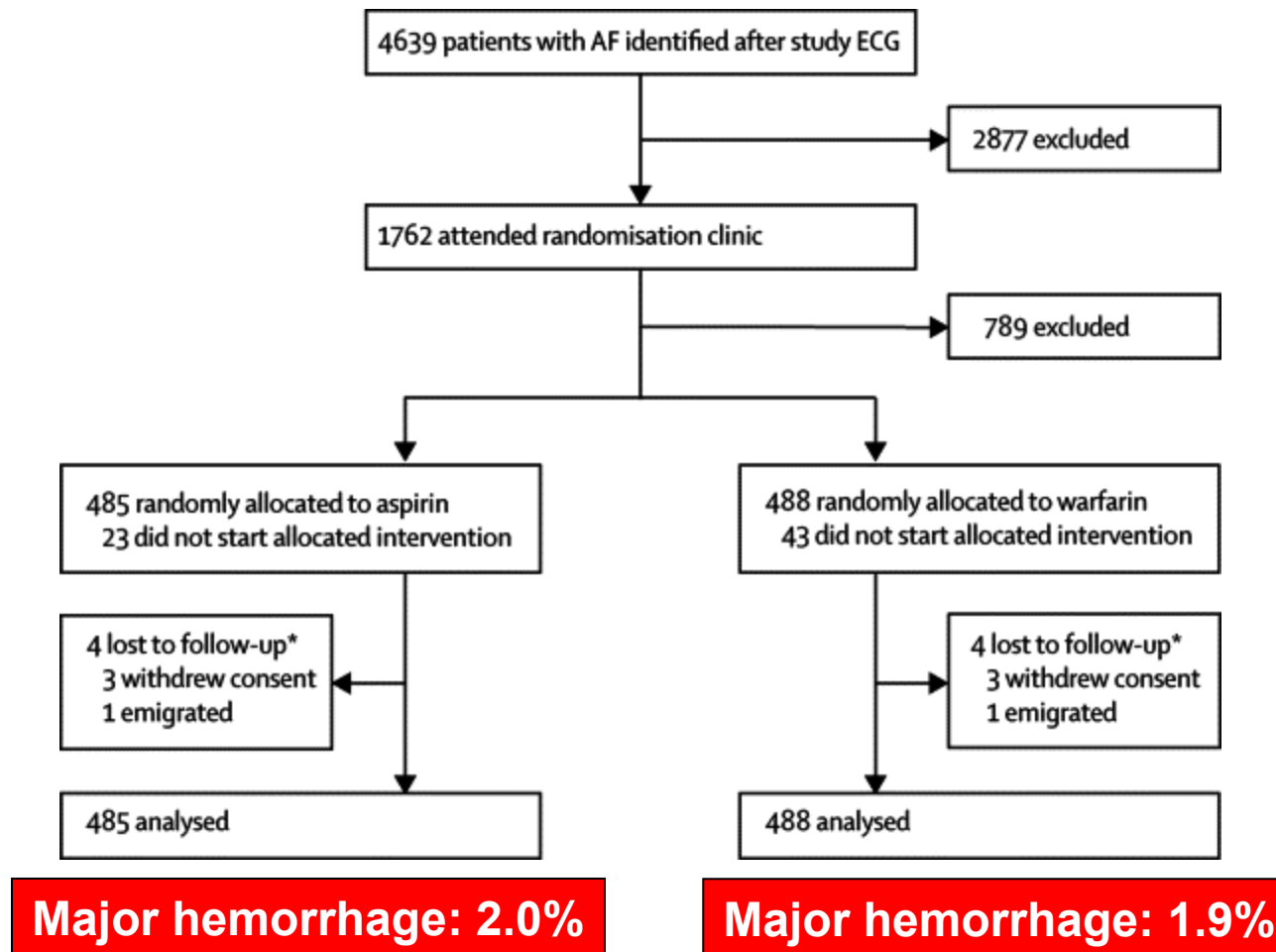


# Large biobanks as a tool for pharmacogenomics

Dan Roden

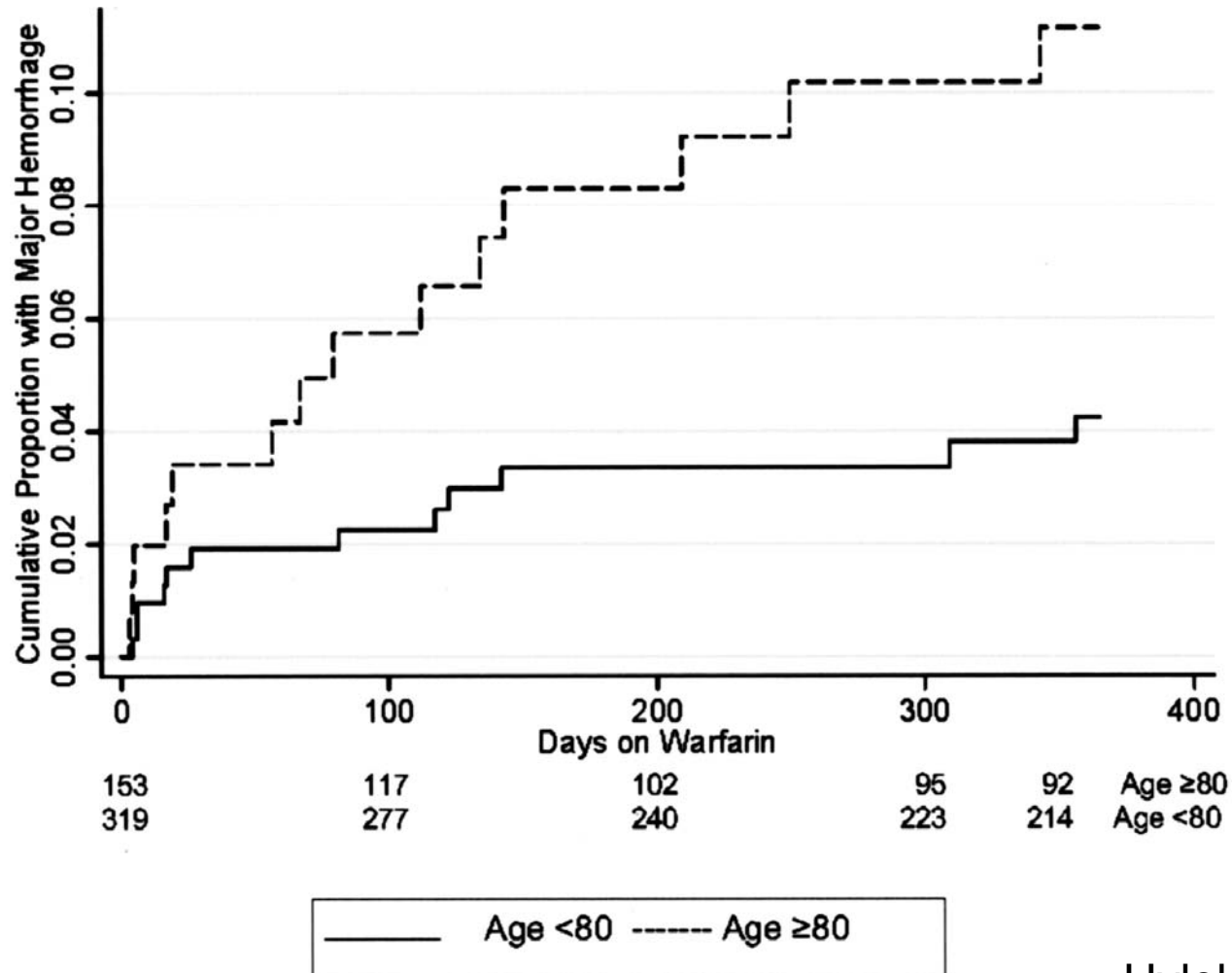


# A trial comparing warfarin to aspirin



# Bleeding during warfarin

## A consecutive inception cohort



# Pharmacogenomics of bleeding during warfarin - (1)

**Table 2: Observed bleeding complications (per 100 treatment-years) and hazard ratios (HR) for bleeding complications in patients having the CYP2C9 variant genotype.**

	Total	Variant genotype	Wild type genotype	HR (95% CI)	
				Unadjusted	Adjusted
Number patients	996	311	685		
Treatment-years	1311.7	390.9	920.7		
All bleeding	255 (19.4)	78 (20.0)	177 (19.2)	1.03 (0.79-1.34)	0.98 (0.75-1.29)
Minor bleeding	203 (15.5)	57 (14.6)	146 (15.9)	0.91 (0.67-1.24)	0.87 (0.64-1.18)
Major bleeding	52 (4.0)	21 (5.4)	31 (3.4)	1.58 (0.91-2.75)	1.57 (0.90-2.75)
Digestive tract	28 (2.1)	12 (3.1)	16 (1.7)	1.74 (0.83-3.69)	1.72 (0.81-3.66)
Intracranial	10 (0.76)	4 (1.0)	6 (0.65)	1.57 (0.44-5.57)	1.97 (0.53-7.29)
Hematuria	3 (0.23)	1 (0.26)	2 (0.22)	1.16 (0.11-12.8)	-
Muscle joint hematoma	2 (0.15)	1 (0.26)	1 (0.11)	2.35 (0.15-37.5)	-
Other	9 (0.69)	3 (0.77)	6 (0.65)	1.16 (0.29-4.64)	1.04 (0.26-4.21)
Fatal bleeding	4 (0.30)	2 (0.51)	2 (0.22)	2.32 (0.33-16.5)	3.37 (0.41-27.8)



# Hypothesis

- Repositories linking DNA to large populations with many phenotypes can be used as a tool for pharmacogenomics

## Approaches to creating repositories

- linking to Medical Records vs population-based
- opt-in versus opt-out



# Consented vs opt-out

## Consented

- recontact possible
- family structure can be included
- identifying phenotypes of interest may be easier
  
- Accrual can be slow and expensive
- how many 80 year-olds on 20 medications?

## Opt-out

- no recontact
- family structure often missing
- identifying phenotypes of interest may be cumbersome
  
- very large numbers
- how many 80 year-olds on 20 medications?



# The Challenge: how to get from "2004" to "2020"

The DNA databank: a  
clinical laboratory for  
modern genomics

**2004**

Research efforts  
to find **markers**  
for Personalized  
Medicine







Vanderbilt **BioVU**

**2020**

routine patient  
visit: **markers**  
are part of the  
record

# Key implementation steps

	2004	2005	2006	2007
<b>Community / Patient</b>		Focus groups Patient mail survey Communications materials Community Advisory Board established		Opt out caller survey Pre-launch awareness generation <i>On-going input</i> 
<b>Methods/ Feasibility</b>		Logistics/process mapping Sample acceptance validation De-Identification effectiveness Proof of Concept	Form implementation Pilot testing	
<b>Regulatory, Legal, Ethics</b>		Protocol development IRB review and modifications Ethics review and modifications Legal review and modifications	Final IRB approval OHRP confirmation	 
<b>Live Operations Phase I</b>				 Sample accrual begins Demonstration project Patient research, live setting

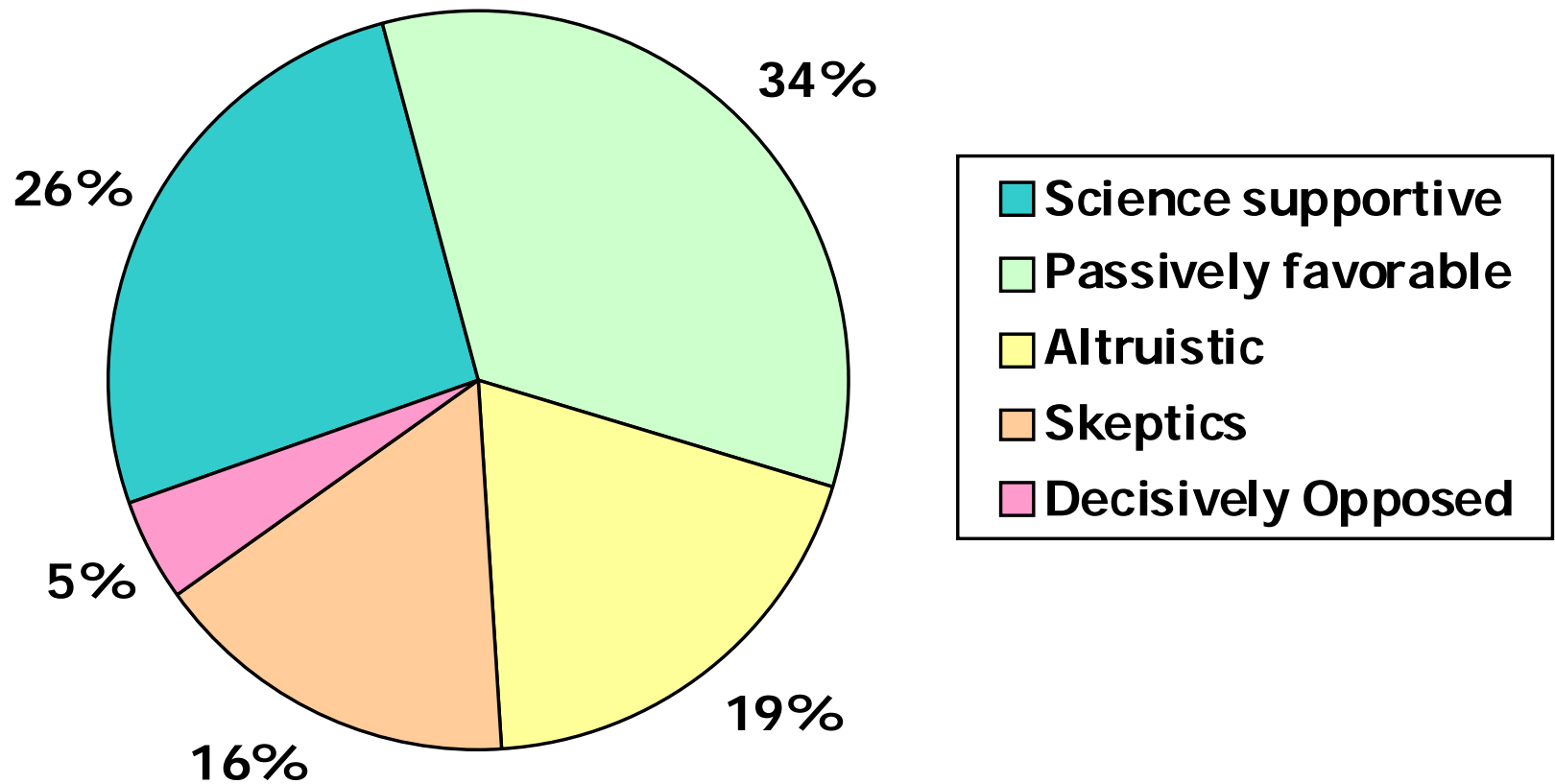
# Most Vanderbilt Patients Support the idea

<p><b>If all personal information is removed, should the hospital be able to use leftover blood for ethically approved medical research?</b></p>	<p><b>Yes</b></p>	<p><b>No</b></p>		
	<p>91.0%</p>	<p>9.0%</p>		
<p><b>How do you feel about genetic information taken from your DNA being used for medical research studies as long as there is no personal information?</b></p>	<p>Very Comfortable</p>	<p>Somewhat Comfortable</p>	<p>Somewhat Uncomfortable</p>	<p>Very Uncomfortable</p>
	<p>61.4%</p>	<p>27.9%</p>	<p>7.3%</p>	<p>3.4%</p>
<p><b>Vanderbilt is considering a research project to collect leftover blood from patients that might help doctors learn more about the ways genes affect health. How important do you think this is?</b></p>	<p>Very Important</p>	<p>Somewhat Important</p>	<p>Somewhat Unimportant</p>	<p>Very Unimportant</p>
	<p>82.4%</p>	<p>16.3%</p>	<p>0.9%</p>	<p>0.4%</p>




# Distinct Attitudinal Groups

(Among Respondents Who Could Be Segmented)



# BioVU: Key implementation steps

- Federal Office for Human Research Protections (OHRP) guidelines allow use of de-identified discarded biologic samples in research:
  - de-identification of the 1.4 million records in the Vanderbilt Electronic Medical Record (StarPanel) → The Synthetic Derivative (**SD**)
- Review by ethics committees, IRB, Community Advisory Board, OHRP, VUMC legal: designated “non-human subjects”
-  Publicity to allow opt-out

Vanderbilt University Medical Center

**CONSENT FOR TREATMENT AND AGREEMENT TO PAY (ADULT)**

Inpatient / Outpatient

**I. CONSENT FOR ROUTINE DIAGNOSTIC PROCEDURES 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 treatment 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 payer (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 TennCare/HAMPUS items or services that are listed on the financial responsibility for 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 my 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 delinquent account referred for collection, I agree to pay the reasonable attorney's fees, costs

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, I agree to be responsible for Guaranter. I hereby agree that all charges associated with this treatment or any other treatment rendered to the above patient or future, not covered by any insurance program, government or other third party coverage, may have a 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 my 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 for collection agency fees associated with the collection process.

**V. Volatile Release** - 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, PRESERVATION 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 my such invention.

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

**I do 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.**

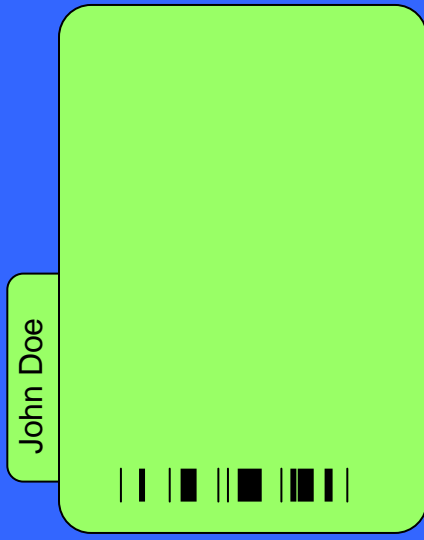


***Do not use my leftover blood for the DNA Databank***

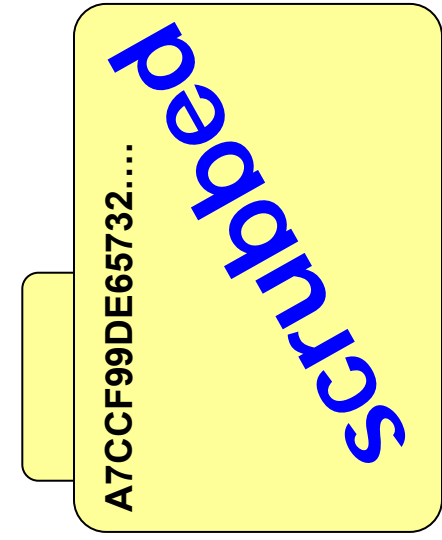


John Doe





One way hash



1.4 million records; fall 2006

The **SD**: can be updated

- ◆ Clear all
- ◆ Patient Lists
- ◆ Consults
- ◆ Inpt. census
- ◆ Outpt. visits
- ◆ PatientsView
- ◆ Panels
- ◆ Recent pts.
- ◆ Scratch cens.
- ◆ Work Lists
- ◆ Inf. Resources
- ◆ Customize
- ◆ LOG OUT
- ◆ Help
- ◆ Lock

User  
Go to: **Pt.Chart** StarVisit StarNotes Forms **Pt.Lists** NewResults SignDrafts  
Miscellaneous

----- SMITH, HELLEN (02/01/1949 - 56YO F) <999-99-9999> (555) 555-5555 Alert PCP: Mary, Johanson																	
ALL	ALL	Appntm.	Calendar	Clin.Comm	EnterData	Faxed	Labs	Meds	Msgs?	Orders	Probl.List	Radiol.	Reports	Search	ToPanel	VitalSigns	
Cancer	Disclosure	Forms	Immuniz.	IntakeAssess.	NewMsg	Pt.Letter	ReferralMsg	Reminder	StarNotes	StarVisit	TypeNewDocument	UploadImage	VitalSigns	AuthorizeAccess			
<input type="checkbox"/>	2004/09/28	Notes														Carter, Meredith	Patient Follow Up
<input checked="" type="checkbox"/>	2004/09/28	Orders	Medication Orders													Carter, Meredith	Chemo Orders
<input type="checkbox"/>	2004/09/28		Oncology Clinic Note													Meredith Carter-Grant, M.D.	
<input type="checkbox"/>	2004/09/28	Admin	Release Of Information													Radiology	
<input type="checkbox"/>	2004/09/28	Orders	Orders													Carter, Meredith	

----- SMITH, HELLEN (02/01/1949 - 56YO F)  
Oncology Clinic Note 2004/09/28 14:09 By: Meredith Carter-Grant, M.D.  
Signed by: \*\*\*\*\* Actions:

**DIAGNOSIS:** Stage II invasive mammary breast cancer "T2 NO MO."

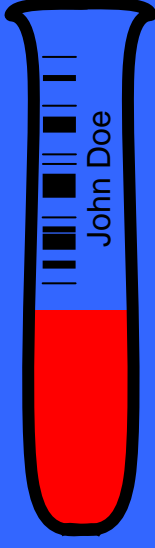
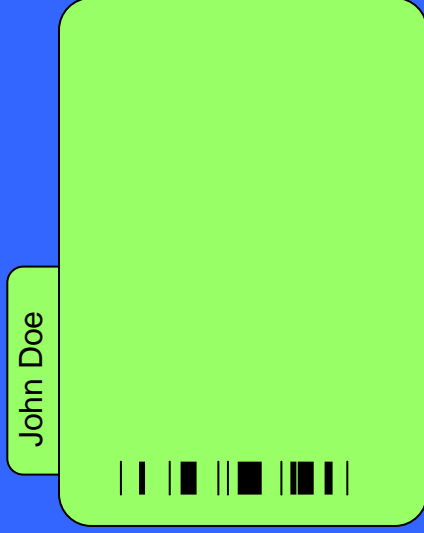
**ONCOLOGIC HISTORY:** Ms. Smith is a 55-year-old female who is post menopausal. She was found to have an abnormality on her mammogram. She subsequently had an ultrasound-guided FNA which showed malignant cells. She was referred to the breast Center where she underwent a core biopsy on August 30, 2004, which showed infiltrating mammary carcinoma. She subsequently was seen by Dr. Owens who, on August 30, 2004, did a left modified radical mastectomy. Pathology from this revealed an invasive mammary carcinoma, no special type, with lobular features, 2.2 cm in greatest dimension, which was intermediate combined histologic grade with low proliferative rate tumor, extending to 2 mm in the lower, lateral, deep margin. There was no evidence of lymphovascular invasion present. Thirteen lymph nodes were negative for malignancy. Her tumor was ER positive, PR 1% positive, HER2/neu negative. She, at the time of surgery, had placement of a tissue expander, for immediate first stage reconstruction of her left breast, by Dr. McDonald. It was decided, since her final pathology showed tumor extending to 2 mm from the lower, lateral deep margin that she be referred to Wilburn Clouse who was planning on doing radiation therapy after she received chemotherapy. She had a MUGA scan done on September 28, 2004, which showed a normal ejection fraction with a left ventricular ejection fraction of 63%. She is here to receive her first cycle of Adriamycin and Cytoxan. We discussed the risks and benefits of chemotherapy and she has decided to proceed with chemotherapy.

**REVIEW OF SYSTEMS:**  
**General:** Denies weakness, fatigue, fever, sweats, or itching.

# Examples over-marked

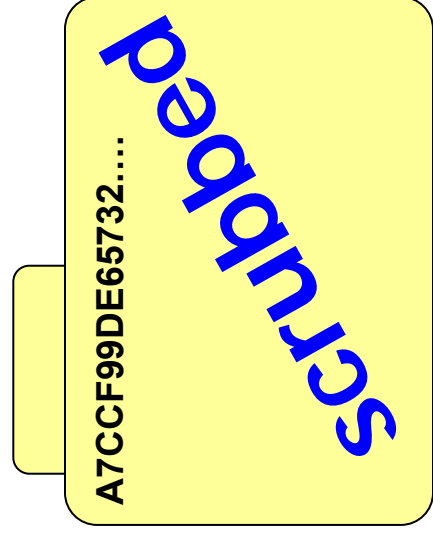
Pre-scrub	After scrub
GI: <b>soft, ND</b> , normal bowel sounds, non tender, no hepatomegaly, no splenomegaly	GI: <b>**PLACE</b> , ND, normal bowel sounds, non tender, no hepatomegaly, no splenomegaly
with iron, 40 gm protein daily, and <b>1500-2000</b> calories daily.	with iron, 40 gm protein daily, and <b>**ID-NUM</b> calories daily.
Standardized Balance Tests: <b>BERG Total</b> score: 34 Pt required frequent rest	Standardized Balance Tests: <b>**NAME[XXX: WWW]</b> score: 34 Pt required frequent rest
An attending <b>Cardiologist</b> was present throughout the diagnostic study.	An attending <b>**NAME[SSS]</b> was present throughout the diagnostic study.
filled through the <b>Easter Seals</b> . The patient is also requesting additional	filled through the <b>**NAME[VVV UUU]</b> . The patient is also requesting additional



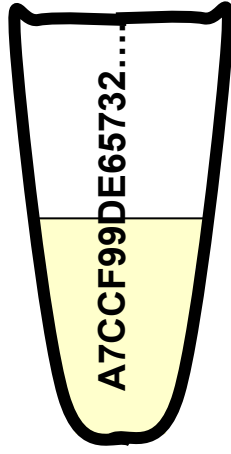


eligible

One way hash



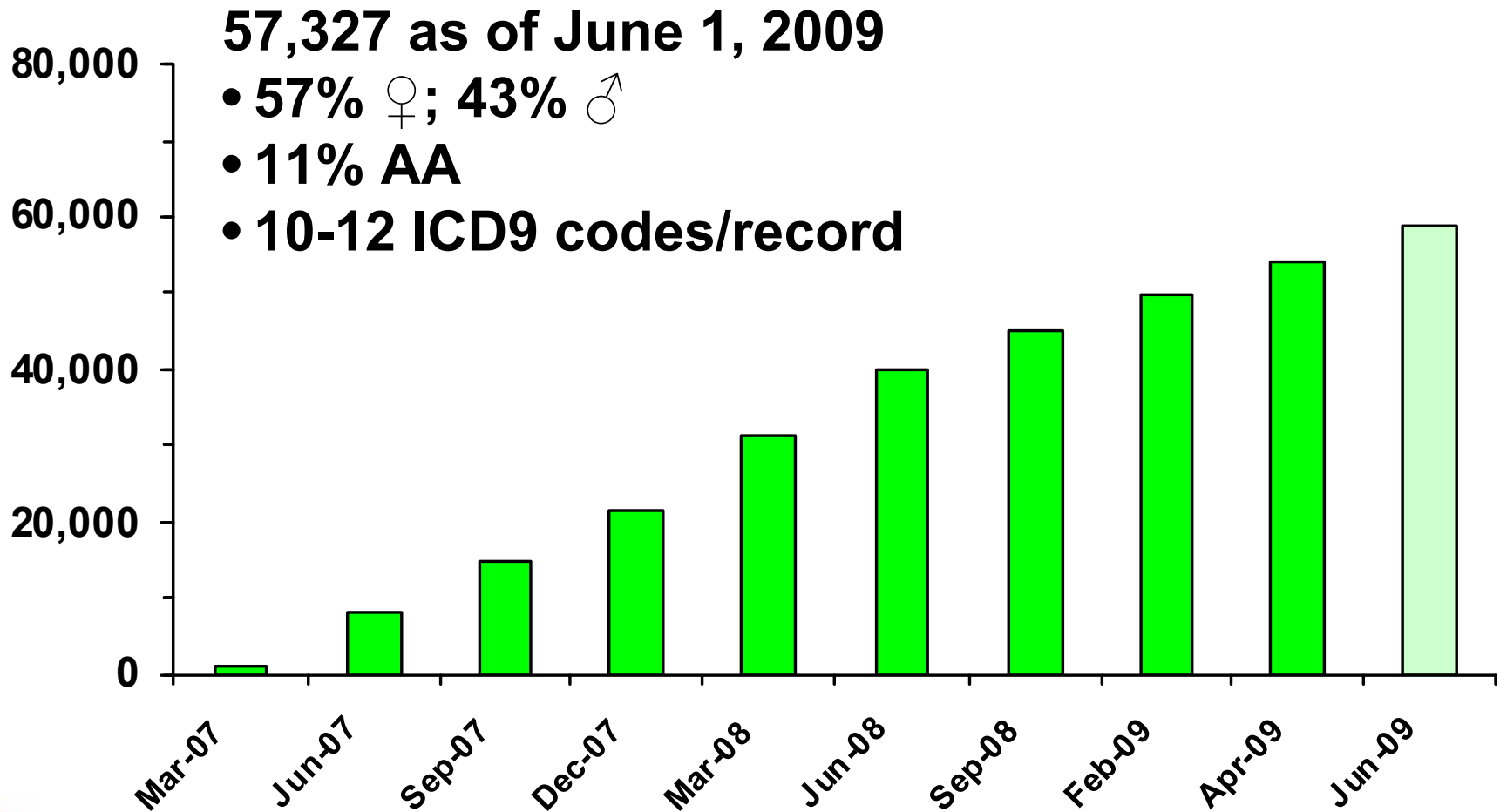
Extract DNA



1.4 million records; fall 2006

The SD: can be updated

# Cumulative sample accrual: current and projected



**Investigator  
query**



**Data use  
agreement**



**cases**



**controls**

# One way hash

**Investigator query**



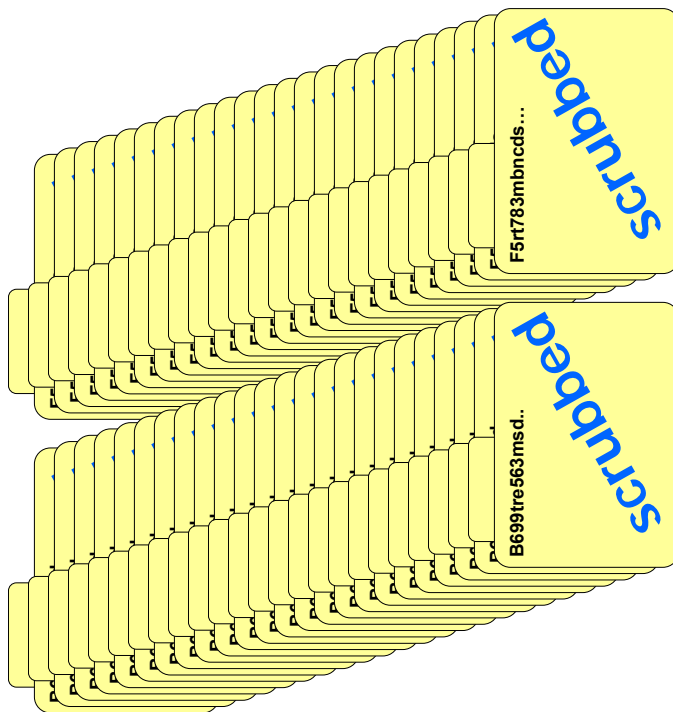
**Data use agreement**



**cases**



**controls**



**Data analysis**

# Record Counter

Search **Results**

[Help and Documentation](#) | [Video Tutorial](#)

[Delete Query](#)

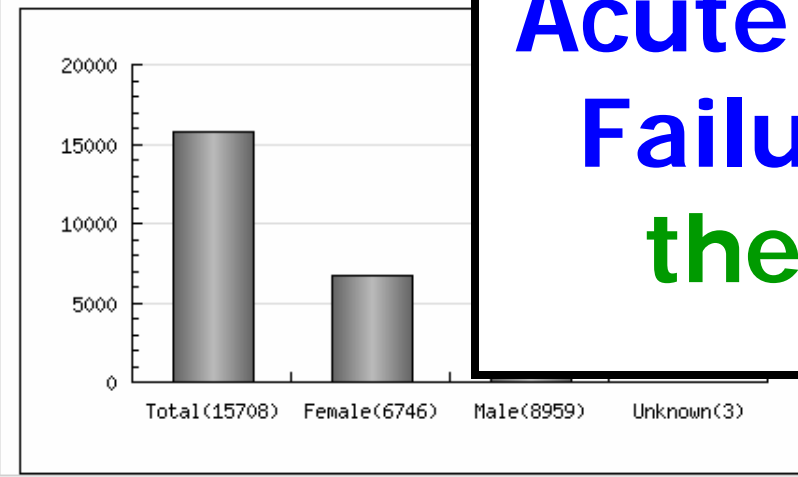
Date Created	Name
06/03/2009	acute renal failure
05/27/2009	all biovu
05/19/2009	aspirin clopidogrel asa-dip
05/17/2009	non-steroidals
05/17/2009	antiplatelet or nonsteroids
05/15/2009	nicotine and Zyban
05/11/2009	statins
05/11/2009	prednisone dexamethasone
05/08/2009	asthma
05/06/2009	essential hypertension

**Criteria**

Include Where ( ICD Include 584 or ICD Include 584 )

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

## Result Count - acute renal failure



**Search for Acute Renal Failure in the SD**

## Details - acute renal failure

Gender	Total	Afr Amer	Asian	Cauc	Hisp	Nat Amer	Other	Unk
<b>Age Group: ALL</b>								
Male	8959	1470	46	6682	109	9	9	634
Female	6746	1447	40	4753	63	9	6	428
Unknown	3*	0	0	0	0	0	0	3*
<b>Age Group: Under 2</b>								
Male	57	9	0	32	6	0	0	7
Female	36	9	0	21	3*	0	0	3*
Unknown	0	0	0	0	0	0	0	0

# One way hash

Investigator query



Data use agreement

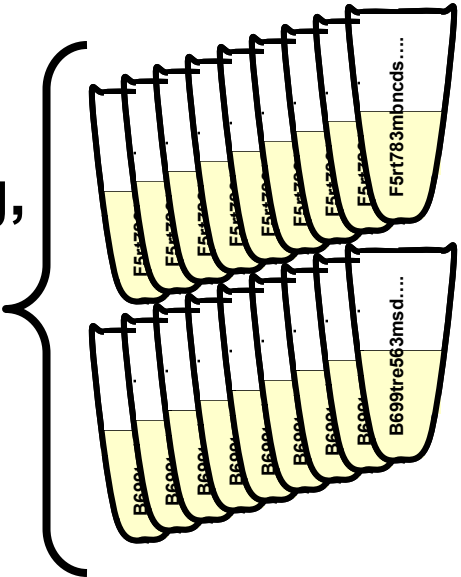
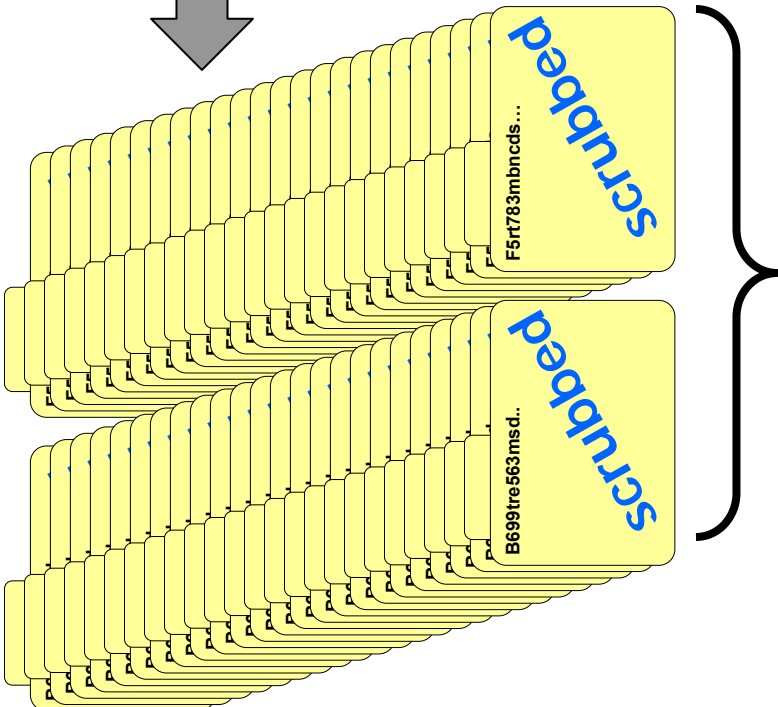
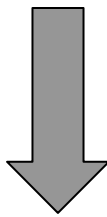


cases



controls

Genotyping,  
genotype-  
phenotype  
relations



cases



controls



Sample  
retrieval

# Record Counter

Search **Results**  
[Help and Documentation](#) | [Video Tutorial](#)

[Delete Query](#)

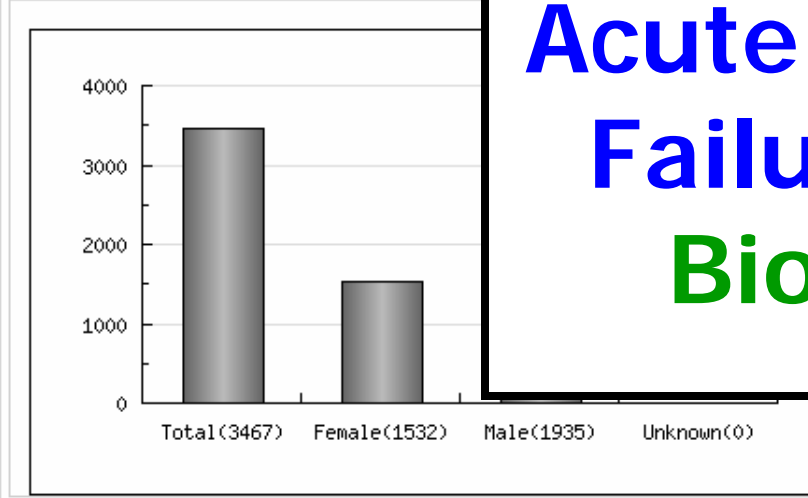
Date Created	Name
06/03/2009	acute renal failure BioVU
06/03/2009	acute renal failure
05/27/2009	all biovu
05/19/2009	aspirin clopidogrel asa-clip
05/17/2009	non-steroidals
05/17/2009	antiplatelet or nonsteroids
05/15/2009	nicotine and Zyban
05/11/2009	statins
05/11/2009	prednisone dexamethasone
05/08/2009	asthma

**Criteria**

Include Where ( ICD Include 584 or ICD Include 584 )

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

## Result Count - acute renal failure BioVU

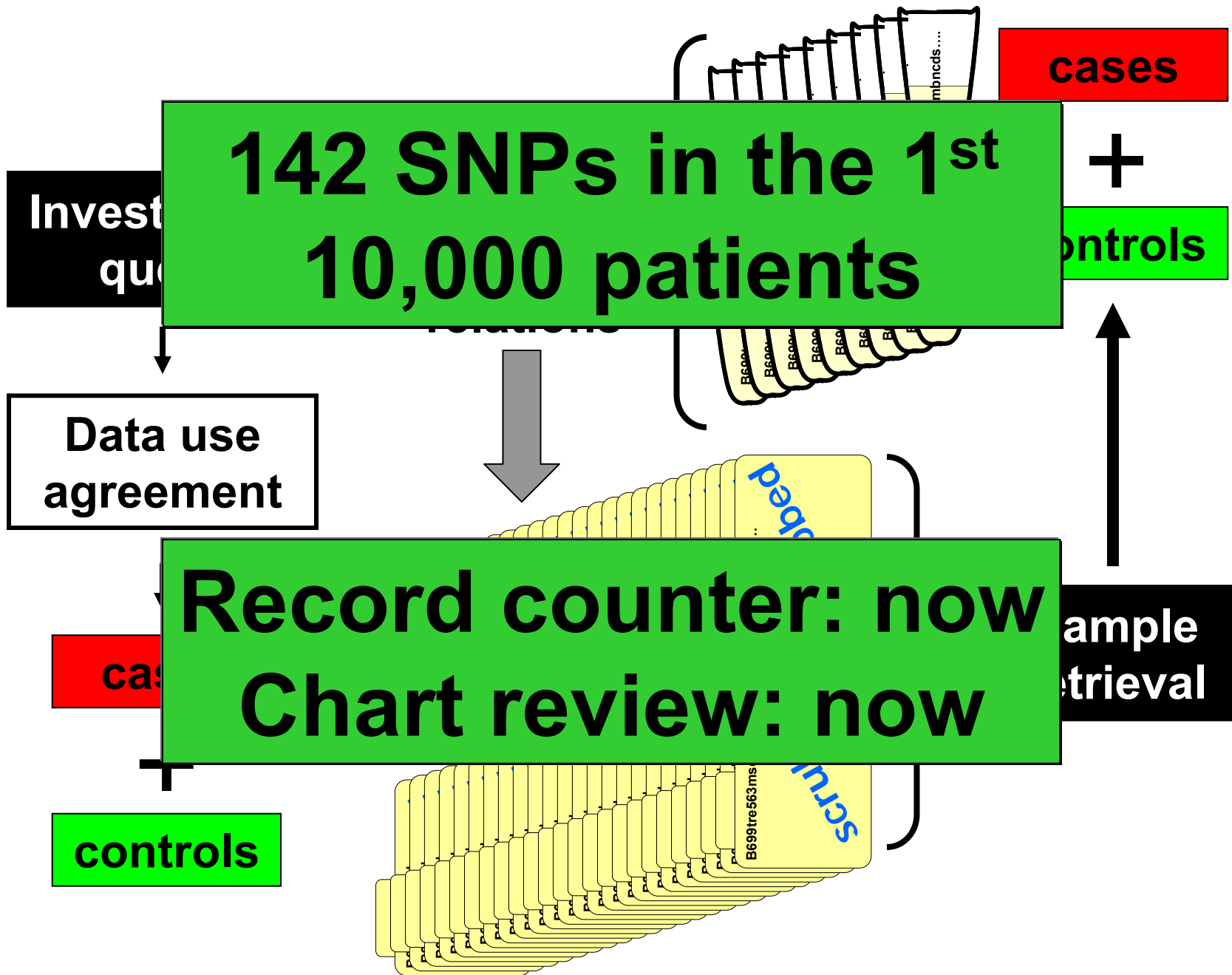


**Search for  
Acute Renal  
Failure in  
BioVU**

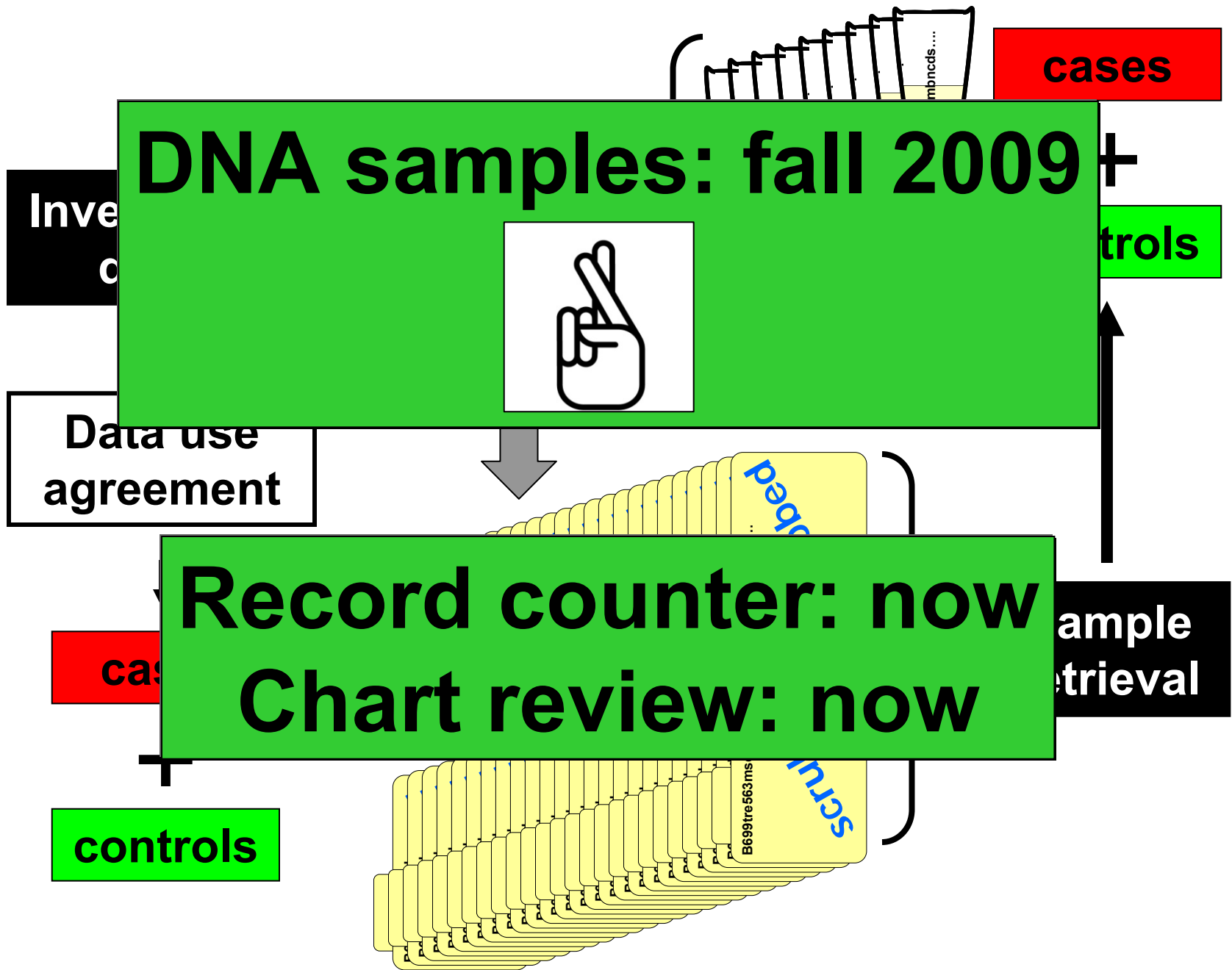
## Details - acute renal failure BioVU

Gender	Total	Afr Amer	Asian	Cauc	Hisp	Nat Amer	Other	Unk
<b>Age Group: ALL</b>								
Male	1935	319	9	1532	15	0	0	60
Female	1532	359	14	1110	13	3*	0	33
Unknown	0	0	0	0	0	0	0	0
<b>Age Group: Under 2</b>								
Male	0	0	0	0	0	0	0	0
Female	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0

One way hash



One way hash



# BioVU projects

## Phase I

Gender match

## Phase II

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

## Phase III

Validate known  
associations

## Phase III

New discovery: The  
VGER project

## Phase IV

Widespread use by VU  
investigators



- Clear all
- Patient Lists
- Consults
- Inpt. census
- Outpt. visits
- PatientsView
- Panels
- 10/06/2005
- Recent pts.
- Scratch cens.
- Work Lists
- Inf. Resources
- Customize
- LOG OUT
- Help
- Lock

User pull00p (Pulley, Jill N)

Alert PCP: Siddiqui, Farrukh A

ALL AllDocs Appntn. Calendar Clin.Comm EnterData Faxed Flows Labs Meds Msgs? Orders ProblList Radiol. Reports Search ToPanel VitalSigns  
CancerStage ClinicIntake Disclosure Forms Immuniz. NewMsg Pt.Letter ReferralMsg Reminder StarNotes StarVisit

HLA DATA: matched at A, B, C, Dr

PATIENT DATA:  
 CMV: Positive  
 VZV: Positive  
 ABO TYPE: A RH POS  
 ANTIBODY SCREEN: NEG (11/15/05)

**DONOR DATA:**  
 NAME: [redacted] (brother)  
 MRN: [redacted]  
 AGE: 38 yo  
 SEX: male  
 CMV: POSITIVE  
 ABO TYPE: A , RH POSITIVE  
 ANTIBODY SCREEN: NEGATIVE

HPI: Pretransplant disease history summarized in [redacted]

INTERVAL HISTORY: Pt feels well; appetite 90%; energy improving; some nausea this am; No V/D; rash improving.

REVIEW OF SYSTEMS:  
 General: Act/energy stable at 90%. Tired by afternoon. Denies any weakness, fever, chills, sweats, itching  
 Head / Neck: + dry mouth. Denies sore throat, headache, hoarseness, difficulty swallowing, swollen lymph glands or mouth ulcers

# BioVU projects

## Phase I

Gender match

## Phase II

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

## Phase III

Validate known  
associations

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investigators



# VGER

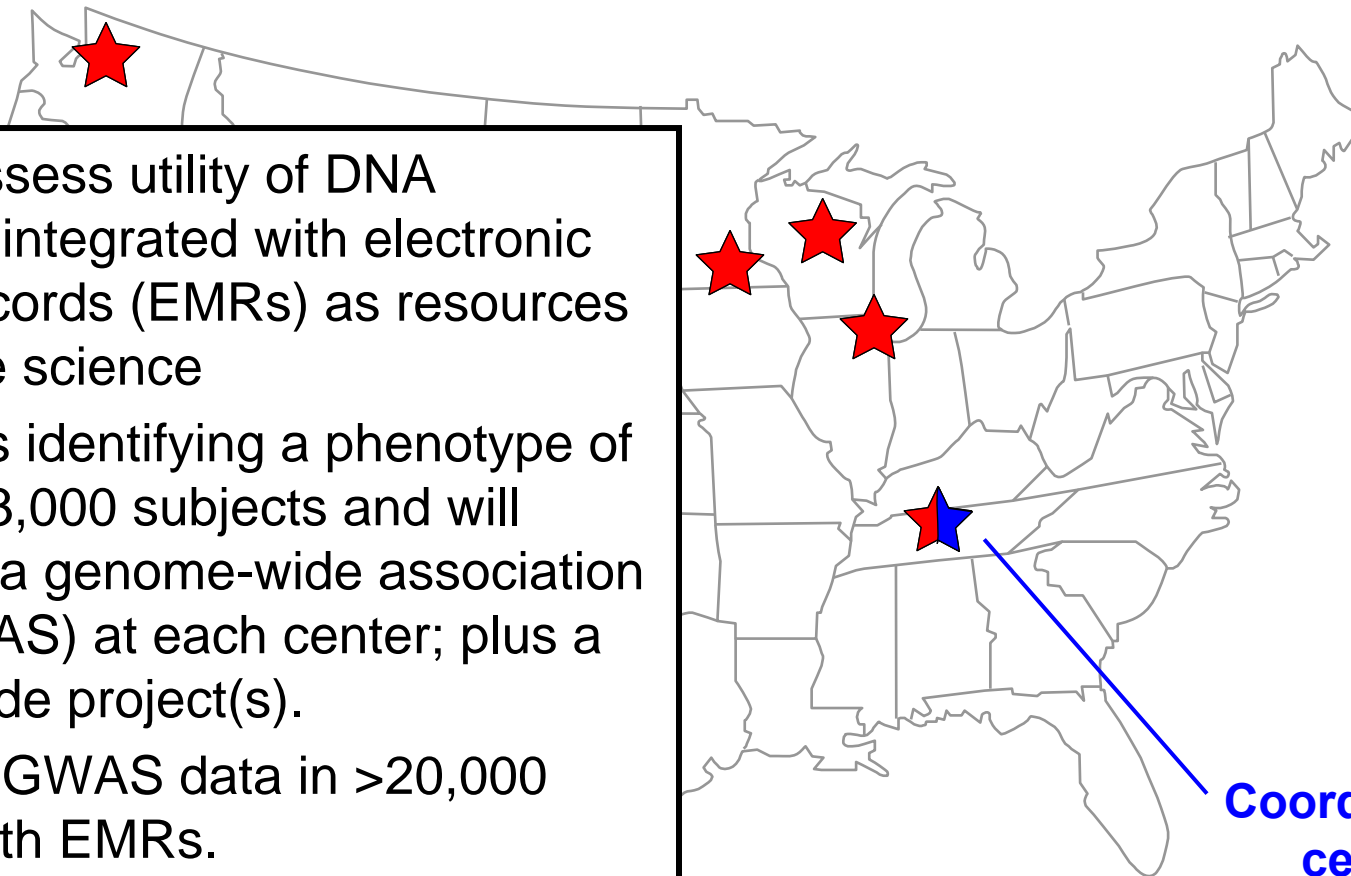
The Vanderbilt Genome-  
Electronic Records Project



# 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 (EMRs) 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 (GWAS) at each center; plus a network-wide project(s).
- **Outcome:** GWAS data in >20,000 subjects with EMRs.

# BioVU projects

## Phase I

Gender match

## Phase II

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

## Phase III

Validate known  
associations

## Phase III

New discovery: The  
VGER project

## Phase IV

Widespread use by VU  
investigators



# The “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
    - Bipolar disorder
    - Crohn’s disease
    - Prostate cancer
    - Type I Diabetes
    - Alzheimer’s Disease
    - Breast cancer
    - MI at age <50
    - Rheumatoid arthritis
    - Type II Diabetes
- Develop Natural Language Processing methods to identify cases and controls
- Are genotype-phenotype relations replicated?

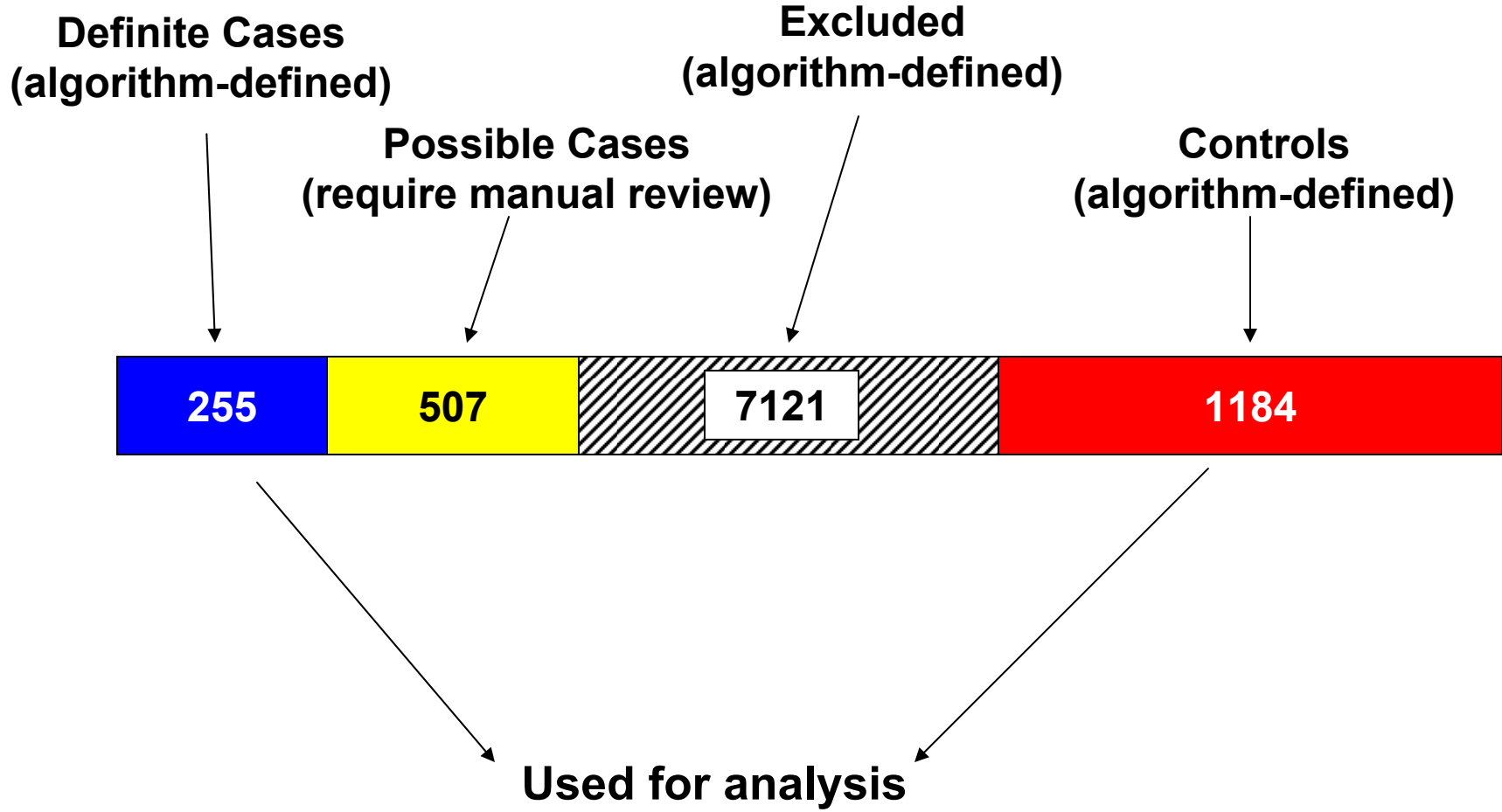


# RA – Case Definition Evolution

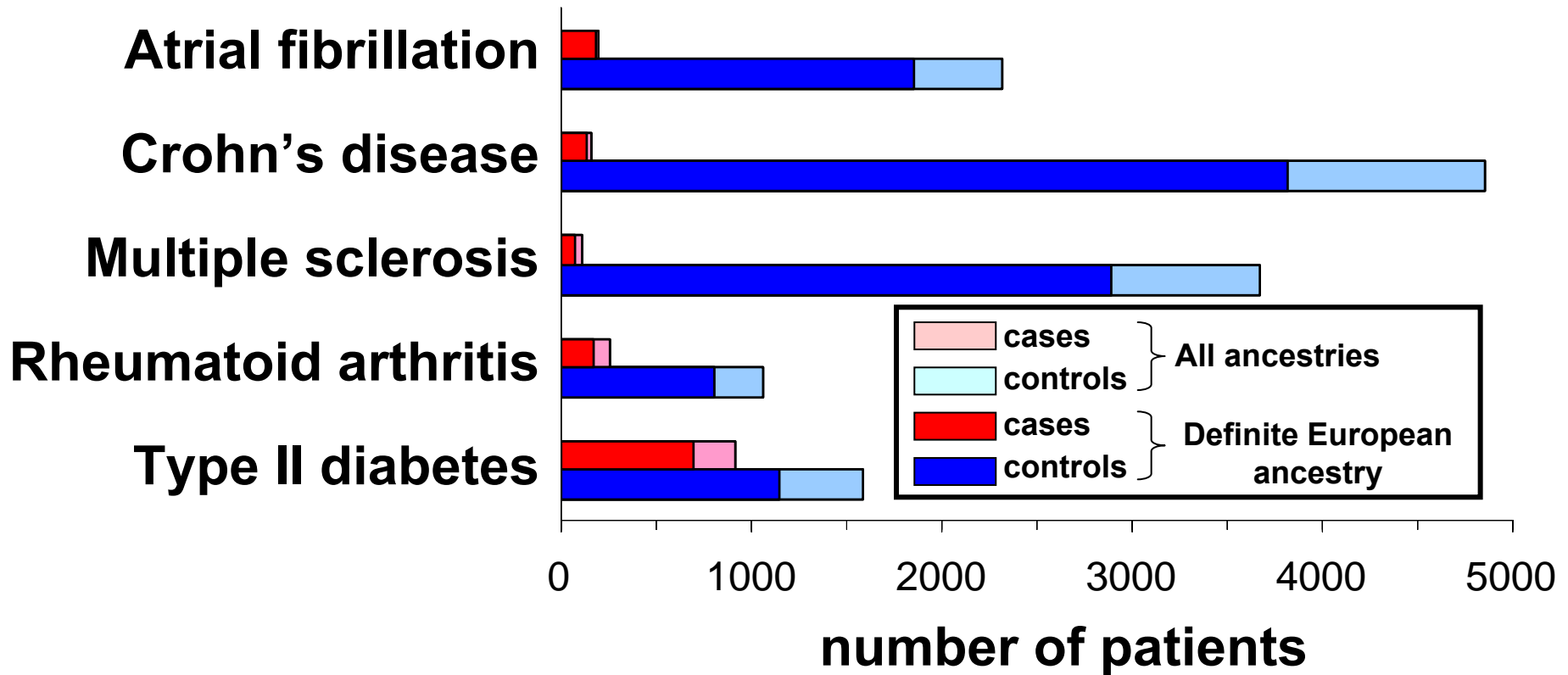
#	Definition	# Cases	Problem
1	ICD9 codes for RA + Medications (only in problem list)	371	Found incomplete problem lists
2	Same as above but searched notes	411	Patients billed as RA but actually other conditions, overlap syndromes, juvenile RA
3	Above + require “rheumatoid arthritis” and small list of 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



# Testing the “null hypothesis”

(unpublished data removed prior to posting)



# Conclusions

- The null hypothesis can be rejected:  
Biobanks can be used to identify cases and controls for disease susceptibility.
- Next step: disease followed by drug followed by outcome

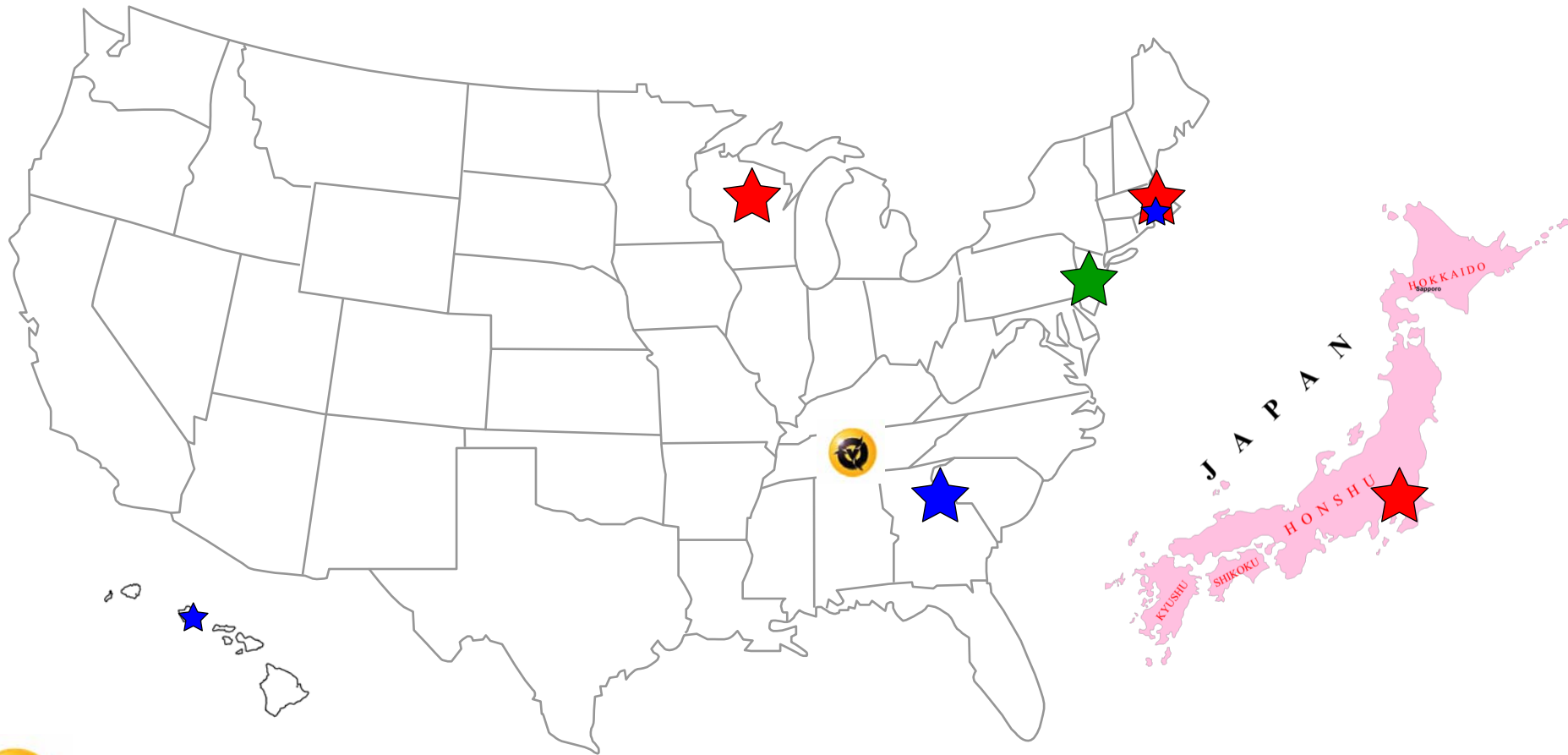


# BioVU searches April-May 2009

Statins	10,216
Clopidogrel	4,407
Prednisone/dexamethasone	10,584
Warfarin	4,842
Metformin + Type 2 DM + HgA1C	1,794
Hypertension	21,102
Atrial fibrillation	2,765
Rheumatoid arthritis	1,777
HCM	203
CHF	3,419
Asthma	3,916
HDL>100	737



# PGPop: PharmacoGenomic discovery and replication in very large patient POPulations



# PGPop nodes

Resource	Current size	DNA in hand	Ethnicity (%)			
			Caucasian	African American	Asian	Hispanic
BioVU	56,363	Y	85	12	1	1
PMRP	20,000	Y	98	0.5		1
Crimson	800,000		60	10	15	15
Biobank Japan	300,000	Y			100	
HMORN CERT	11,000,000		varies	1-33	1-9	1-39
Medco	65,000,000					



# Models

- Consented
  - Marshfield
  - BioBank Japan
- opt-out
  - BioVU
  - Crimson



# Models

- Consented
  - Marshfield
  - BioBank Japan
  - EHR
  - disease-selected
- opt-out
  - BioVU
  - Crimson
  - EHR
  - EHR



# Models

- Consented
  - Marshfield
  - BioBank Japan
  - 20,000
  - 300,000
- opt-out
  - BioVU
  - Crimson
  - 100,000 by end 2010
  - Varies by disease



# DNA repositories linked to Health Records

- Huge challenges
- 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...

