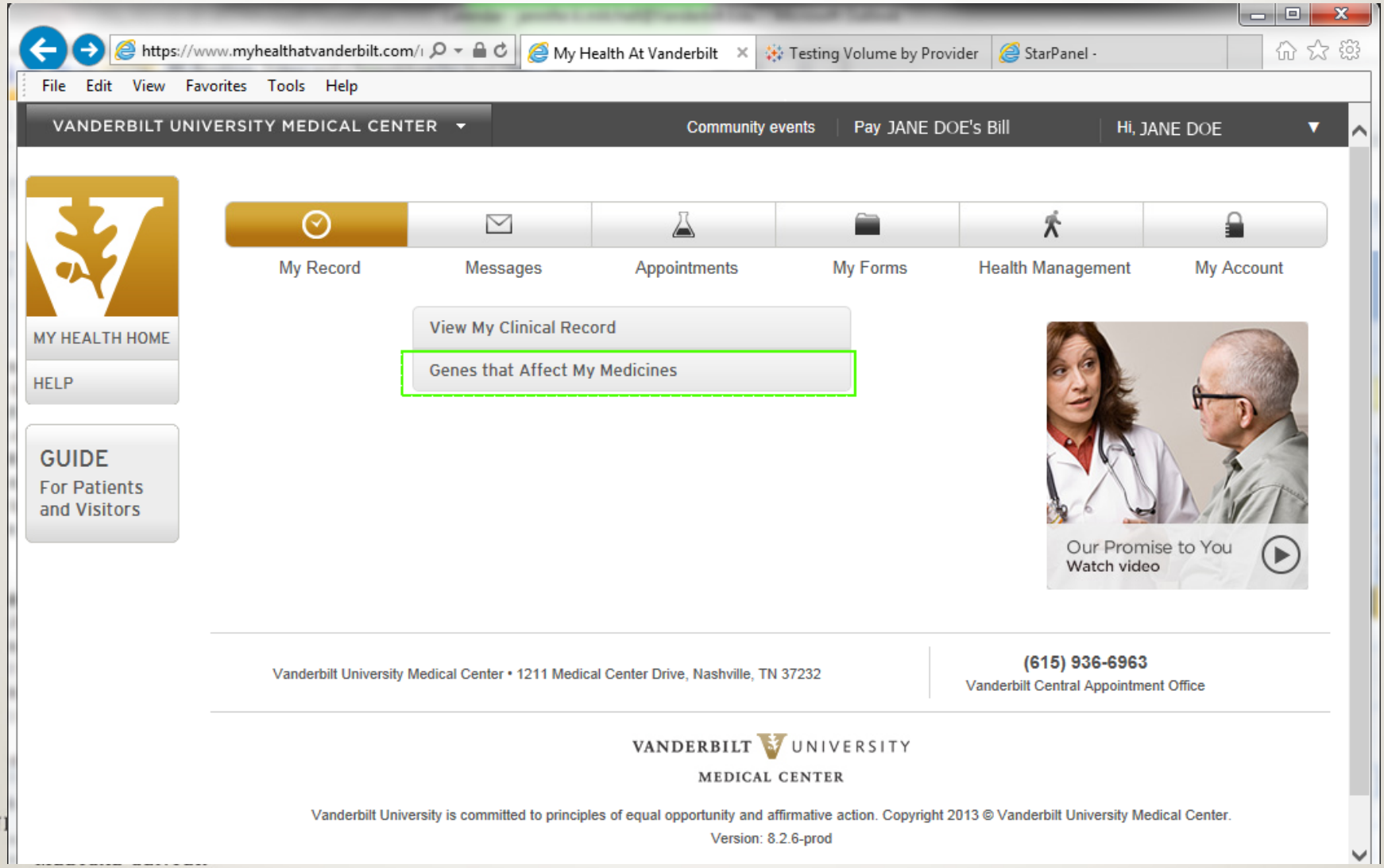
MEDICAL CENTER

Engaging patients

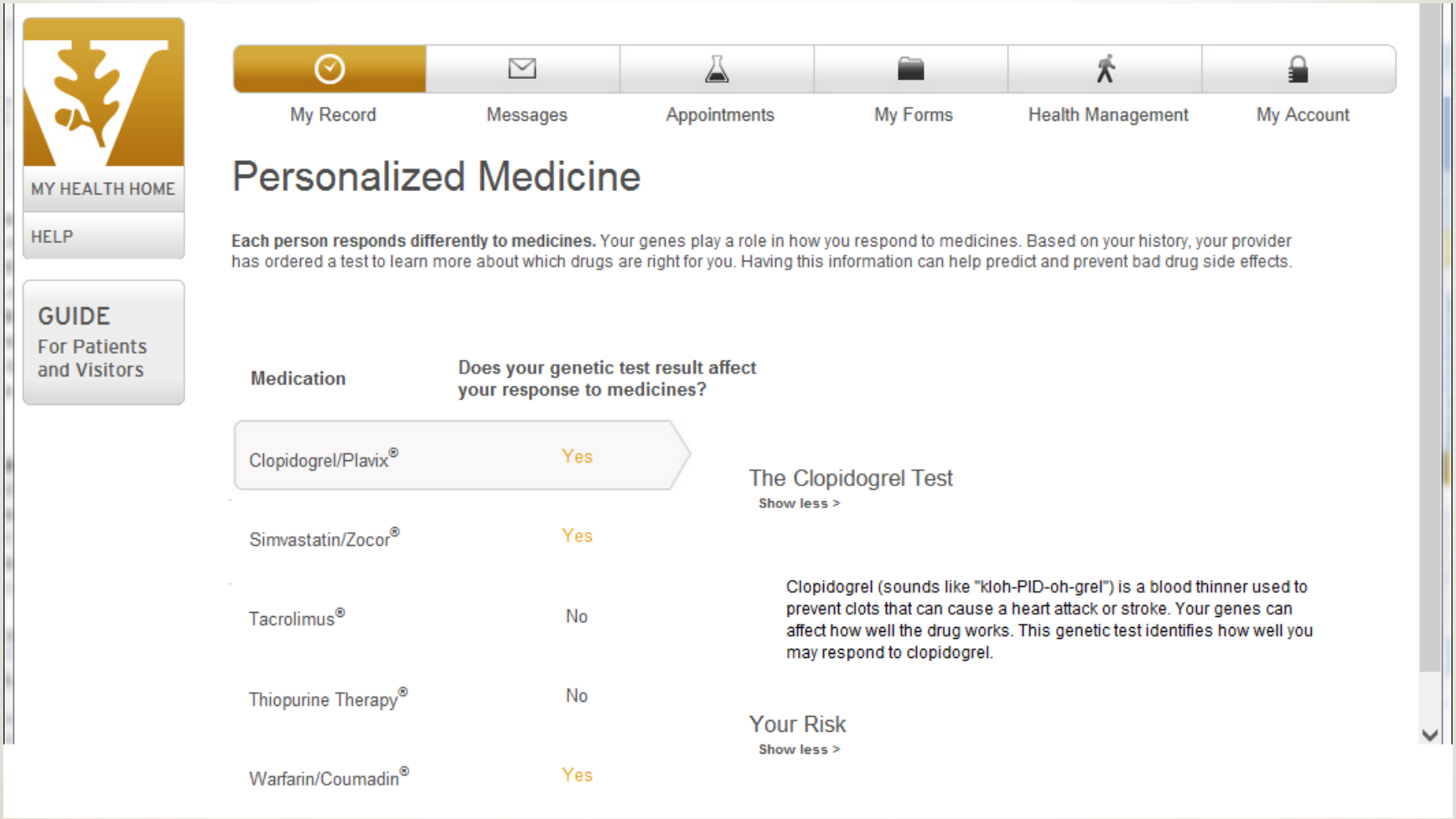


VANDERBILT MEDICAL CENTER

Engaging patients



Engaging patients



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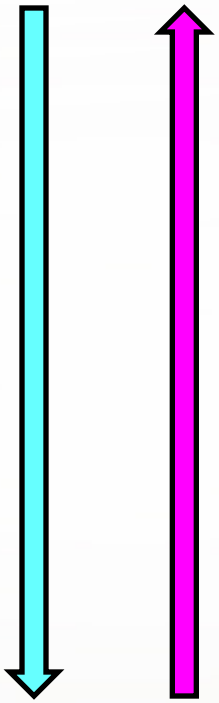
eMERGE-PGRN Partnership

PGRN Pharmacogenomics Research Network

PGx capabilities:

- Array-based assay for pharmacogenes
- Drug-gene guidelines
- CLIA & QC standards



EMR-informatics capabilities

- Privacy
- Electronic phenotyping
- Large populations

The eMERGE Network
electronic Medical Records & Genomics

VANDERBILT UNIVERSITY MEDICAL CENTER

Lessons (1)

- A key role for discovery
- Even “low-hanging fruit” is complicated:
  - Multiple variant alleles
    - some common
    - some rare and of unknown function
    - some not so simple to genotype
  - Variability by ancestry

Lessons (2)

- Multidisciplinary:
  - basic & clinical pharmacology
  - genome science
  - statistics
  - informatics
  - ethics
  - hospital administration
  - clinical pathology
  - clinicians
  - user interface expertise
  - nursing
  - pharmacy
  - outcomes; economics
- Engagement:
  - Domain expertise/users: each new “pair” requires coupled pharmacogenomic and clinical domain expertise
  - Patients
  - Need for specific domain physician champions

Lessons (3)

- Educational needs from students to practitioners
- Understanding changing levels of evidence
- Need for extremely high quality genomic data for clinical purposes
- Absolute (?) requirement for advanced electronic medical records to
- Institutional will

The Teams

The *eMERGE* Network
electronic Medical Records & Genomics
A consortium of biorepositories linked to electronic medical records data for conducting genomic studies

PGRN
Pharmacogenomics Research Network

First data peek…

- 7405 PREDICT genotyped patients from 10/1/2010 to 6/30/2012:
  - 1620 with stent placed
  - “final” antiplatelet therapy identified at 90 days