DNA Biobanks and Personalized Medicine: Translating genomics to the bedside

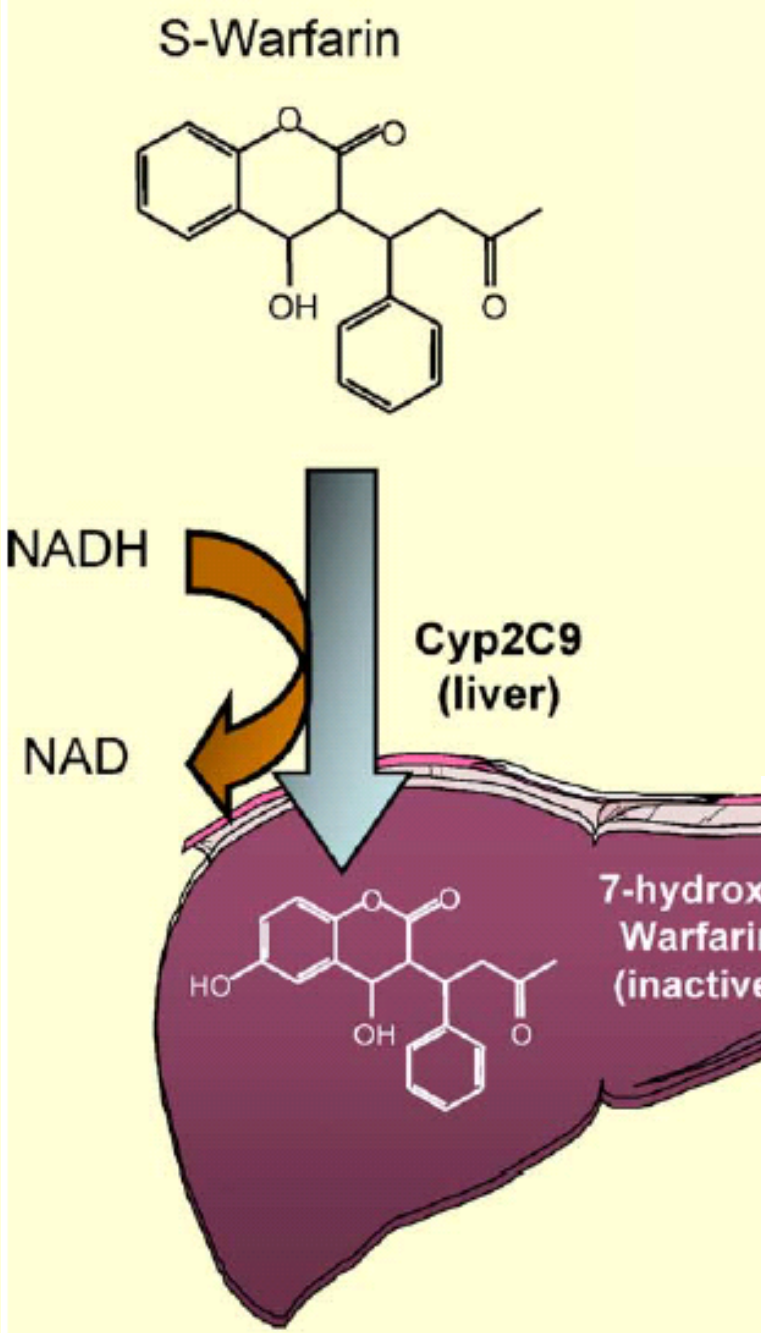
Dan M. Roden MD
Assistant Vice Chancellor for Personalized Medicine
Director, John Oates Institute for Experimental Therapeutics
Principal Investigator, BioVU
Vanderbilt University

"Here's my sequence..."

New Yorker, 2000

38 year old man

- presents with transient left arm weakness
- found to have atrial fibrillation
- placed on warfarin 5 mg/day
- day 4: hematuria
  - variable warfarin response
  - variable atrial fibrillation susceptibility
  - common and rare genetic variants
  - an approach to translating to the bedside



Variants in multiple genes contribute to warfarin dose

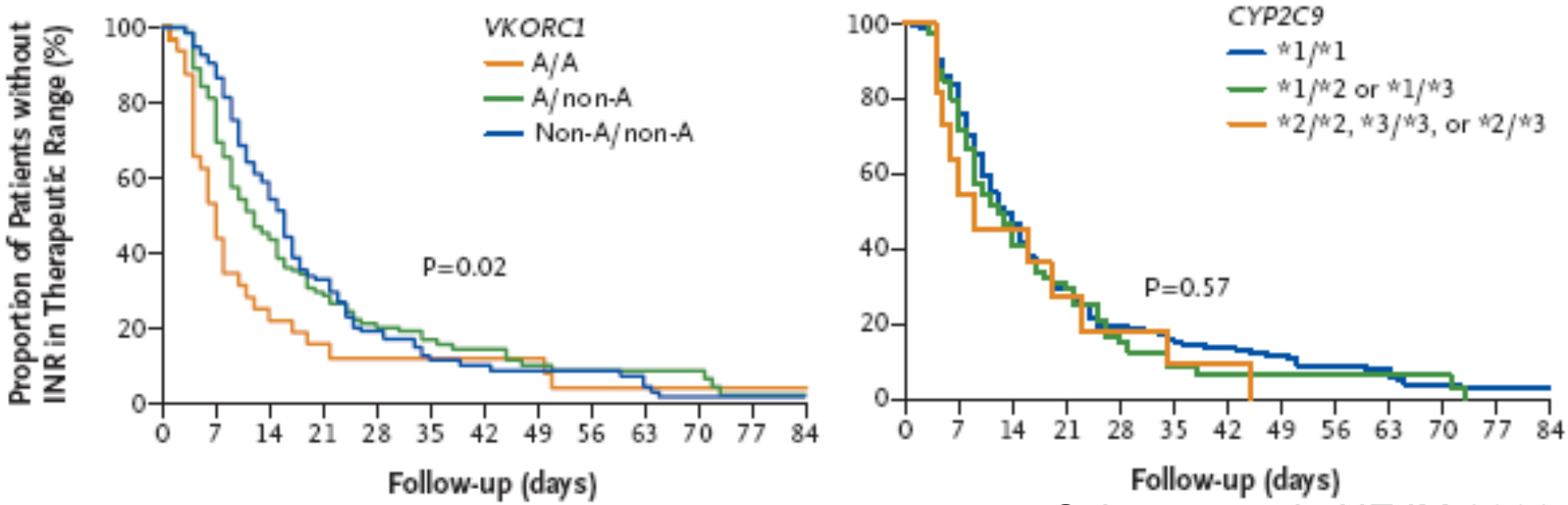
letters to nature

Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2

Simone Rost[1,2*], Andreas Fregin[1*], Vytautas Ivaskevicius[3], Ernst Conzelmann[4], Konstanze Hörtnagel[2], Hans-Joachim Pelz[5], Knut Lappegard[6], Erhard Seifried[3], Inge Scharrer[7], Edward G. D. Tuddenham[8], Clemens R. Müller[1], Tim M. Strom[2,9] & Johannes Oldenburg[1,3]

When therapy is started, VKORC1 is the key

Time to first therapeutic INR:

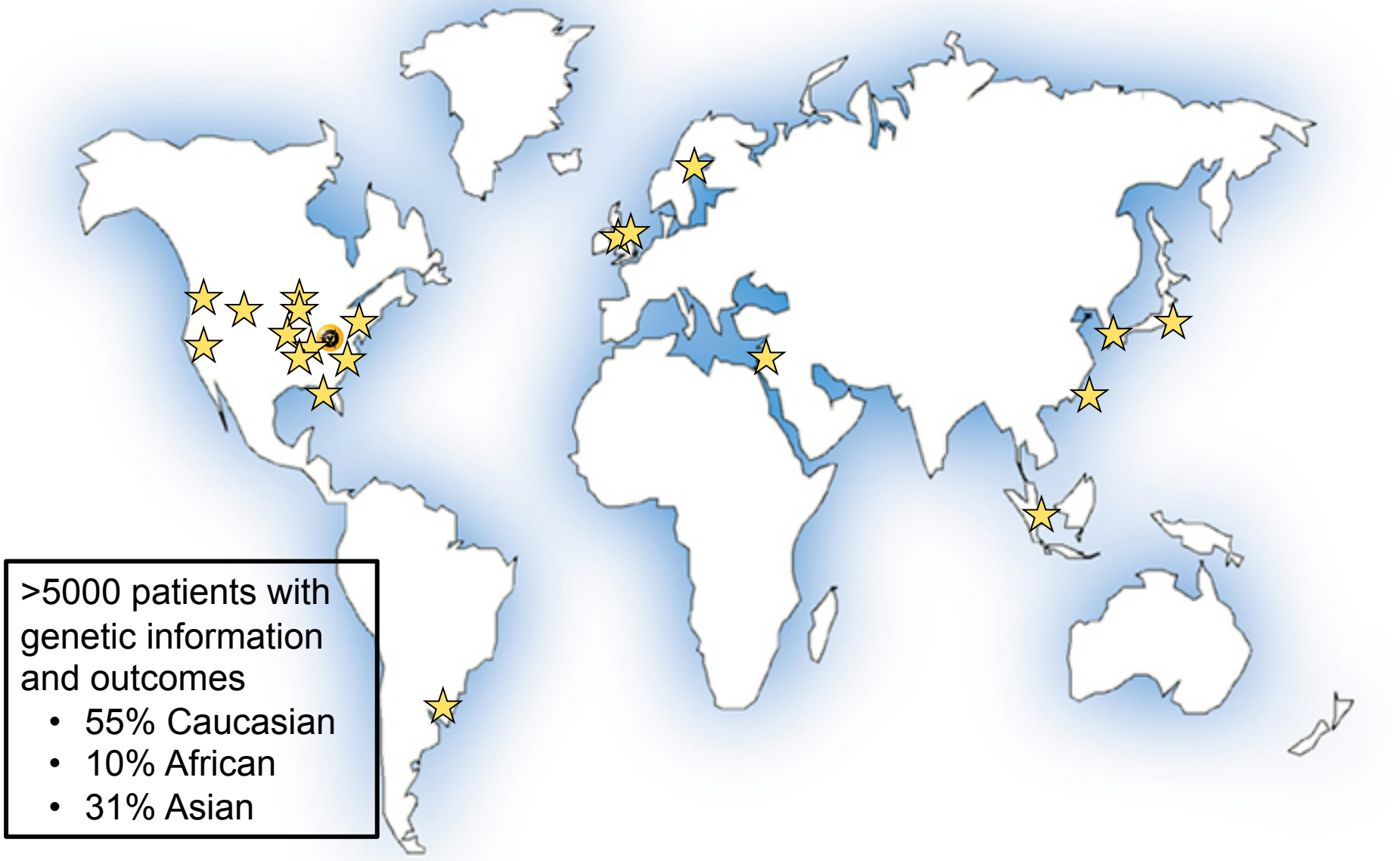


Schwarz et al., NEJM 2008

What is the best way to use this kind of information in dosing?

- Does this apply across ethnicities?
- Are there other genes?

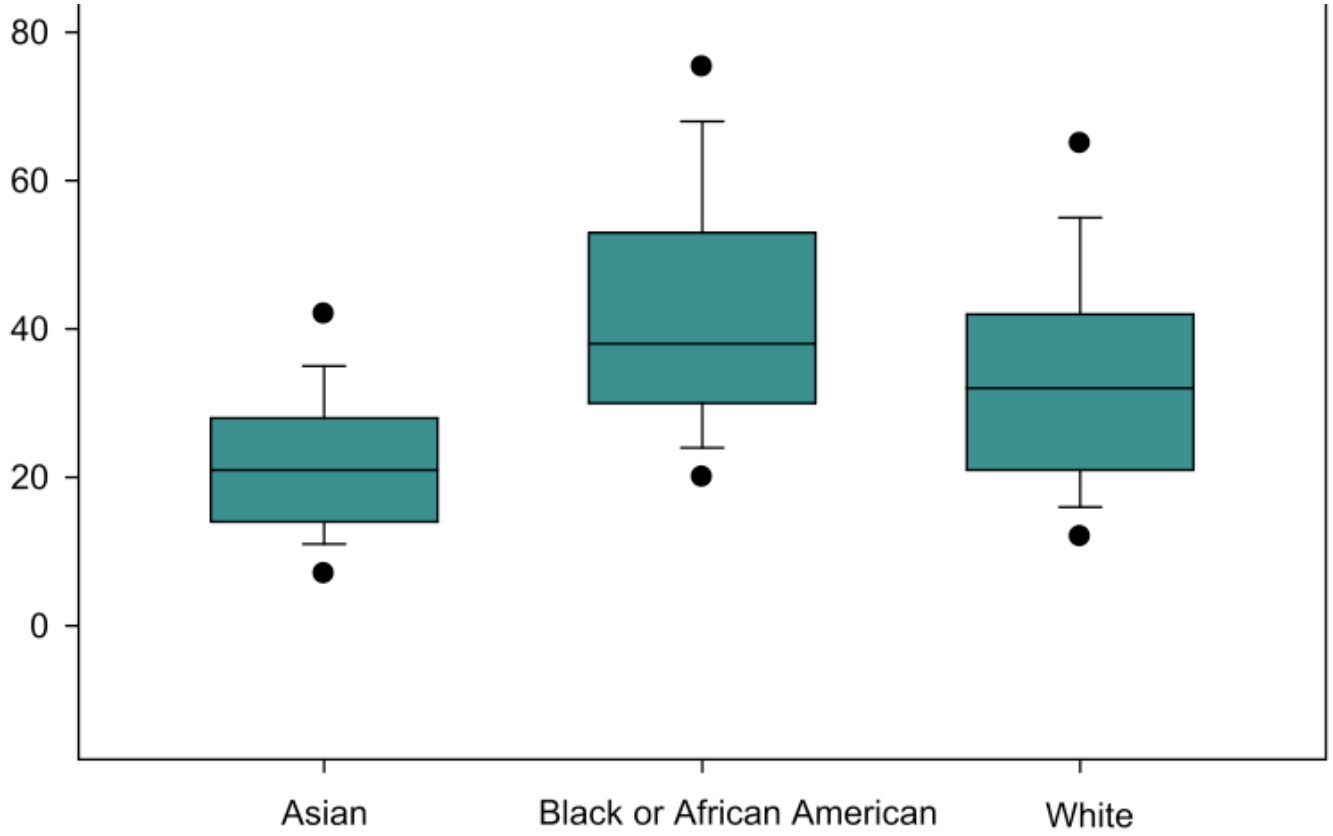
The International Warfarin Pharmacogenomics Consortium



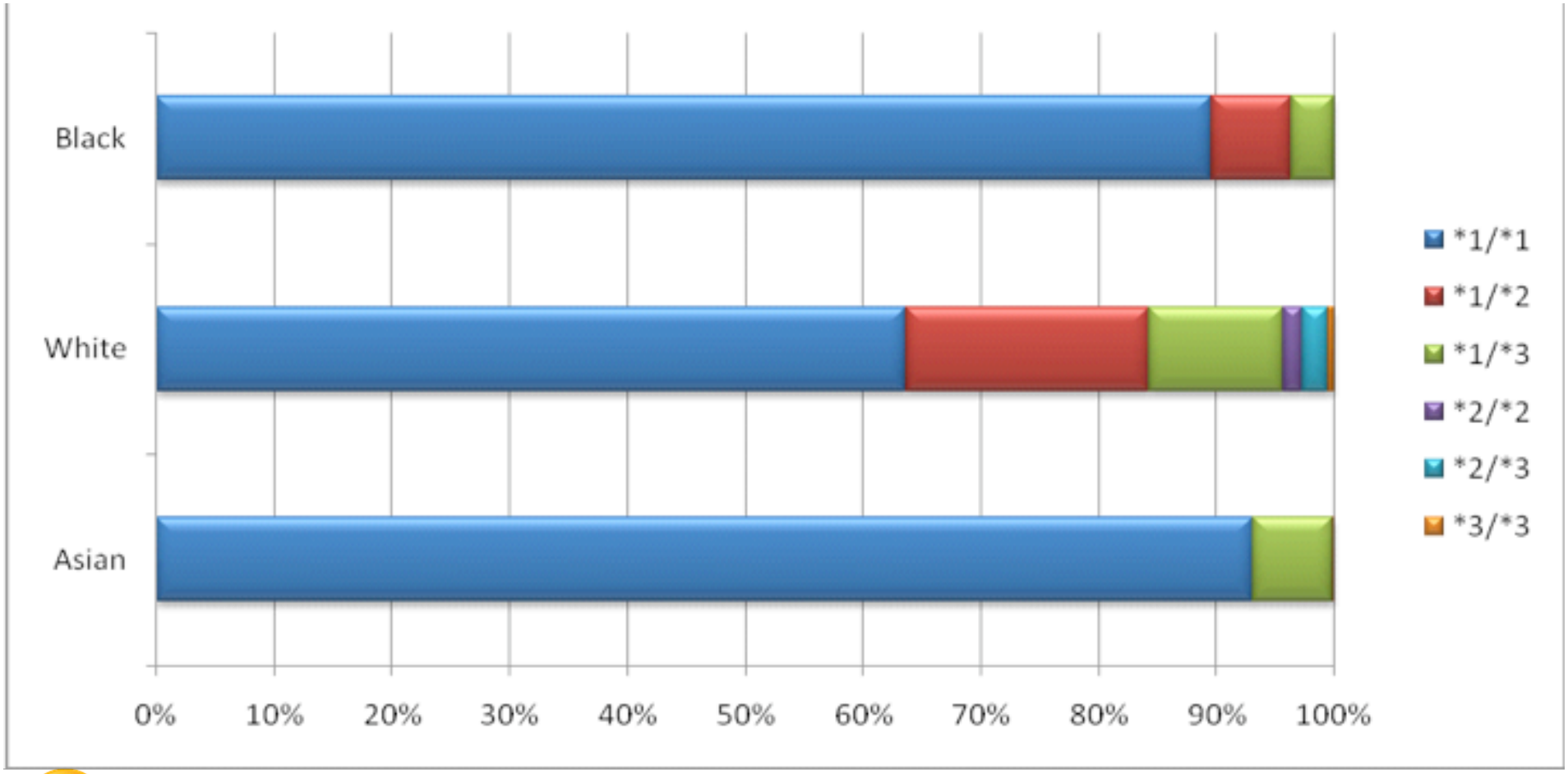
>5000 patients with genetic information and outcomes

- 55% Caucasian
- 10% African
- 31% Asian

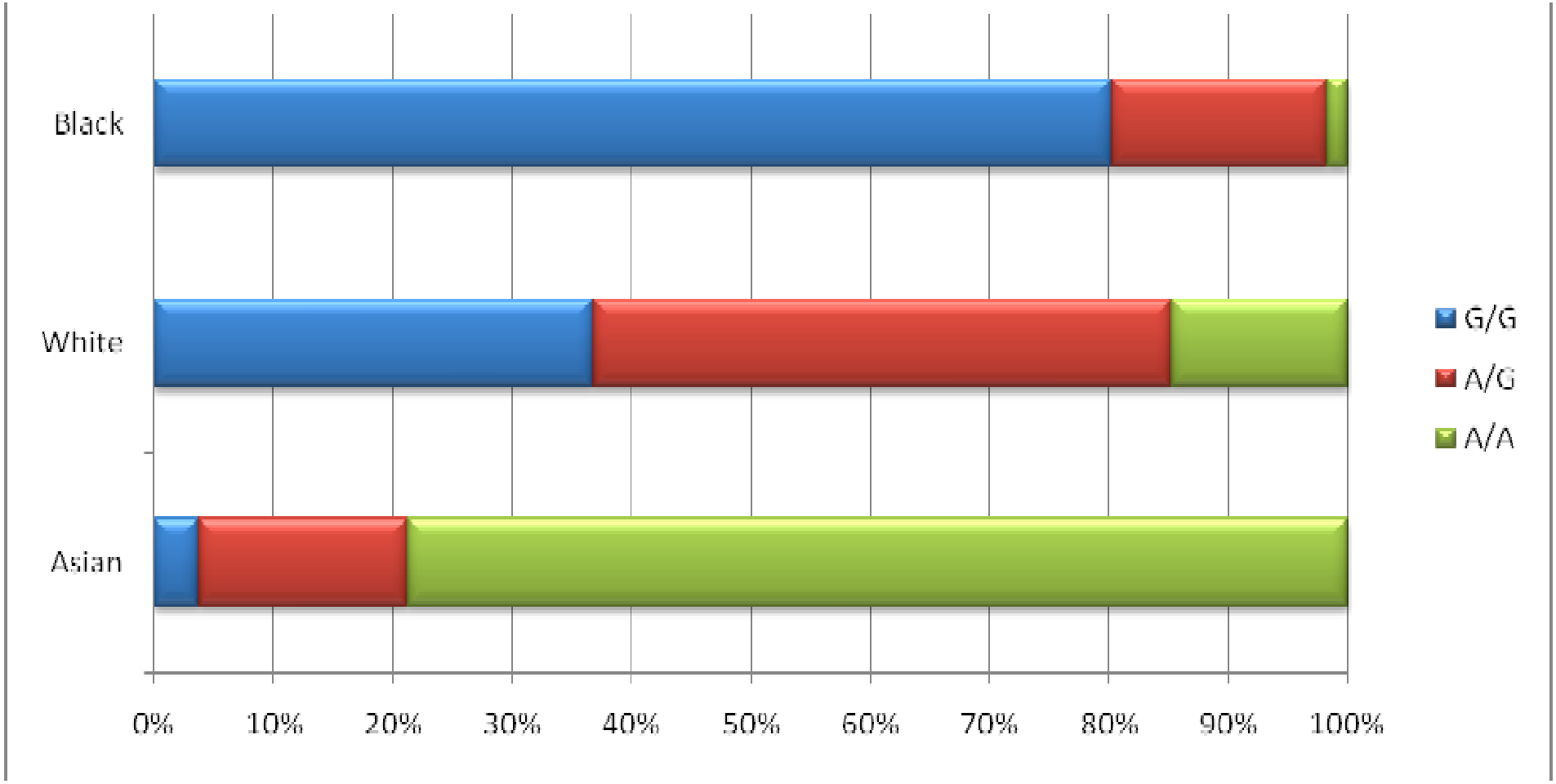
Average weekly warfarin doses for stable INR



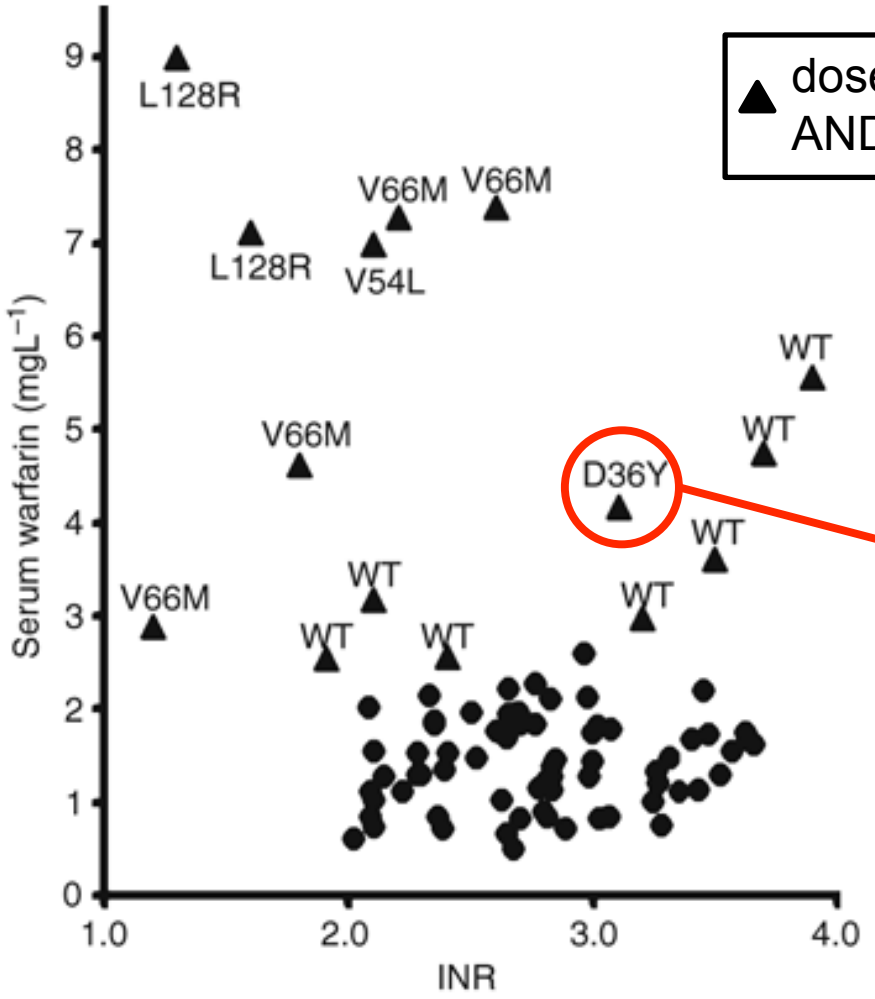
CYP2C9 genotype by race



VKORC1 -1639 genotype by race



Rare VKORC1 variants associated with high warfarin dose requirements



▲ dose requirement >20 mg/day AND serum warfarin >2.3

identified in 8/15 Ashkenazi patients requiring >11 mg/day

Harrington et al., 2008

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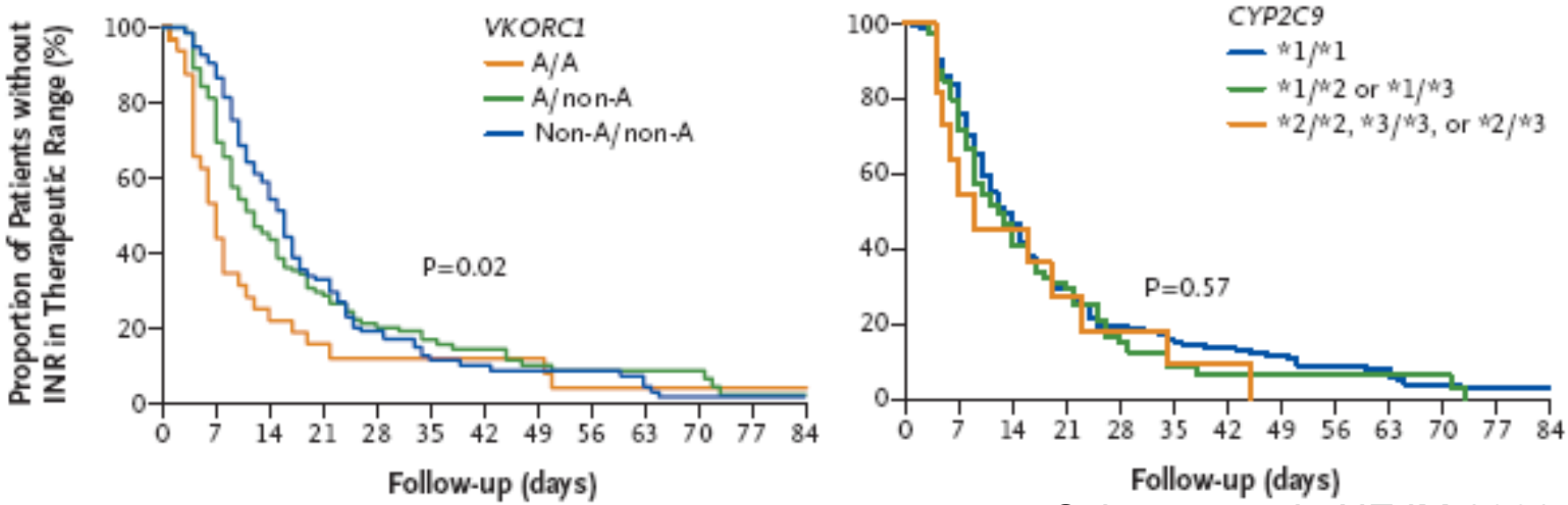

Schwarz et al., NEJM 2008

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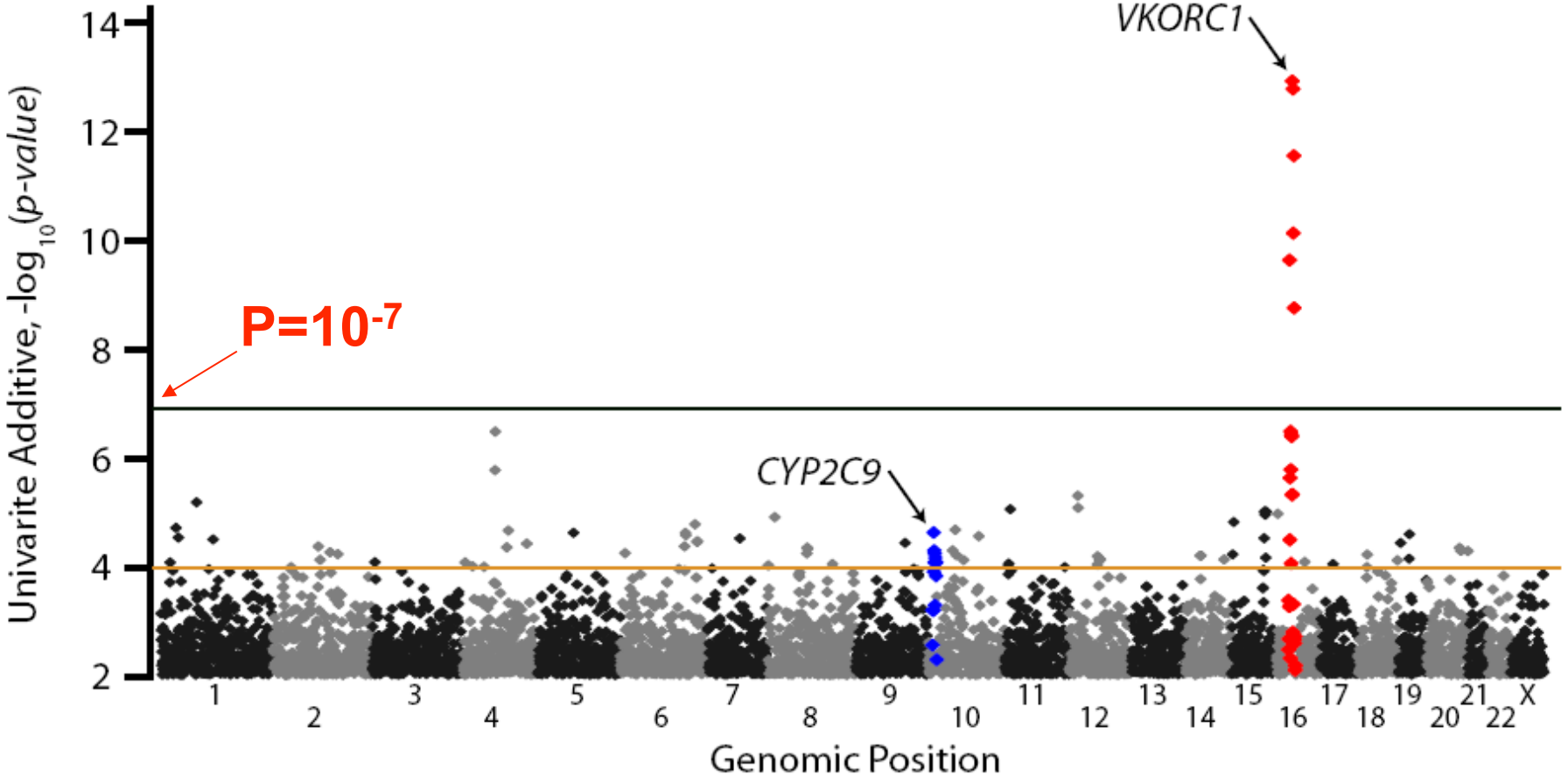
- Are there other genes? ***Genome-Wide Association***

Genome-wide association to analyze warfarin response



Cooper et al., Blood 2008

Genome-wide analysis identifies a common variant for AF risk

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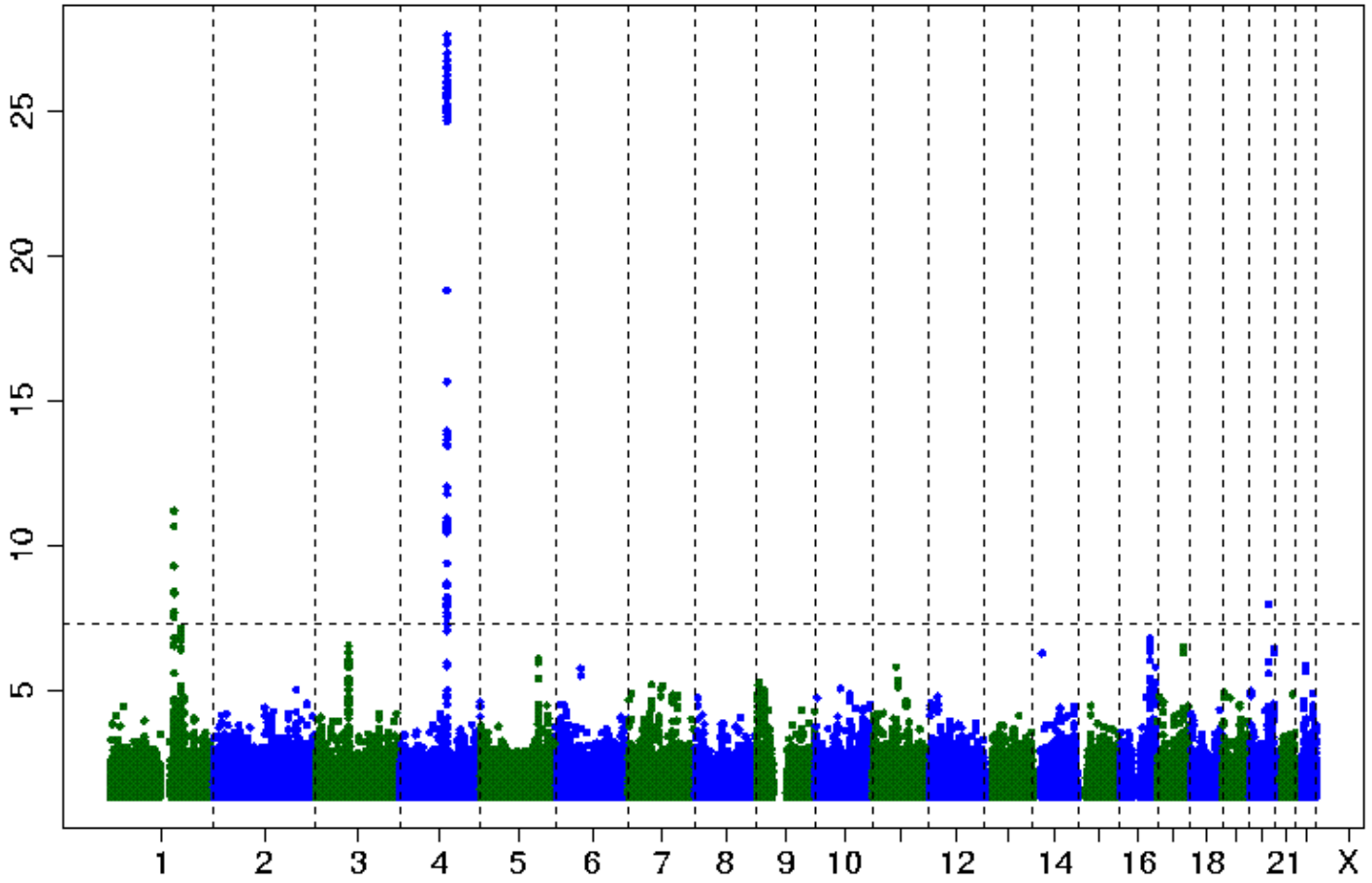

Rare genetic variants can contribute to risk for common diseases like atrial fibrillation

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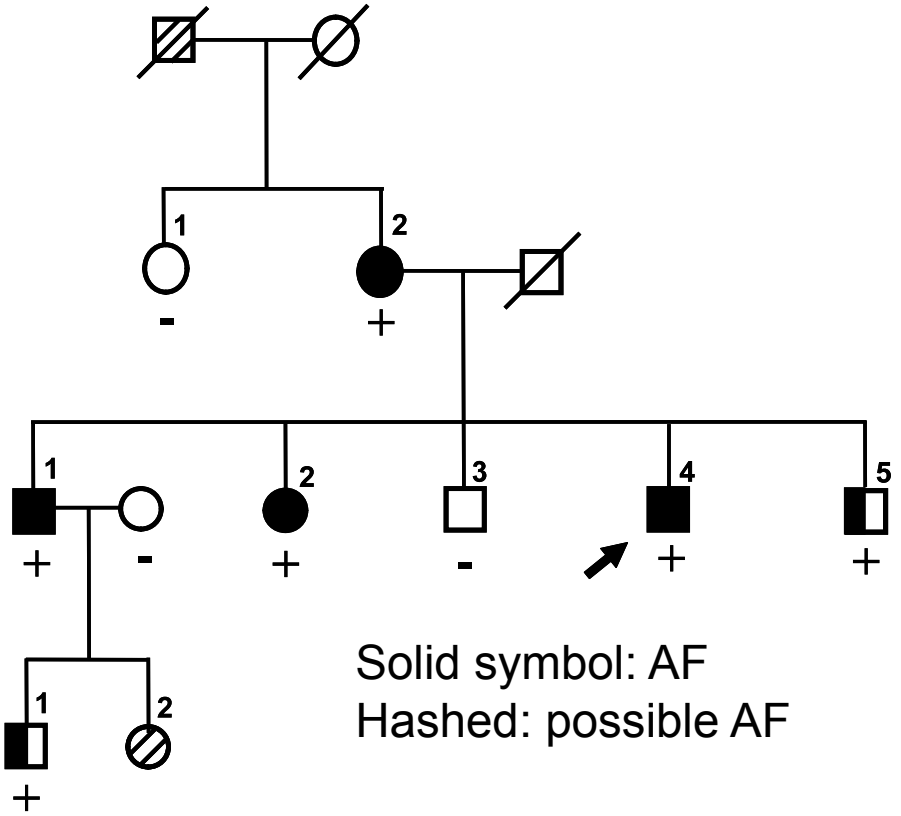
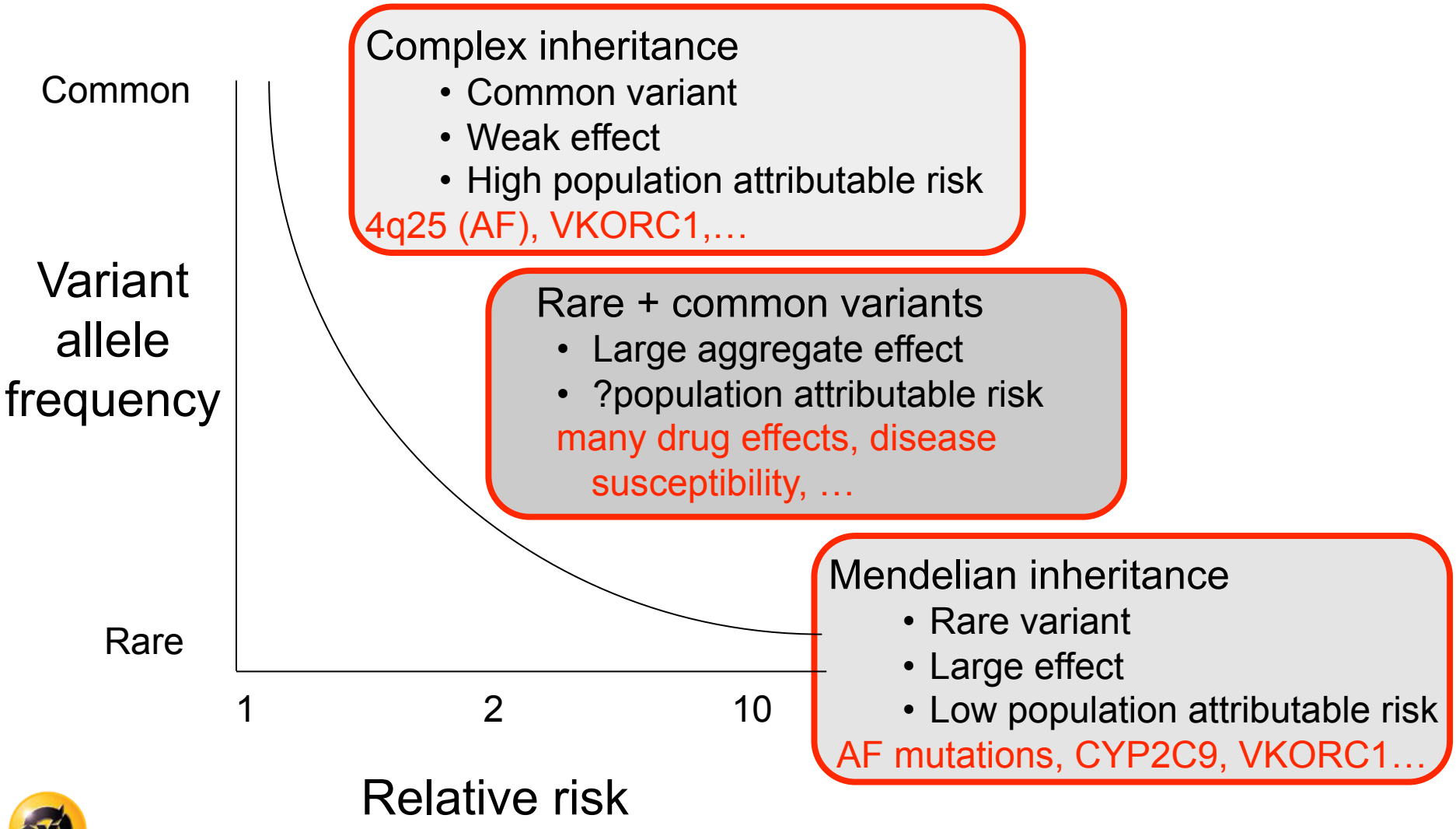


"wild-type": …TACGCGCCC----------ATCGCGCCCGGC…

mutation: …TACGCGCCCATCGCGCCCATCGCGCCCGGC…

Allele frequencies and risk in families and populations



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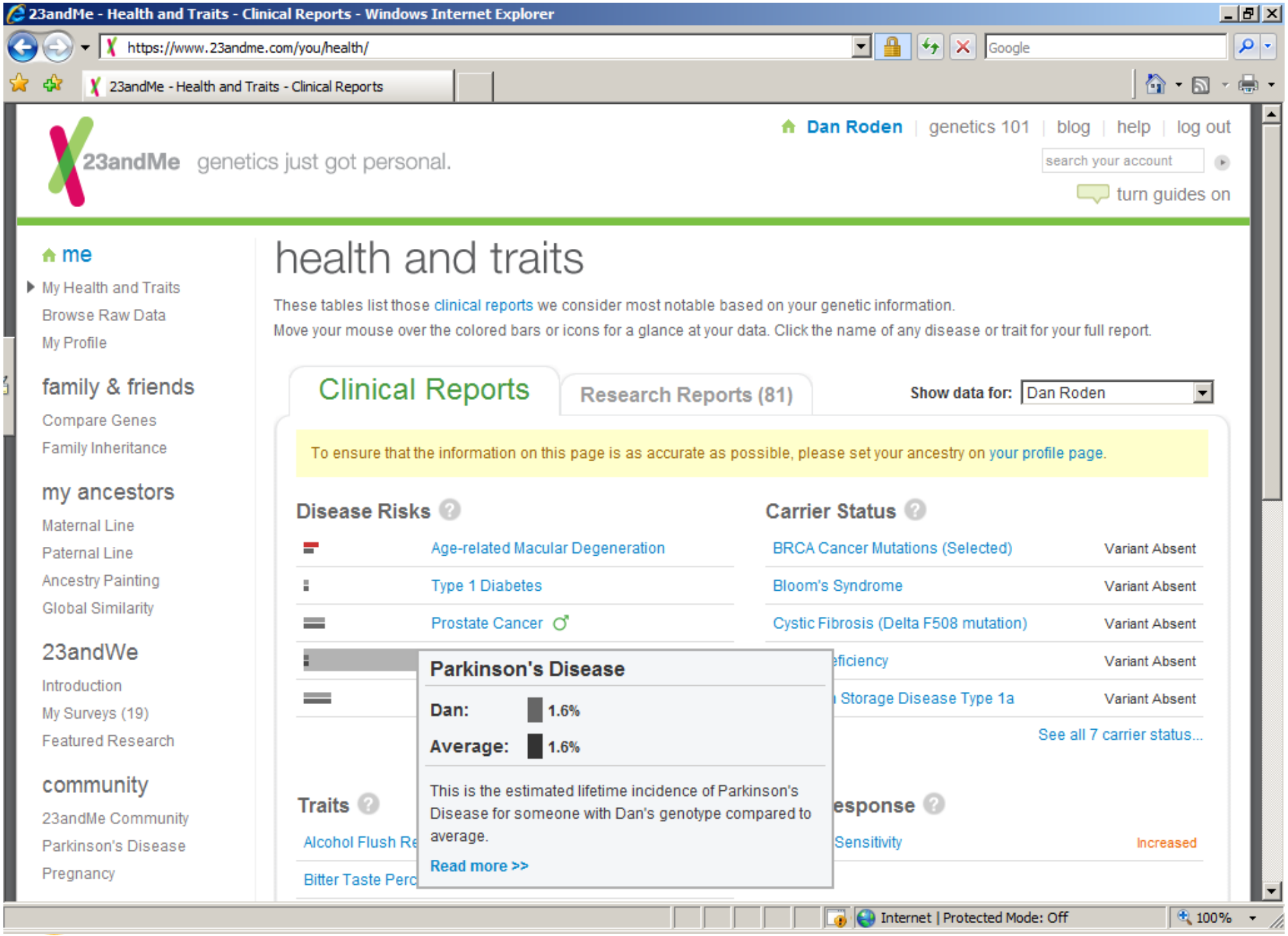
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Browse Raw Data
My Profile
family & friends
Compare Genes
Family Inheritance
my ancestors
Maternal Line
Paternal Line
Ancestry Painting
Global Similarity
23andWe
Introduction
My Surveys (19)
Featured Research
community
23andMe Community
Parkinson's Disease
Pregnancy
health and traits
These tables list those clinical reports we consider most notable based on your genetic information.
Move your mouse over the colored bars or icons for a glance at your data. Click the name of any disease or trait for your full report.
Clinical Reports
Research Reports (81)
Show data for: Dan Roden
To ensure that the information on this page is as accurate as possible, please set your ancestry on your profile page.
Disease Risks
Age-related Macular Degeneration
Type 1 Diabetes
Prostate Cancer
Parkinson's Disease
Dan: 1.6%
Average: 1.6%
This is the estimated lifetime incidence of Parkinson's Disease for someone with Dan's genotype compared to average.
Read more >>
Carrier Status
BRCA Cancer Mutations (Selected) Variant Absent
Bloom's Syndrome Variant Absent
Cystic Fibrosis (Delta F508 mutation) Variant Absent
eficiency Variant Absent
Storage Disease Type 1a Variant Absent
See all 7 carrier status...
Traits
Alcohol Flush Re
Bitter Taste Perc
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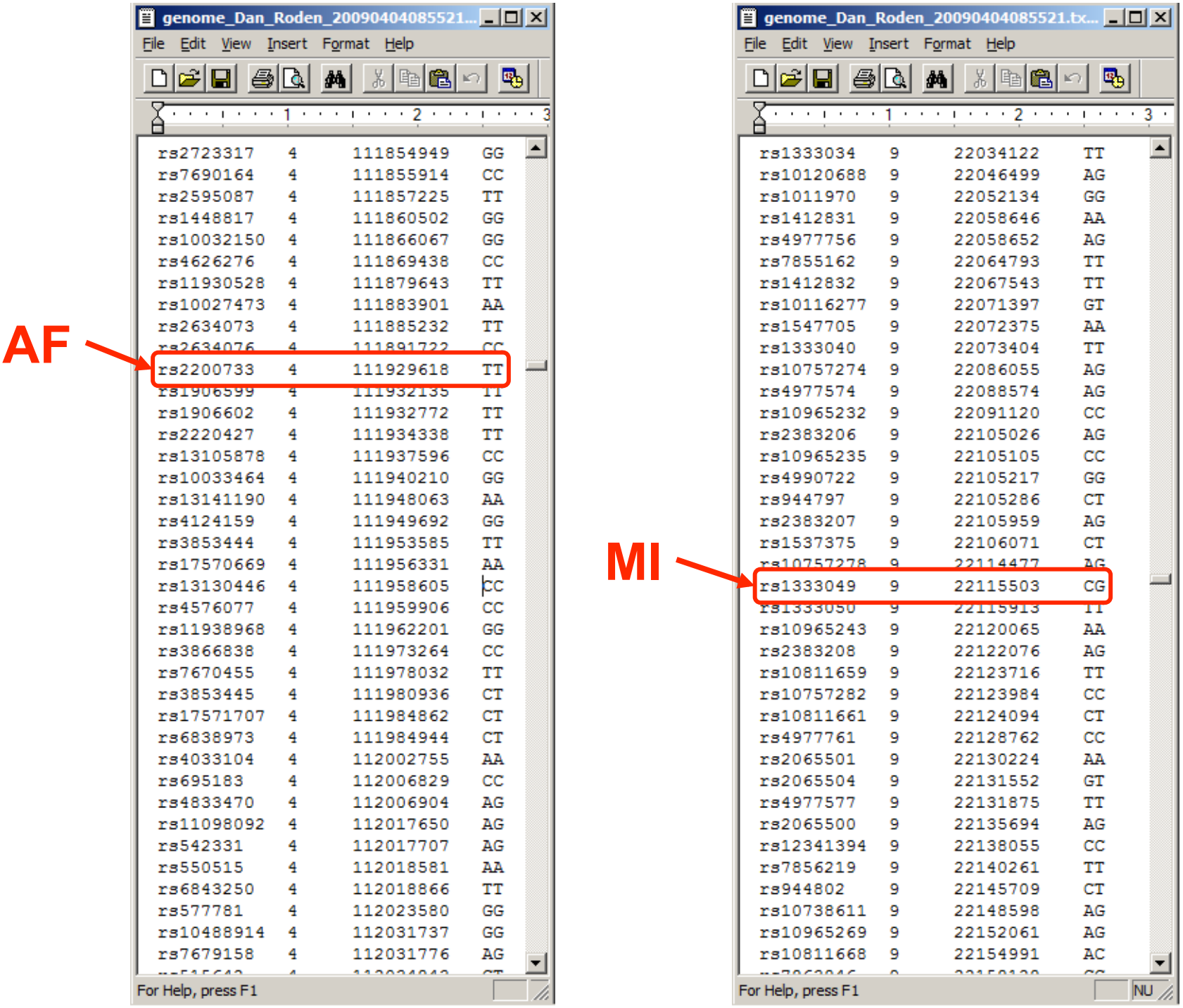
Sensitivity Increased
Internet | Protected Mode: Off
100%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rs11930528 4 111879643 TT
rs10027473 4 111883901 AA
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rs6838973 4 111984944 CT
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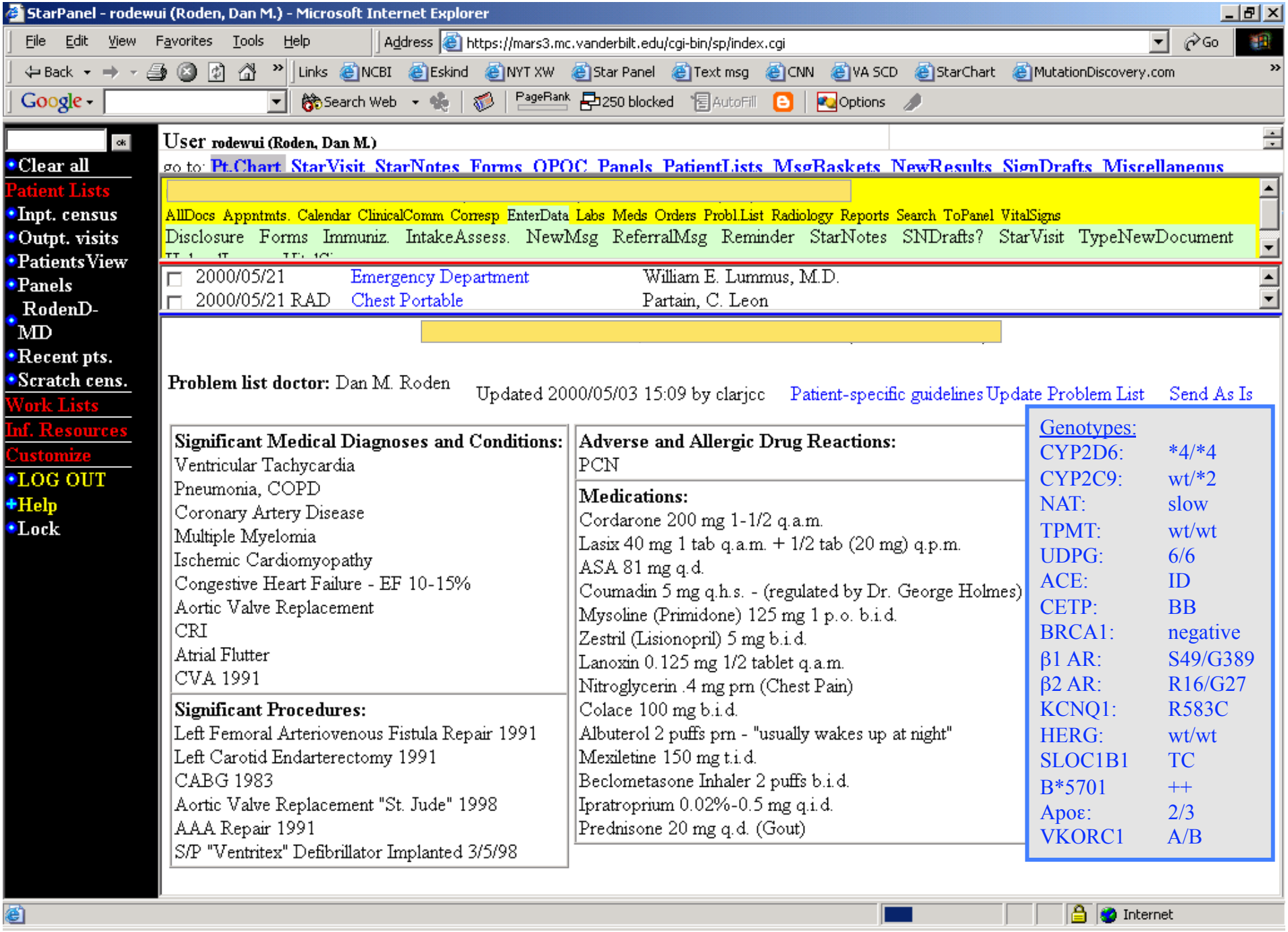
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Update Problem List
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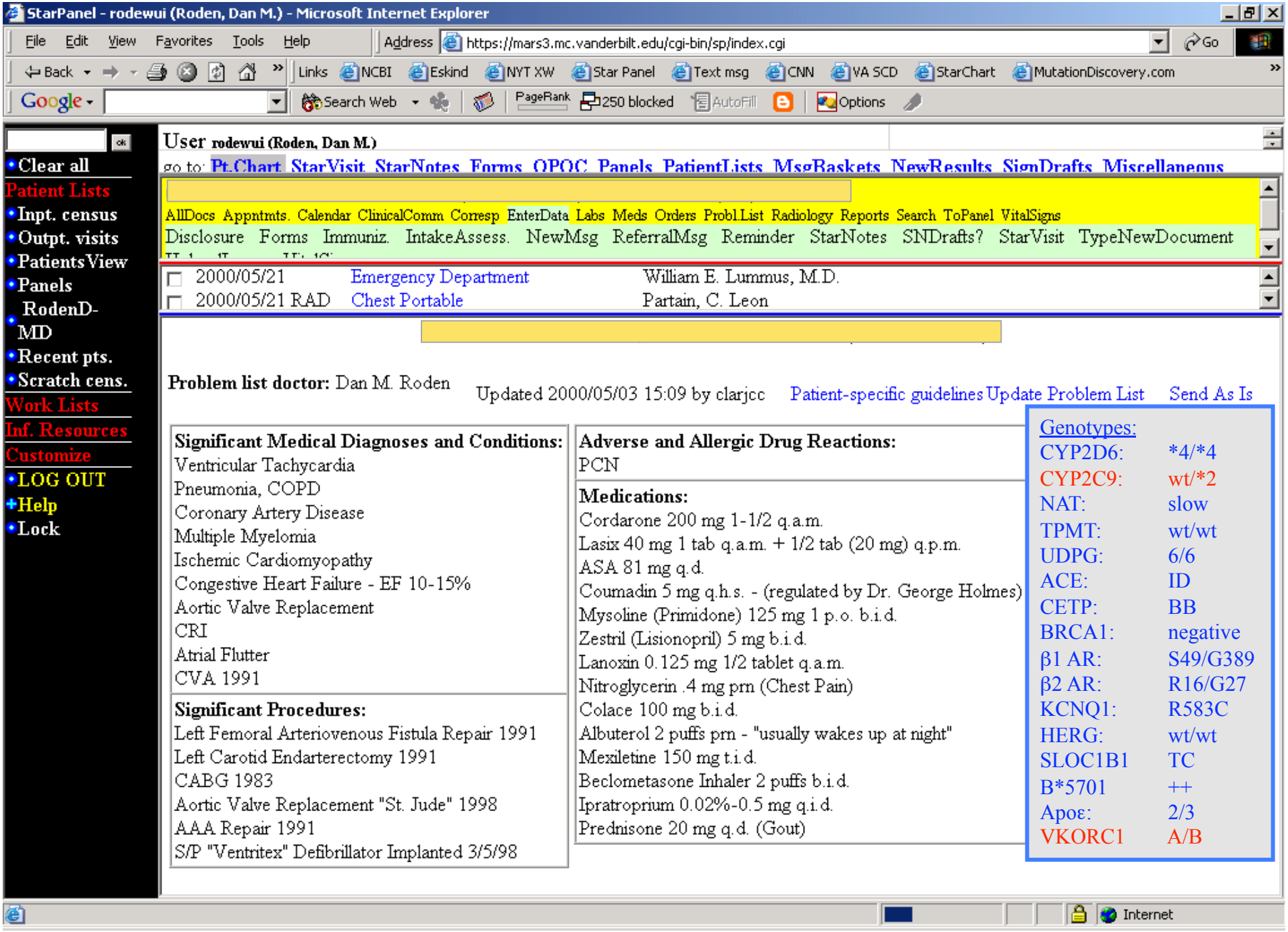
S/P "Ventritex" Defibrillator Implanted 3/5/98
Adverse and Allergic Drug Reactions:
PCN
Medications:
Cordarone 200 mg 1-1/2 q.a.m.
Lasix 40 mg 1 tab q.a.m. + 1/2 tab (20 mg) q.p.m.
ASA 81 mg q.d.
Coumadin 5 mg q.h.s. - (regulated by Dr. George Holmes)
Mysoline (Primidone) 125 mg 1 p.o. b.i.d.
Zestril (Lisionopril) 5 mg b.i.d.
Lanoxin 0.125 mg 1/2 tablet q.a.m.
Nitroglycerin .4 mg prn (Chest Pain)
Colace 100 mg b.i.d.
Albuterol 2 puffs prn - "usually wakes up at night"
Mexiletine 150 mg t.i.d.
Beclometasone Inhaler 2 puffs b.i.d.
Ipratroprium 0.02%-0.5 mg q.i.d.
Prednisone 20 mg q.d. (Gout)
Genotypes:
CYP2D6: *4/*4
CYP2C9: wt/*2
NAT: slow
TPMT: wt/wt
UDPG: 6/6
ACE: ID
CETP: BB
BRCA1: negative
β1 AR: S49/G389
β2 AR: R16/G27
KCNQ1: R583C
HERG: wt/wt
SLOC1B1 TC
B*5701 ++
Apoε: 2/3
VKORC1 A/B
Internet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HERG: wt/wt
SLOC1B1 TC
B*5701 ++
Apoε: 2/3
VKORC1 A/B
Internet

2000: one draft human genome sequence, 10+ years, $2.7 billion

2010: A full human genome in 4 minutes, $1000

The Race to Read Genomes on a Shoestring, Relatively Speaking

By ANDREW POLLACK FEB. 9, 2008

A person wanting to know his or he genetic blueprint can already have it d $350,000.

But whether a personal genome r comes affordable to the rest of us co on efforts like the one taking place s nondescript Silicon Valley industrial p Pacific Biosciences has been developi sequencing machine that within a few y be able to unravel an individual's ent in minutes, for less than $1,000. Th plans to make its first public presenta the technology on Saturday.

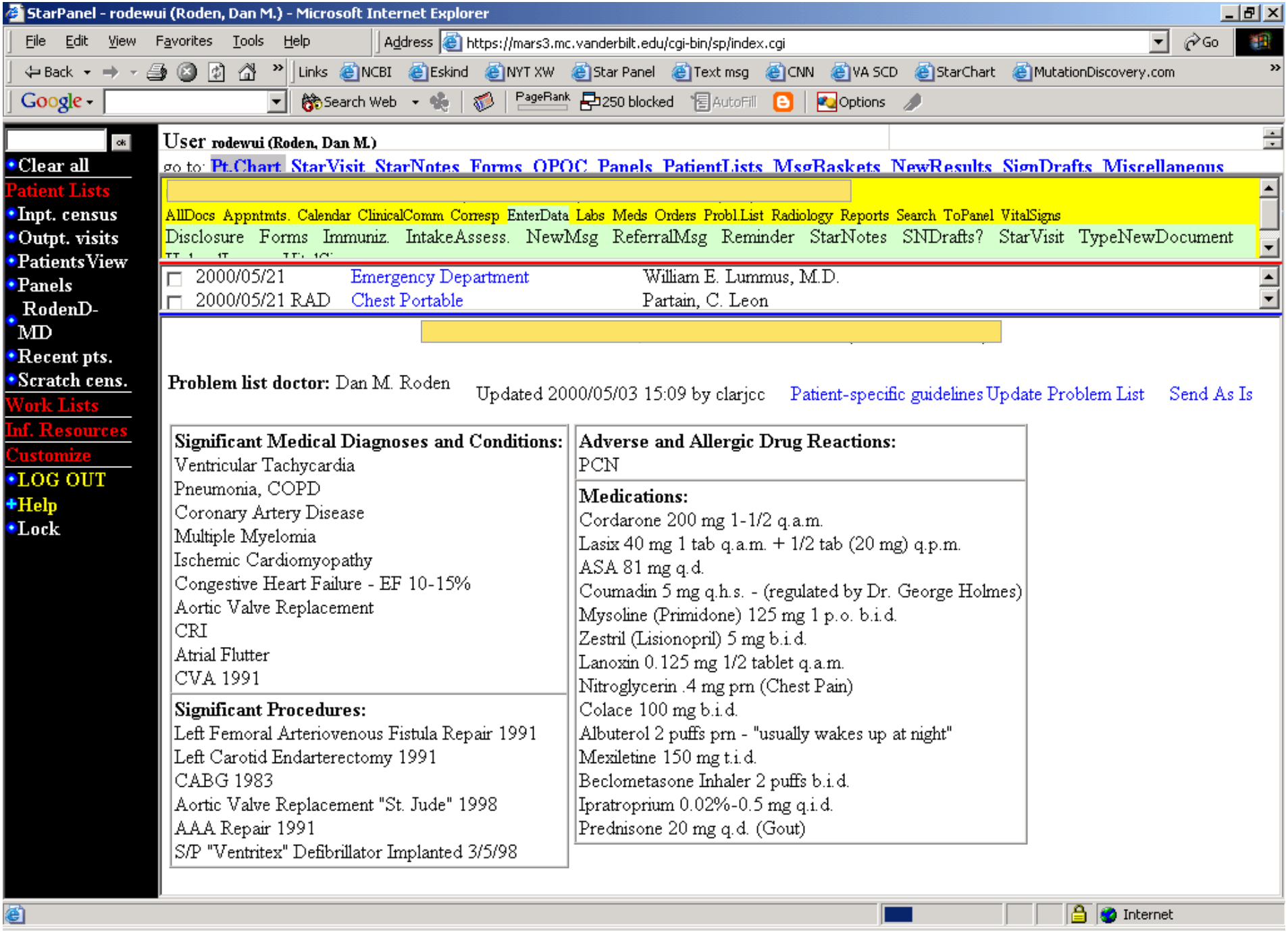
Technology / Genetics

The Jiffy Lube of Genome Decoding

A new company promises to map your DNA while-U-wait—for only a few hundred bucks.

by Boonsri Dickinson

published online September 20, 2008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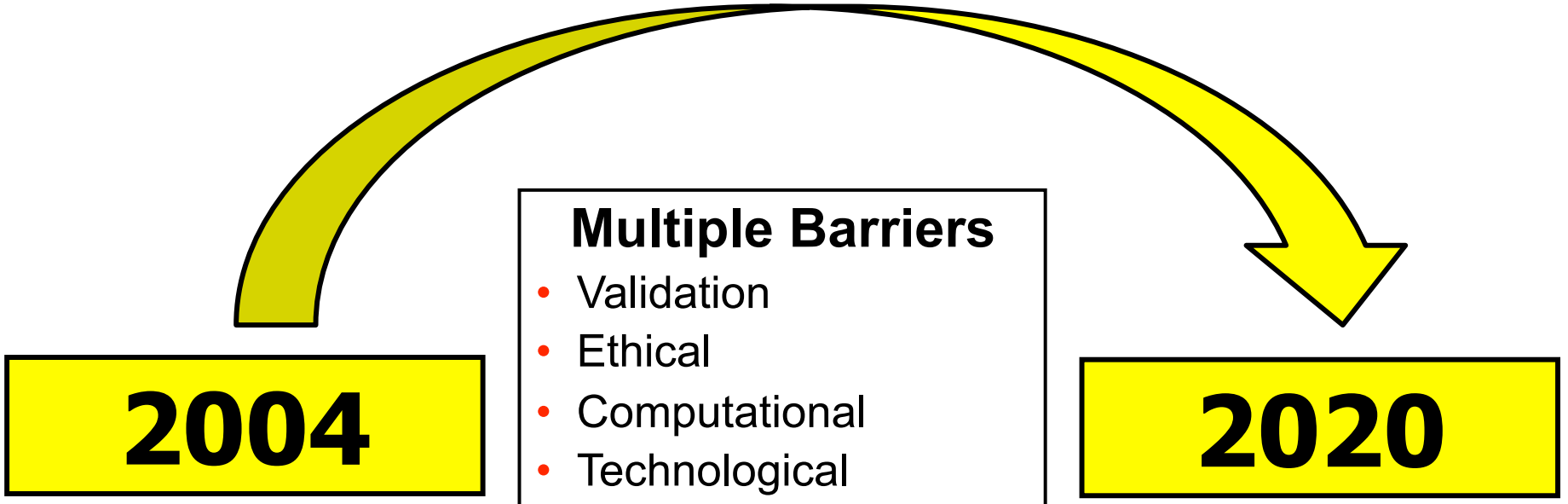
The Challenge: how to get from "2004" to "2020"



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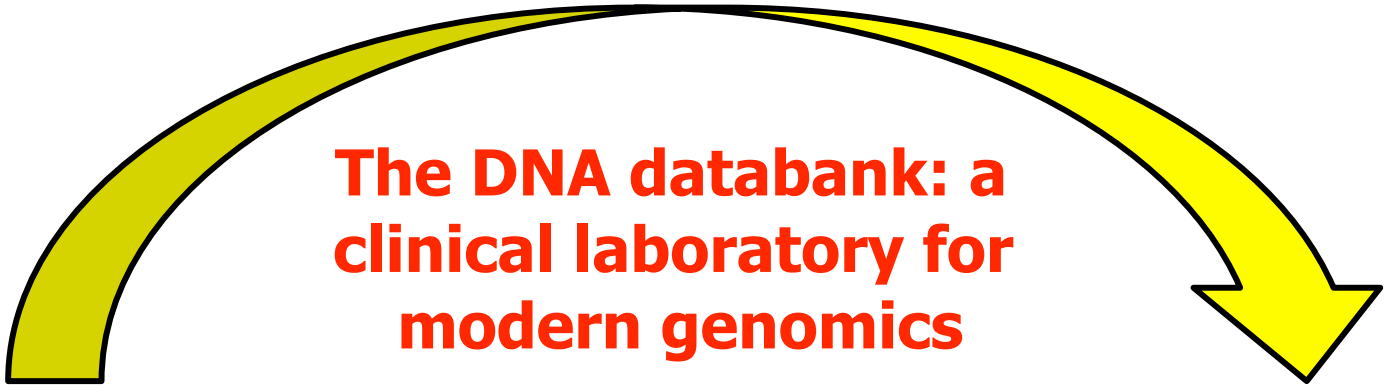


2004

Research efforts to find markers for Personalized Medicine

Vanderbilt BioVU

2020

routine patient visit: markers are part of the record

BioVU: Key implementation steps

- Federal Office for Human Research Protections (OHRP) guidelines allow use of de-identified discarded biologic samples in research
- Review by ethics committees, IRB, Community Advisory Board, OHRP, VUMC legal: designated “non-human subjects”
- Publicity to allow opt-out

MC 6360 (7/2005) - front

Vanderbilt University Medical Center

CONSENT FOR TREATMENT AND AGREEMENT TO PAY (ADULT)

Inpatient / Outpatient

I. **CONSENT FOR ROUTINE DIAGNOSTIC PROCEDURE AND MEDICAL TREATMENT**

I hereby consent to the performance of such diagnostic procedures and/or medical treatment as deemed necessary or advisable by my physician(s) at Vanderbilt University Medical Center, including the administration of blood products. I hereby consent to the performance of all nursing and technical procedures and tests as directed by my physician(s). Further, I understand that should any hospital or emergency medical personnel, physician, or other person(s) be exposed or report an exposure to my blood or body fluids, my blood will be tested for blood borne infections including Hepatitis B and C as well as HIV/AIDS. I am aware that the practice of medicine and surgery is not an exact science and I acknowledge that no guarantees have been made to me as a result of treatments or examination at Vanderbilt University Medical Center.

II. **AGREEMENT TO PAY**

I acknowledge and agree that I am responsible for and will pay for all regular charges, which are contained in the applicable VUMC price list ("chargemaster") which is in effect on the dates of services rendered, for items or services and treatment provided to me, including any amount not paid by my insurance plan. I understand that I can request additional information about charges for procedures, devices, pharmaceuticals, and other items or services, or can obtain a non-binding estimate prior, or subsequent, to signing this agreement.

I understand that some items or services that VUMC may provide to me may not be covered by my insurance carrier, and I agree to be personally responsible for any such non-covered items or services or items or services in excess of the limits in my member benefit agreement. Examples of items or services that may be deemed to be non-covered include cosmetic, transplant, certain durable medical equipment, personal convenience items, private nursing duty, sitter services, and certain medical supplies. I understand that I am personally responsible for any item or service determined by my third party payor (my insurance company) to be experimental, investigational, or to be non-covered for any other reason.

I understand that I am personally responsible for any non-covered Medicare, Medicaid, TennCare, or TriCare/CHAMPUS items or services that are listed on the financial responsibility form non-covered items or services form. I understand that I am personally responsible for deductibles and co-insurance established by my member benefit agreement, including those required for in-network laboratory and other ancillary services or items.

I hereby agree that if VUMC has agreed to bill my insurance or other third-party carrier, it has agreed to do so as a courtesy, and that VUMC has the right, should VUMC deem it advisable, to demand payment in full from me at any time prior to full payment from any insurance or third-party carrier, unless VUMC and my insurance company or third party carrier have agreed that I will not be billed.

I understand and agree that I have been advised that I may be billed by VUMC and that this Assignment of Benefits and Agreement to Pay applies to any and all VUMC physician services and both inpatient and outpatient VUMC hospital accounts. If a delinquent account referred for collection, I agree to pay the reasonable attorney's fees, court

MC 6360 (7/2005) - back

Vanderbilt University Medical Center

CONSENT FOR TREATMENT AND AGREEMENT TO PAY (ADULT)

Inpatient / Outpatient

IV. **GUARANTOR AGREEMENT** - By signing in the space below as Patient/Legal Representative or Guarantor, I hereby agree that all charges connected with this treatment or any other treatment rendered to the above patient past or future, not covered by any insurance program, sponsorship or other third party coverage, I may have are due and payable at the time of discharge or discontinuation of treatment. I understand that upon request I may be given a non-binding estimate of my hospital charges. I hereby acknowledge that if Vanderbilt University Medical Center has agreed to bill my insurance or other third party carrier, it has agreed to do so as a courtesy and that Vanderbilt has the right, should Vanderbilt deem it advisable, to demand payment in full from me at any time prior to full payment from any insurance or third party carrier, unless Vanderbilt and my insurance company or third party carrier have agreed that I will not be billed. I hereby acknowledge having been told that I may be billed by Vanderbilt and that this assignment and guarantor agreement shall be allowed to cover any and all accounts, including Vanderbilt physician accounts. If the delinquent account is referred for collection, I agree to pay the attorney's fees, court costs and/or collection agency fees associated with the collection process.

V. **Valuable Belongings** - By signing in the space below as Patient/Legal Representative, I acknowledge that I have been given an opportunity to deposit valuables and money for safekeeping. I understand that the hospital assumes no responsibility for personal items or valuables retained by the patient.

VI. **USE, RETENTION AND DISPOSAL OF TISSUE AND BLOOD**

I understand and agree that any specimens or tissues normally removed from my body by VUMC in the course of any diagnostic procedures, surgery, or medical treatment that would otherwise be disposed of may be retained, used for educational purposes or research, including research on the genetic material (DNA) or other information contained in those tissues or specimens.

I acknowledge that such research by VUMC may result in new inventions that may have commercial value and I understand that there are no plans to compensate me should this occur, regardless of the value of any such invention.

I understand that any research using those leftover specimens or tissues will be done in a way that will not identify me or my medical information.

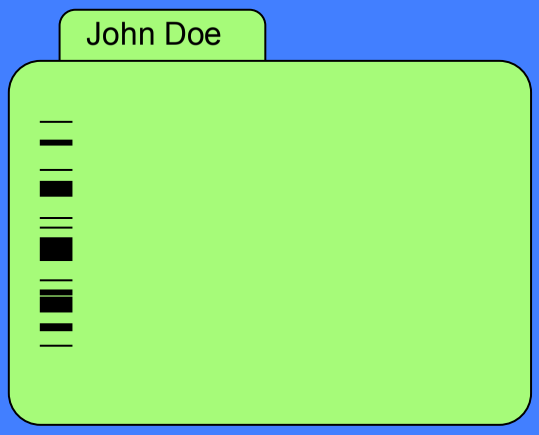
I also understand that if I do not want DNA research to be done using my leftover blood, I need to check the box shown below. If you have questions, please call 1-866-436-4710.

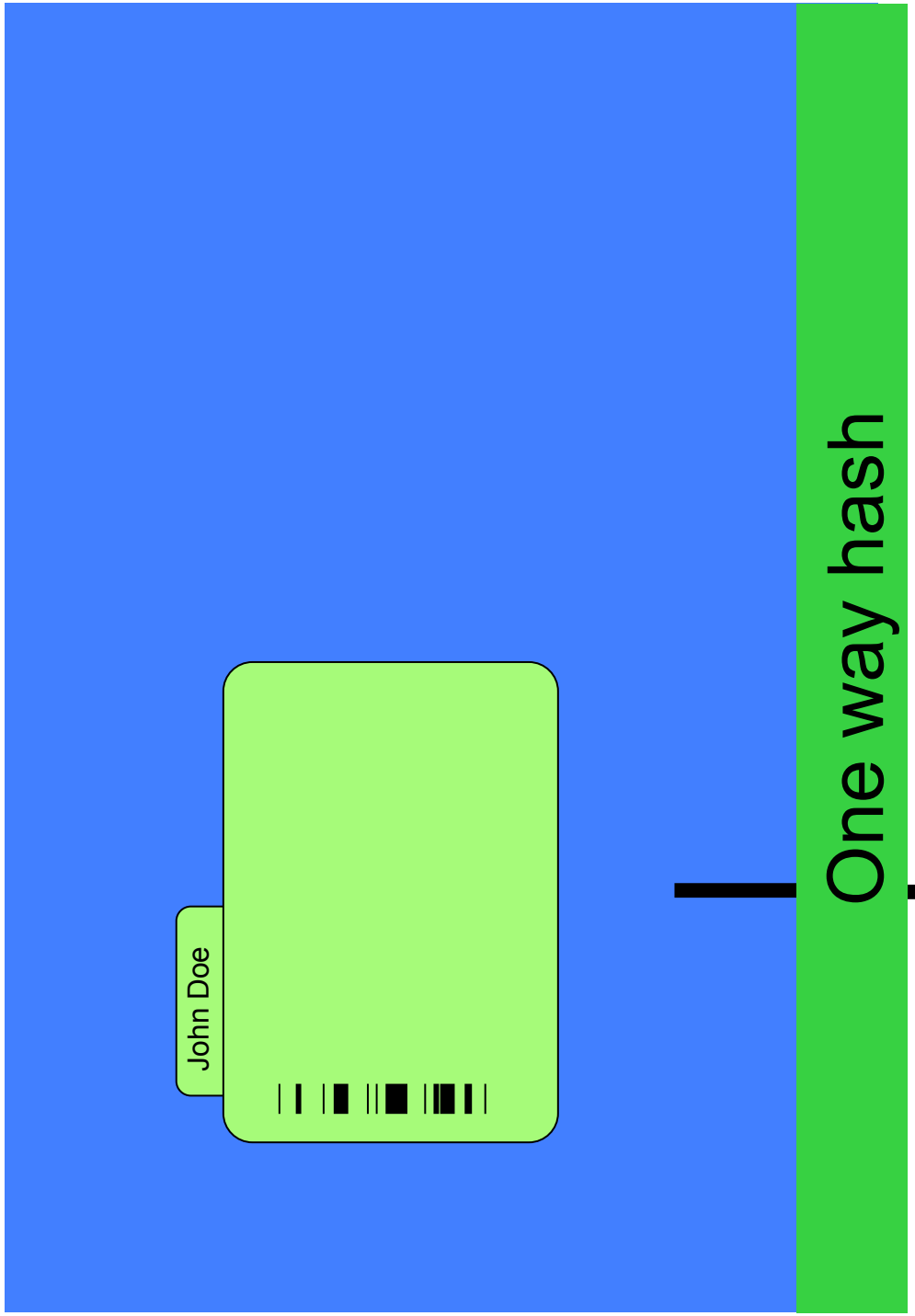
☐ *Do not use my leftover blood for the DNA Databank*

PLEASE READ THIS ENTIRE AUTHORIZATION PRIOR TO SIGNING

I also understand that if I do not want DNA research to be done using my leftover blood, I need to check the box shown below. If you have questions, please call 1-866-436-4710.

☐ ***Do not use my leftover blood for the DNA Databank***


John Doe



One way hash

1. Given same input (medical record #), always generates the same output
2. Given the output, it is not possible to regenerate the input

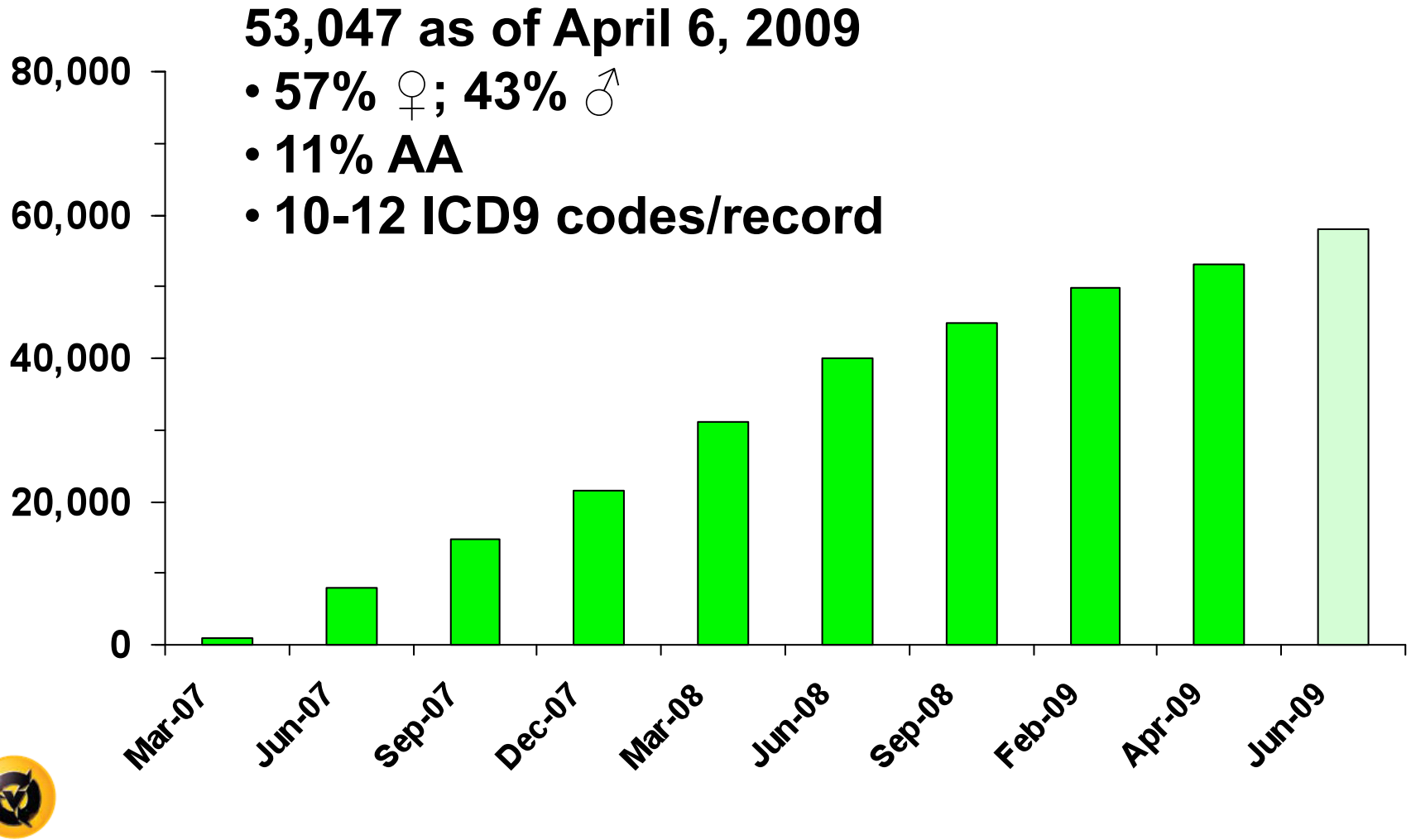
1.4 million records; fall 2006

The SD: updated weekly

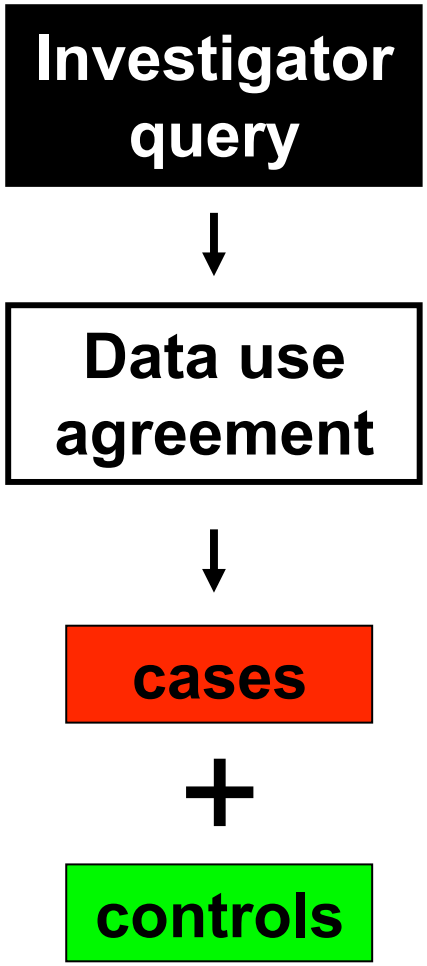
1.4 million records; fall 2006

The SD: updated weekly

Cumulative sample accrual: current and projected



One way hash



One way hash

Investigator query

↓

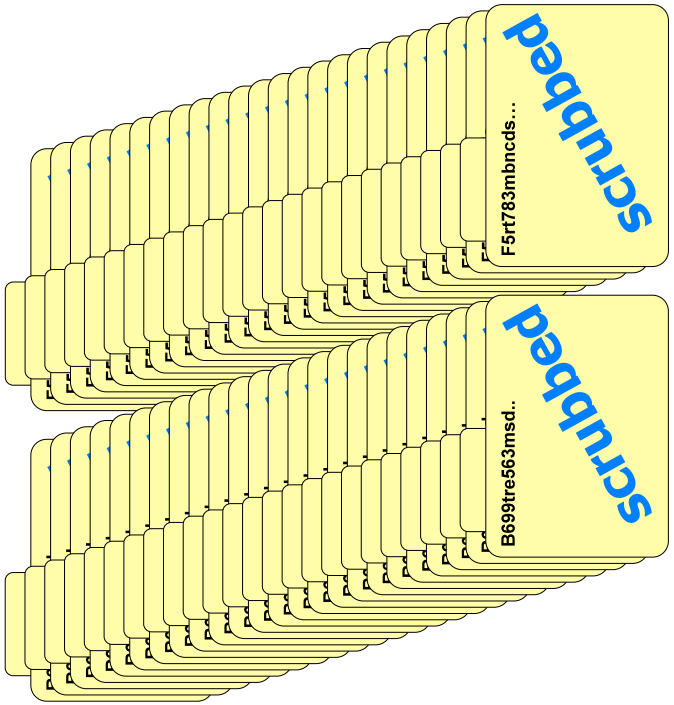
Data use agreement

↓

cases

+

controls



Data analysis

BioVU Record Counter Research Application | VUMC, Nashville, Tennessee - Windows Internet Explorer

https://www.mc.vanderbilt.edu/dnadatabank/RC/index.php

BioVU Record Counter Research Application | VUMC, ...

Record Counter

Search | **Results**

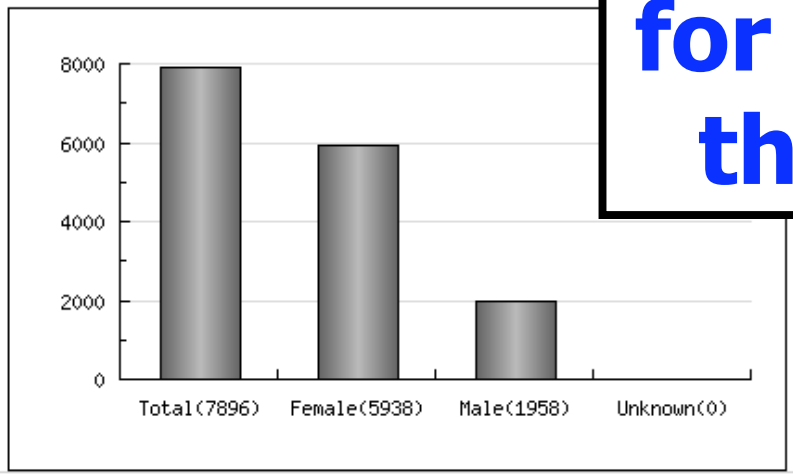
Help and Documentation | Video Tutorial

Search for RA in the SD

Delete Query

Date Created	Name
01/27/2009	RA all
01/23/2009	wasserman2
01/23/2009	wasserman1
01/16/2009	high HDL
01/16/2009	HCM
01/16/2009	HCM with DNA
01/16/2009	quinidine syncope
01/14/2009	CHF with DNA
01/14/2009	CHF all
01/12/2009	Pao set 1

Result Count - RA all



Criteria

Include Where (
ICD Include 714.0-Rheumatoid Arthritis, Arthritis Or Polyarthritis: Atrophic, Rheumatic (Chronic), Use Additional Code To Identify Manifestation, As: Myopathy (359.6), Polyneuropathy (357.1) or
ICD Include 714.2-Other Rheumatoid Arthritis With Visceral Or Systemic Involvement, Rheumatoid Carditis)

Limit By Dna Availability = false
Limit By Genotyping Status = false
Limit By Event Date = false

Details - RA all

Export to Excel

Gender	Total	Afr Amer	Asian	Cauc	Hisp	Nat Amer	Other	Unk
Age Group: ALL								
Male	1958	86	9	1266	15	3*	6	573
Female	5938	518	15	3690	37	6	25	1647
Unknown	0	0	0	0	0	0	0	0
Age Group: Under 2								
Male	29	3*	0	8	3*	0	3*	12

One way hash

Investigator query

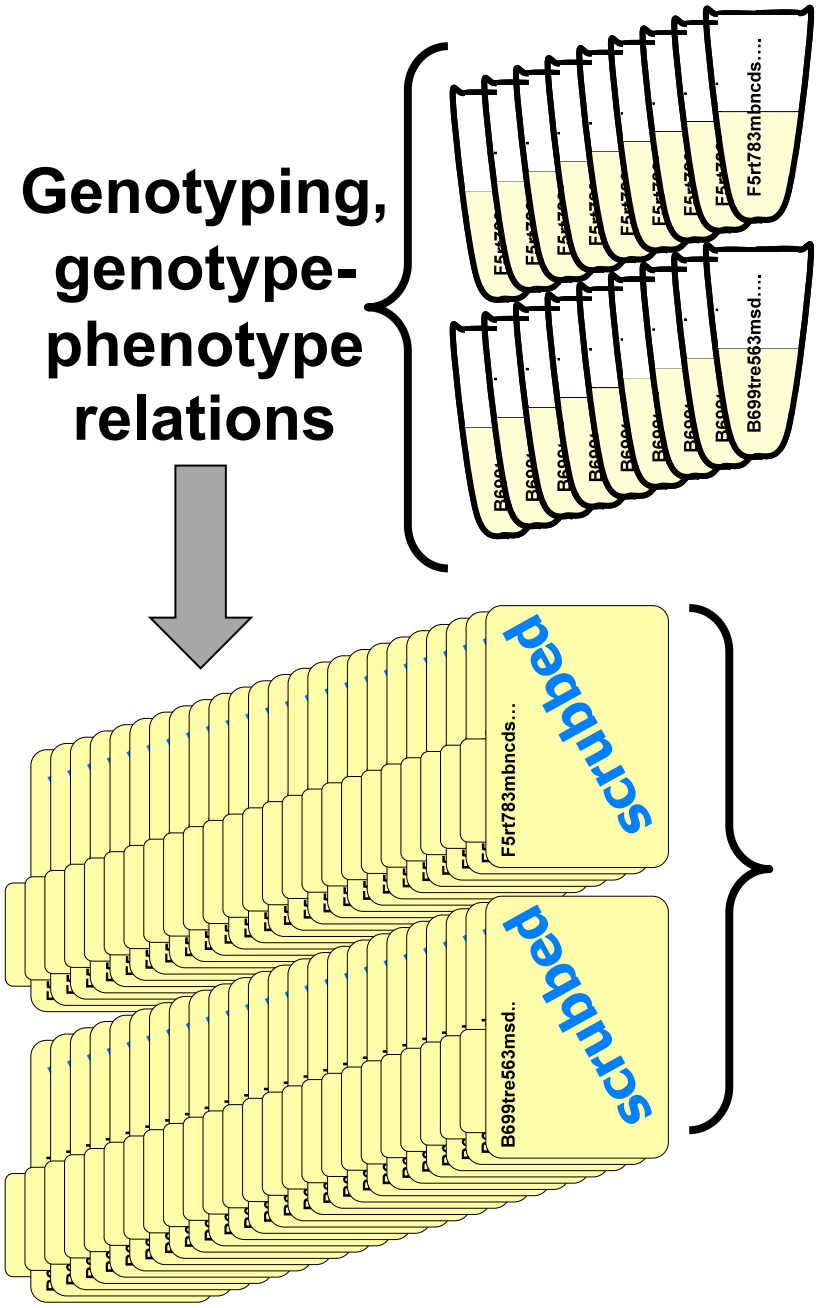
Data use agreement

cases

+

controls

Genotyping, genotype-phenotype relations

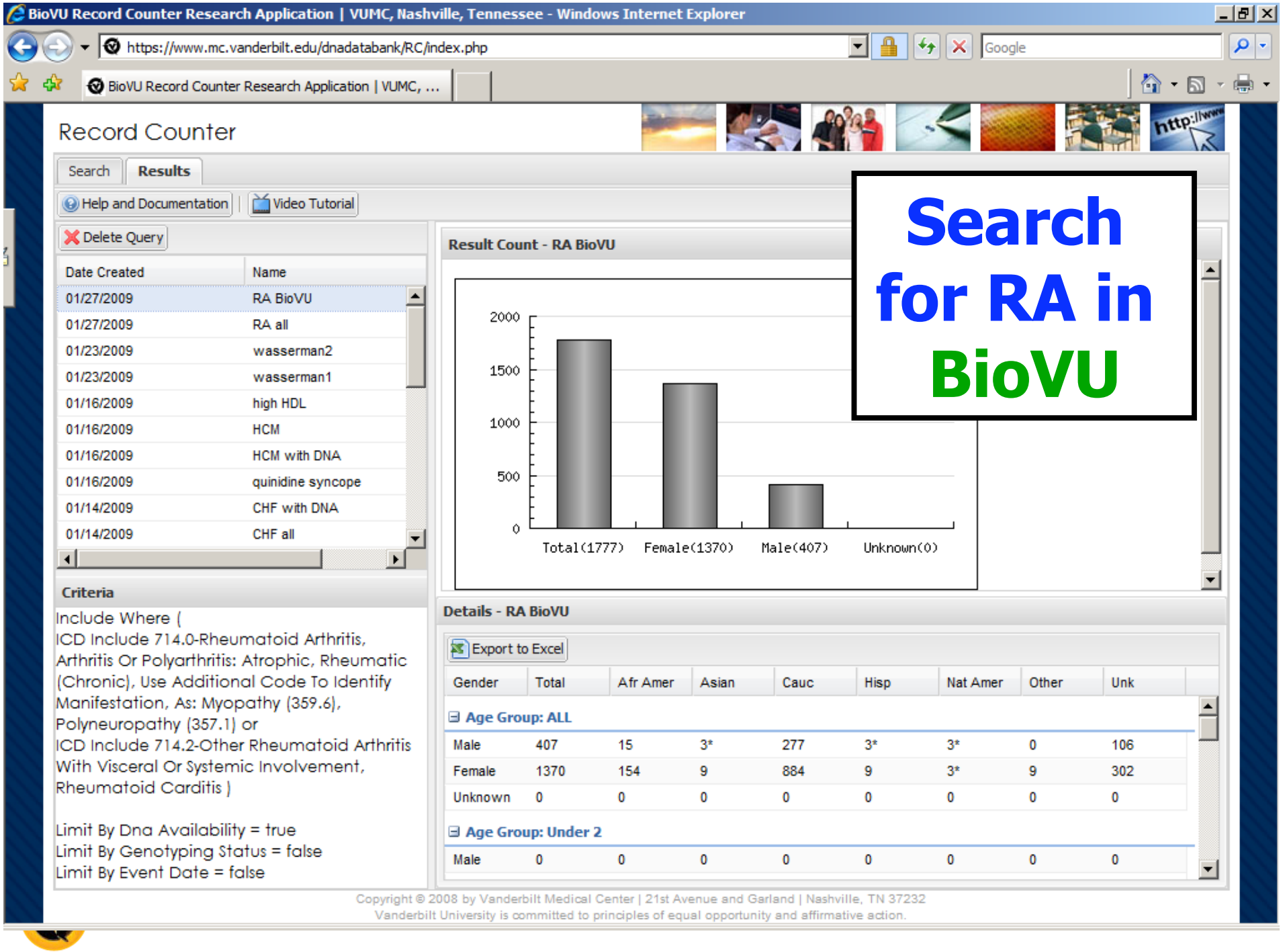


cases

+

controls

Sample retrieval


BioVU Record Counter Research Application | VUMC, Nashville, Tennessee - Windows Internet Explorer
https://www.mc.vanderbilt.edu/dnadatabank/RC/index.php
Google
BioVU Record Counter Research Application | VUMC, ...
Record Counter
Search
Results
Help and Documentation
Video Tutorial
Delete Query
Date Created
Name
01/27/2009 RA BioVU
01/27/2009 RA all
01/23/2009 wasserman2
01/23/2009 wasserman1
01/16/2009 high HDL
01/16/2009 HCM
01/16/2009 HCM with DNA
01/16/2009 quinidine syncope
01/14/2009 CHF with DNA
01/14/2009 CHF all
Criteria
Include Where (
ICD Include 714.0-Rheumatoid Arthritis, Arthritis Or Polyarthritis: Atrophic, Rheumatic (Chronic), Use Additional Code To Identify Manifestation, As: Myopathy (359.6), Polyneuropathy (357.1) or
ICD Include 714.2-Other Rheumatoid Arthritis With Visceral Or Systemic Involvement, Rheumatoid Carditis)
Limit By Dna Availability = true
Limit By Genotyping Status = false
Limit By Event Date = false
Result Count - RA BioVU
2000
1500
1000
500
0
Total(1777)
Female(1370)
Male(407)
Unknown(0)
Search for RA in BioVU
Details - RA BioVU
Export to Excel
Gender Total Afr Amer Asian Cauc Hisp Nat Amer Other Unk
Age Group: ALL
Male 407 15 3* 277 3* 3* 0 106
Female 1370 154 9 884 9 3* 9 302
Unknown 0 0 0 0 0 0 0 0
Age Group: Under 2
Male 0 0 0 0 0 0 0 0
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BioVU projects

Phase I
Gender match

Phase II
The simplest genotype/ phenotype match (e.g. sickle cell)

Sample handling algorithms validated

Phase III
Validate known associations

Phase III
New discovery: The VGER project

Phase IV
Widespread use by VU investigators

The BioVU "demonstration project"

- Genotype "high-value" SNPs in the first 10,000 samples accrued.
  - including SNPs associated by replicated genome-wide experiments with common diseases & traits

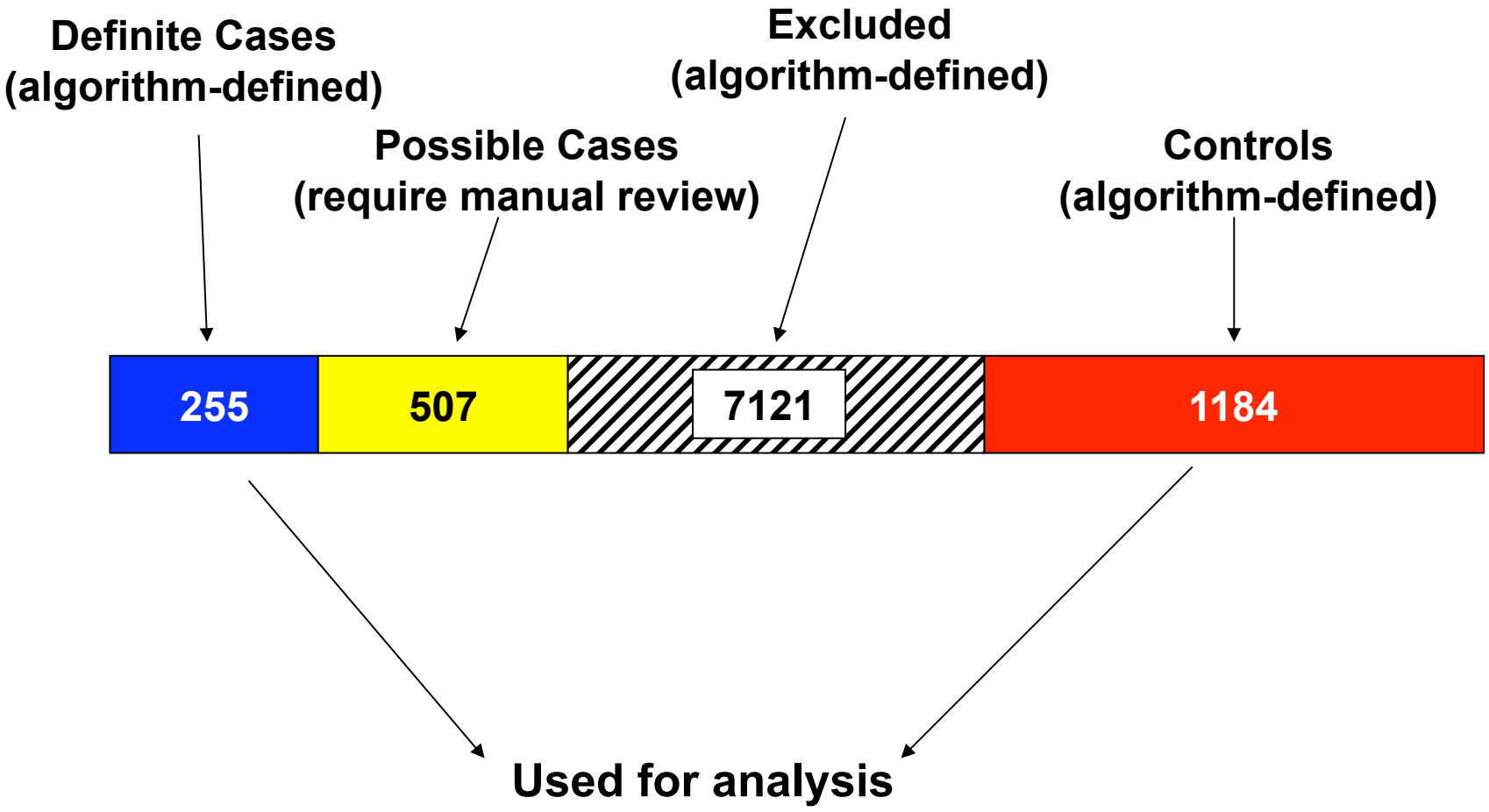
Atrial fibrillation	Alzheimer's Disease
Bipolar disorder	Breast cancer
Crohn's disease	MI at age <50
Prostate cancer	Rheumatoid arthritis
Type I Diabetes	Type II Diabetes

- Develop Natural Language Processing methods to identify cases and controls
- Are genotype-phenotype relations replicated?

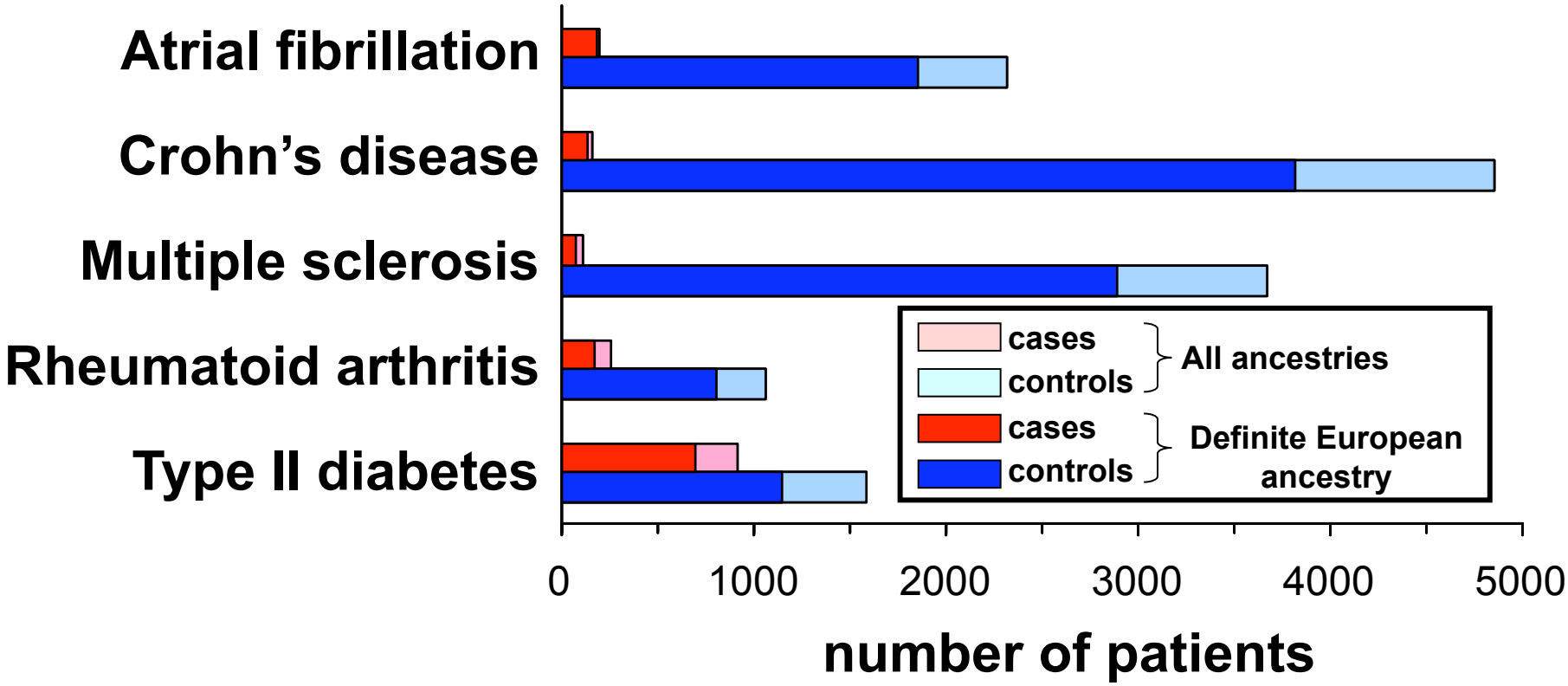
RA – Case Definition Evolution

#	Definition	# Cases	Problem
1	ICD9 codes for RA + Medications (only in problem list)	371	Found incomplete problem lists
2	Same as above but searched notes	411	Patients billed as RA but actually other conditions, overlap syndromes, juvenile RA
3	Above + require “rheumatoid arthritis” and small list of exclusions	358	Overlap syndromes with other autoimmune conditions, conditions in which physicians did not agree
4	Above + exclusion of other inflammatory arthritides	255	PPV = 97%; a few “possible RA” or family history items remained

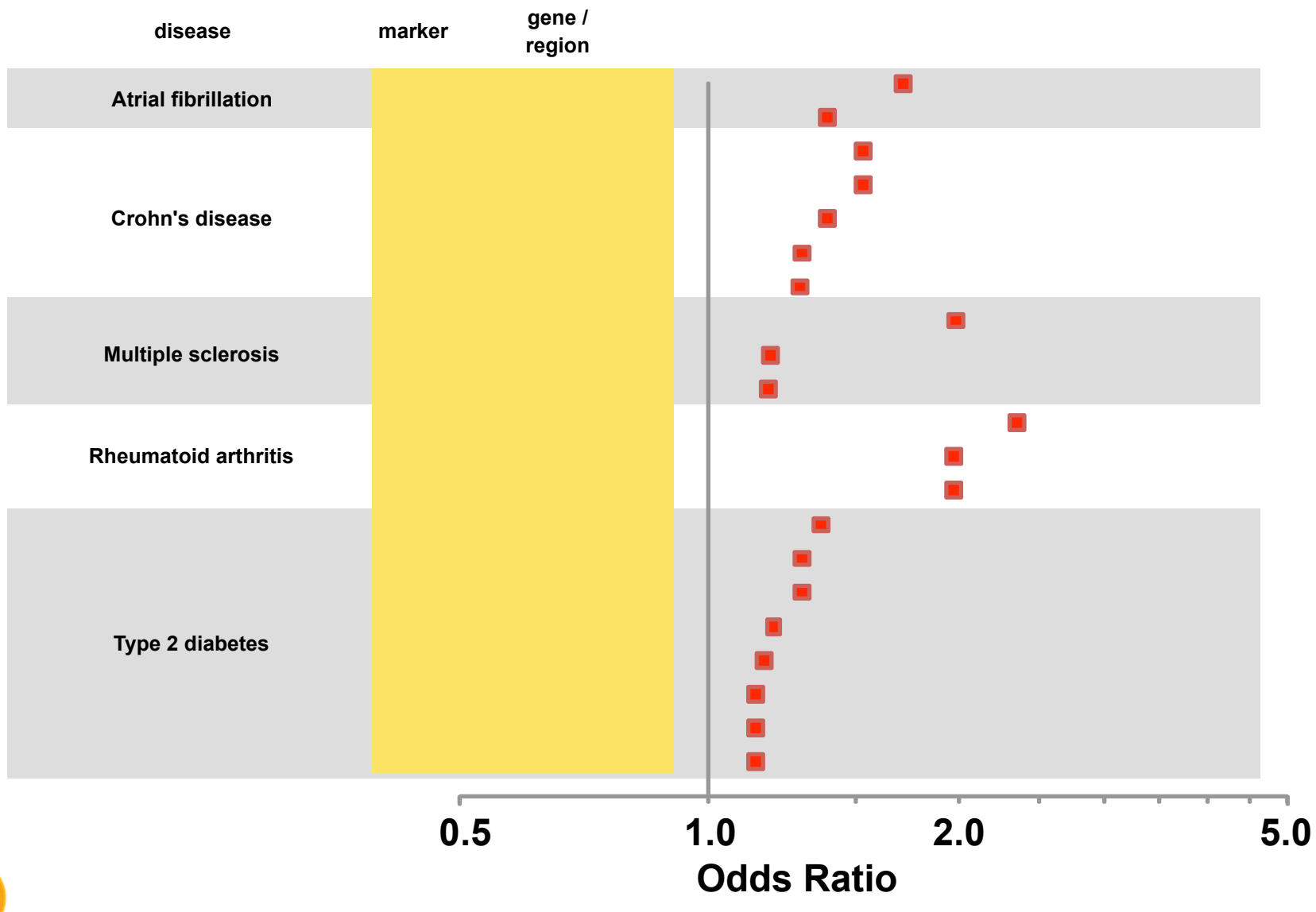
Finding cases: Rheumatoid Arthritis



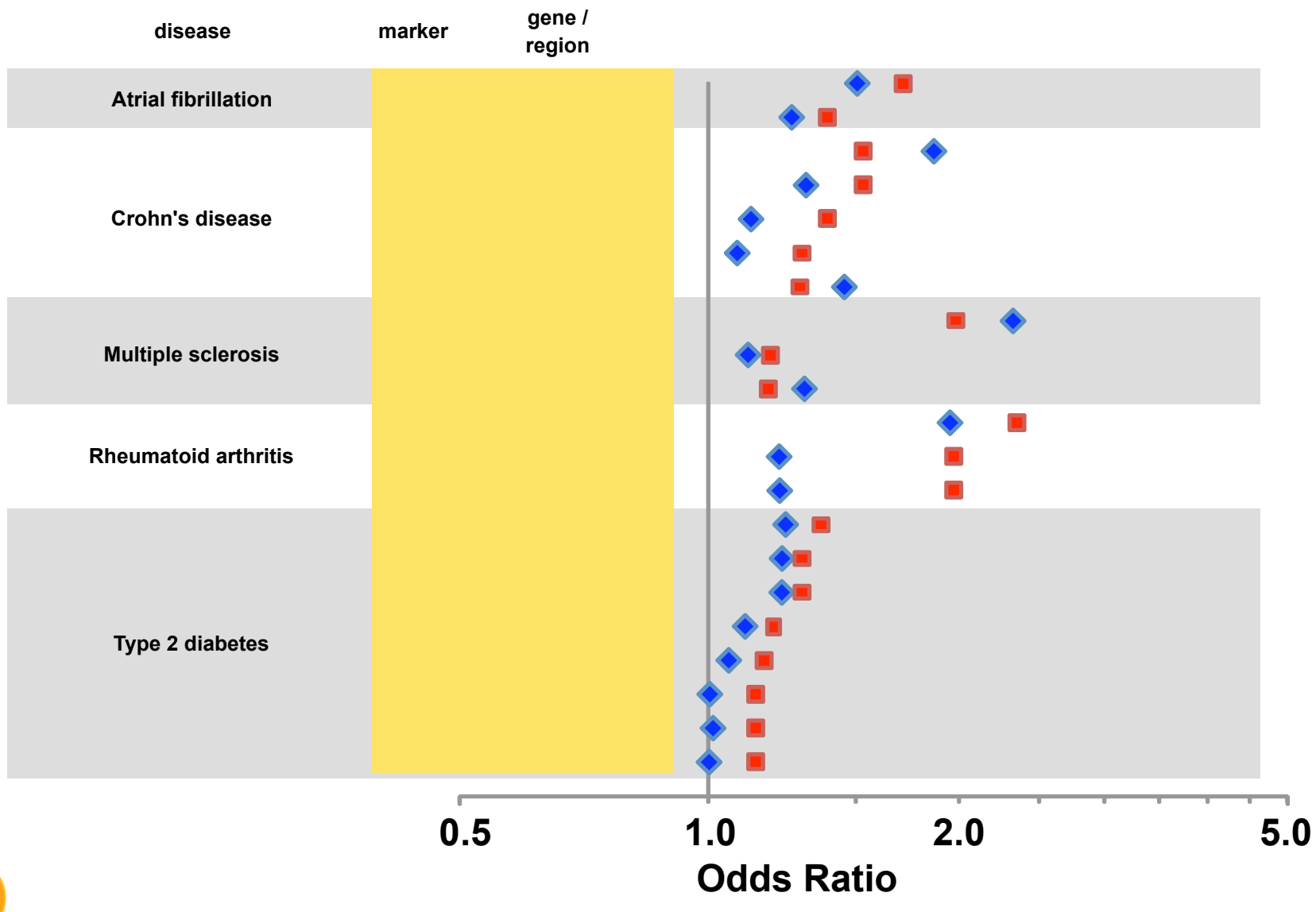
Finding cases



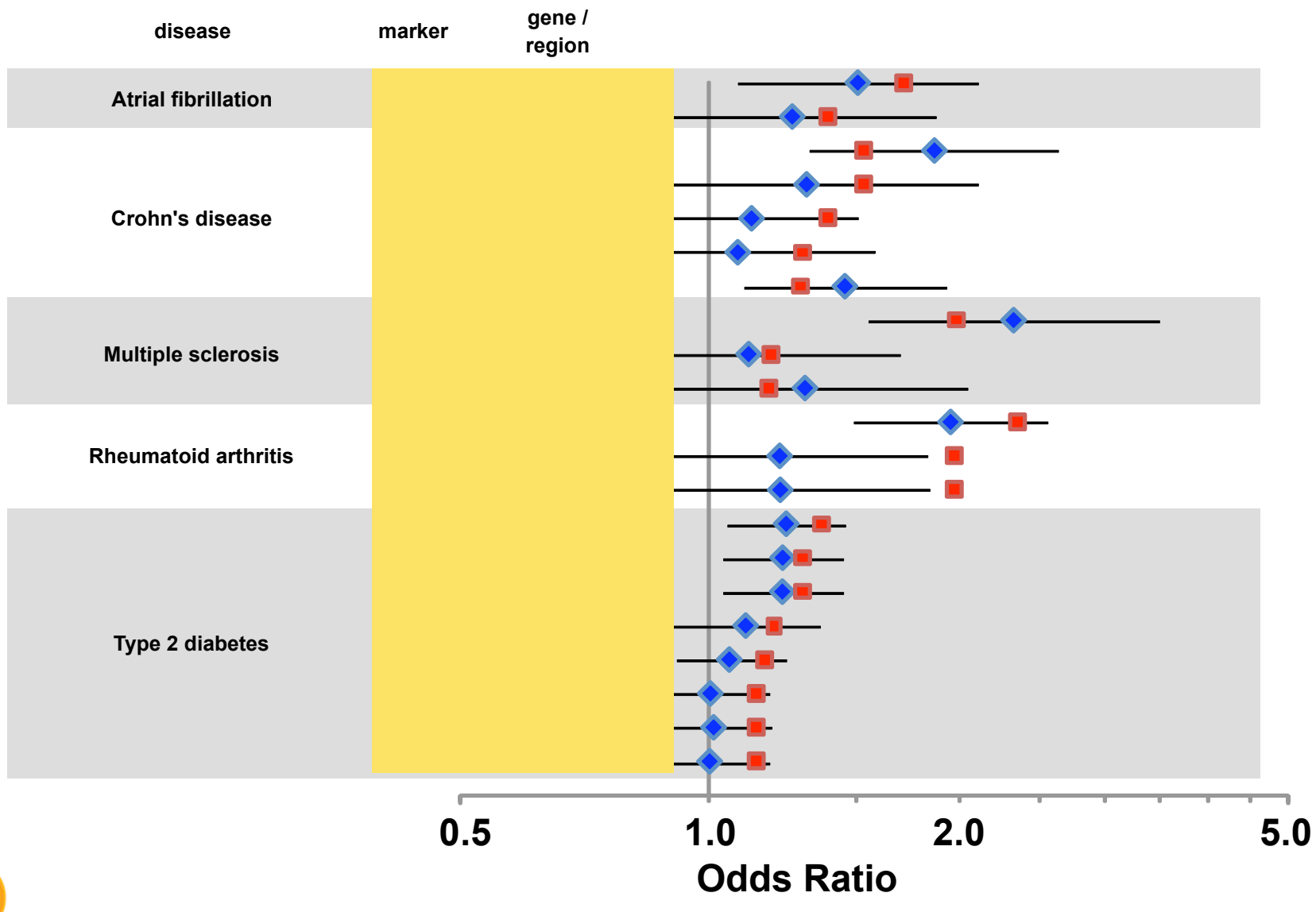
First results



First results



First results



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Phase III
Validate known associations

Phase III
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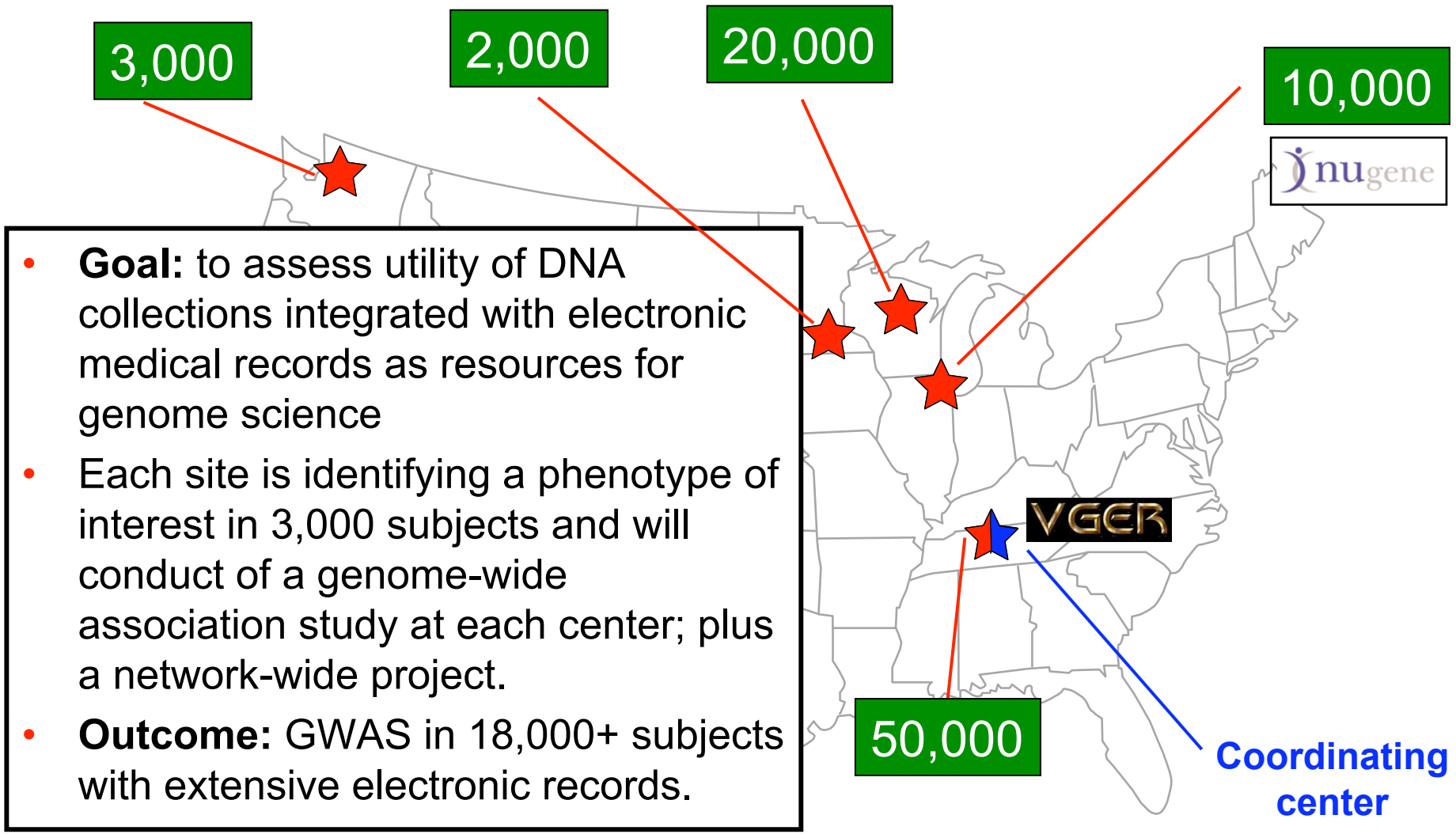
Phase IV
Widespread use by VU investigators

VGER The Vanderbilt Genome-Electronic Records Project

The eMERGE Network

electronic Medical Records & Genomics

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



- **Goal:** to assess utility of DNA collections integrated with electronic medical records as resources for genome science
- Each site is identifying a phenotype of interest in 3,000 subjects and will conduct of a genome-wide association study at each center; plus a network-wide project.
- **Outcome:** GWAS in 18,000+ subjects with extensive electronic records.

DNA repositories linked to Electronic Health Records

- Real world
- Large-scale
- Decreased time and cost to generate sample sets
- Learning how to best use the Electronic Record to incorporate genomic and other omic information into practice.
- Complexity of the sample sets: drug responses, gene x gene, multiple ethnicities, rare events…

Vanderbilt BioVU

PGRN

The *eMERGE* Network

electronic Medical Records & Genomics

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