VANDERBILT UNIVERSITY
MEDICAL CENTER

Using Electronic Medical Records to advance genomic medicine

Josh Denny, MD, MS

Vanderbilt University, Nashville, Tennessee, USA

20th International Symposium on
Microsomes and Drug Oxidations

5/19/2014

The vision

"Here's my sequence..."

New Yorker, 2000

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

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Biomedical research

Commitment to information technology

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Harnessing the healthcare system for discovery

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New Yorker, 2000

Biomedical research

Commitment to information technology

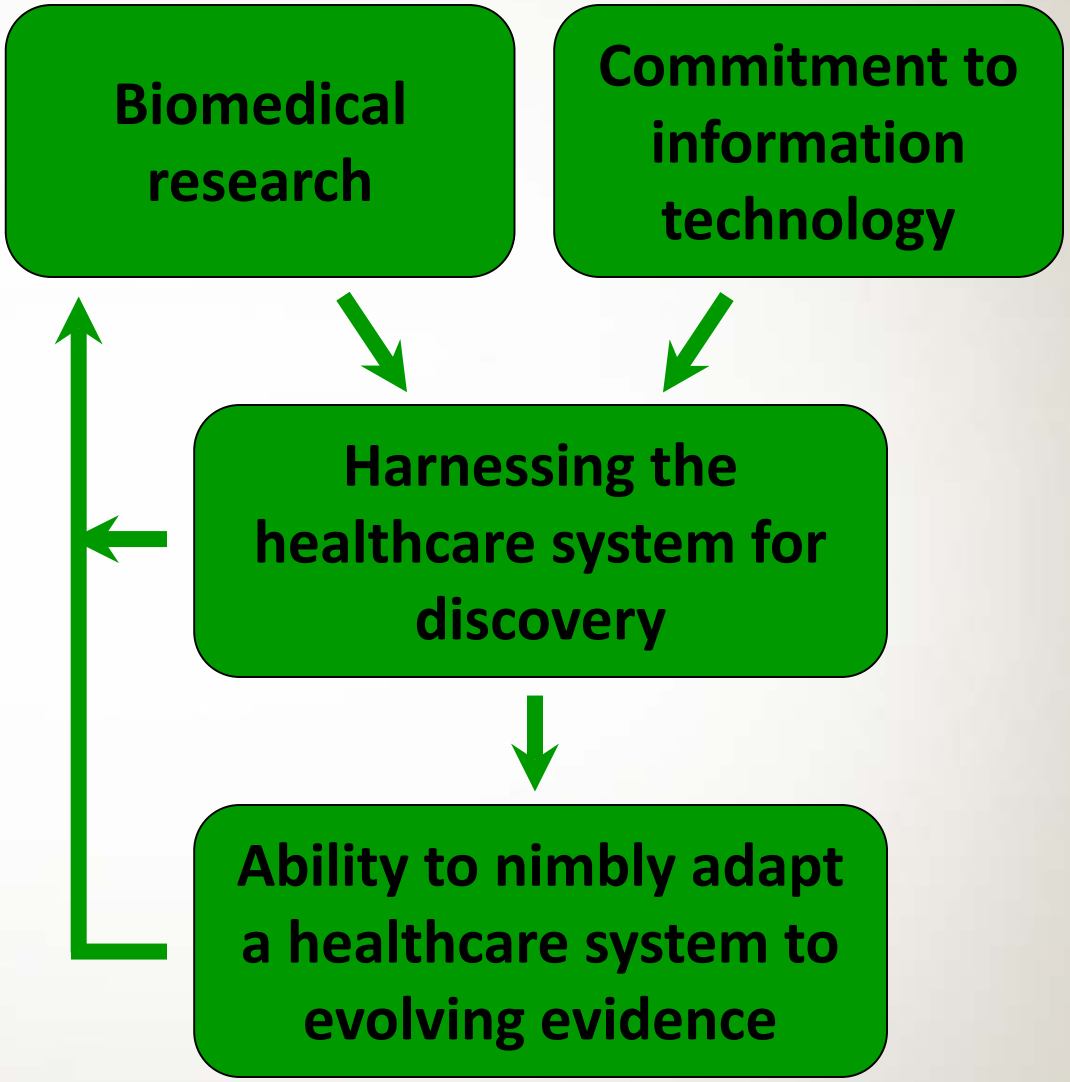
Harnessing the healthcare system for discovery

Ability to nimbly adapt a healthcare system to evolving evidence

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

"Here's my sequence..."

New Yorker, 2000



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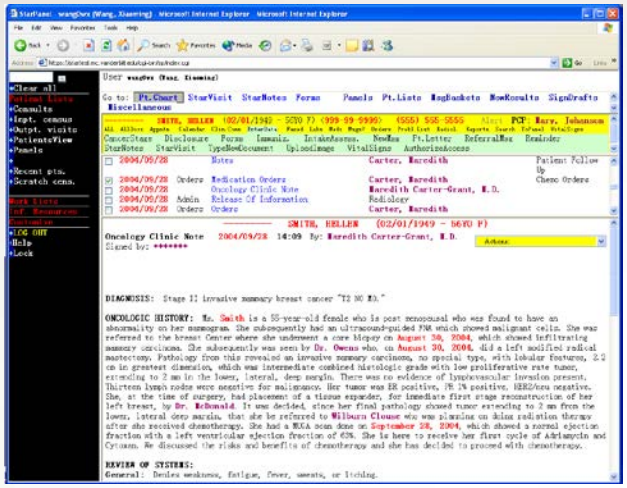

EHR feeds both discovery and implementation

Discovery

VanderbiltBioVU

De-identified DNA repository

>160k samples

Implementation

PREDICT

- CLIA genomics lab
- Integrated decision support for genomics
- Predictive algorithms on who to test
- Genomic databases
- Track outcomes

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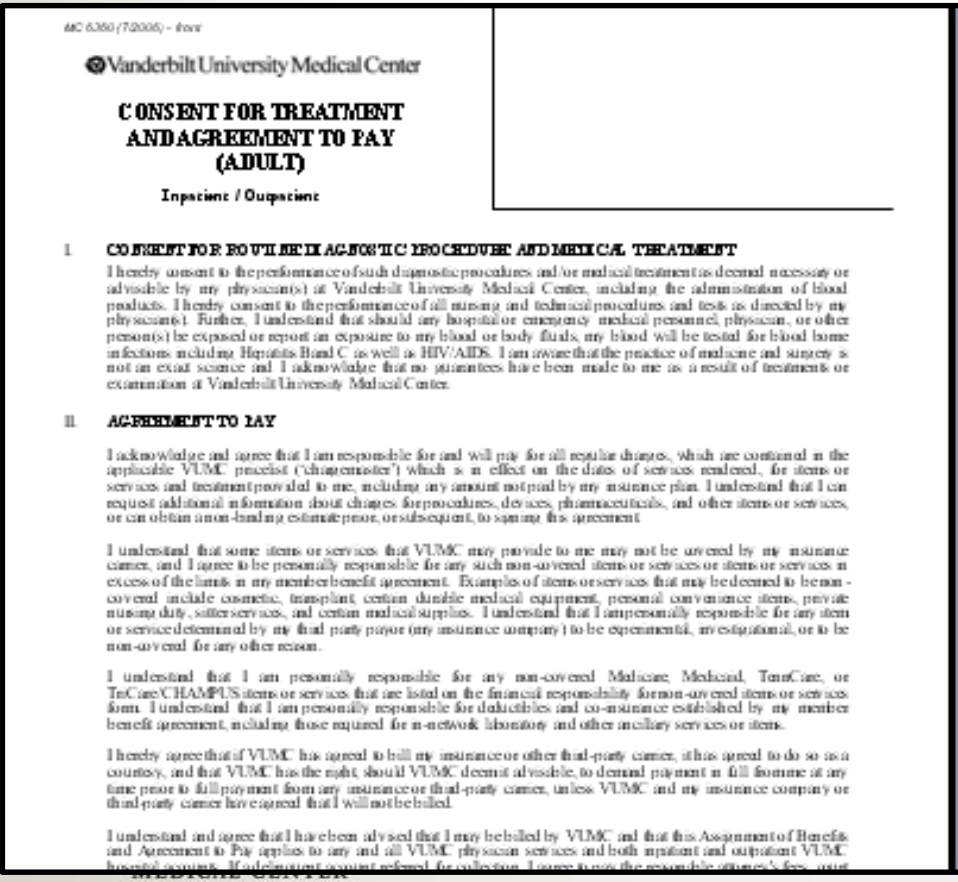
Vanderbilt BioVU: an Opt-Out DNA Biobank

Extracting DNA from left over blood samples



MC 6360 (7/2005) - front

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 pricelist ('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.

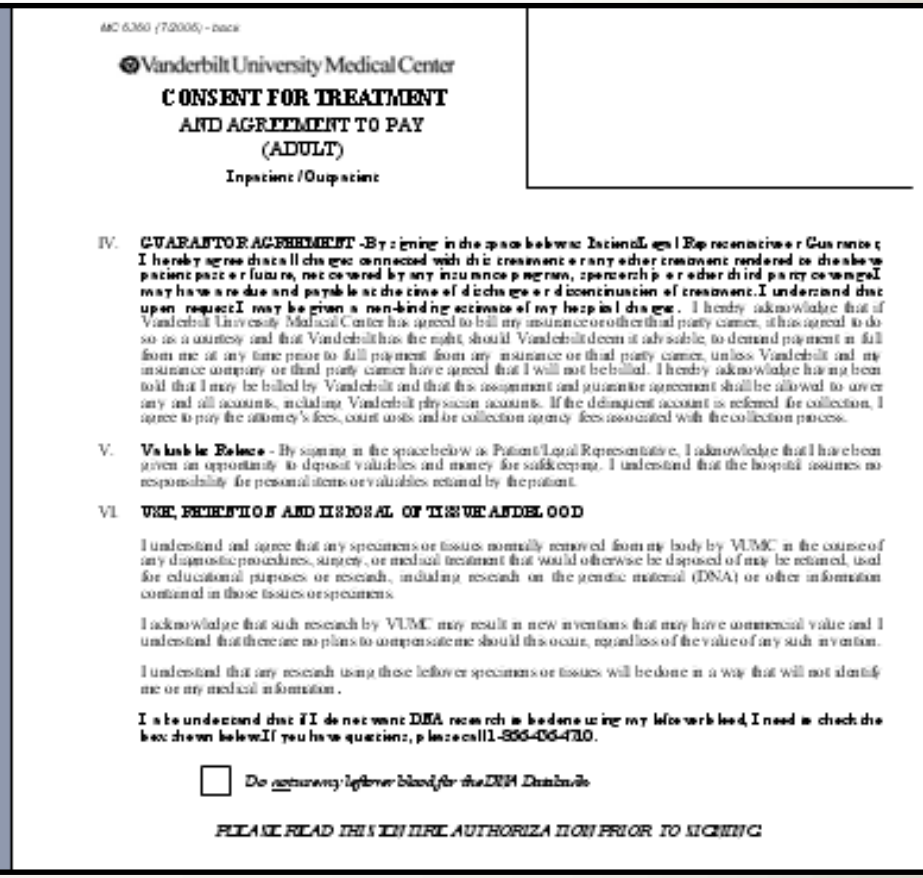
I understand that some items or services that VUMC may provide to me may not be covered by my insurance carrier, and I agree to be personally responsible for any such non-covered items or services or items or services in excess of the limits in my member benefit agreement. Examples of items or services 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 as 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 delinquent account referred for collection, I agree to pay the reasonable attorney's fees, court

MEDICINE CENTER



MC 6360 (7/2005) - back

Vanderbilt University Medical Center

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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 a reduced 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 these leftover specimens or tissues will be done in a way that will not identify me or my medical information.

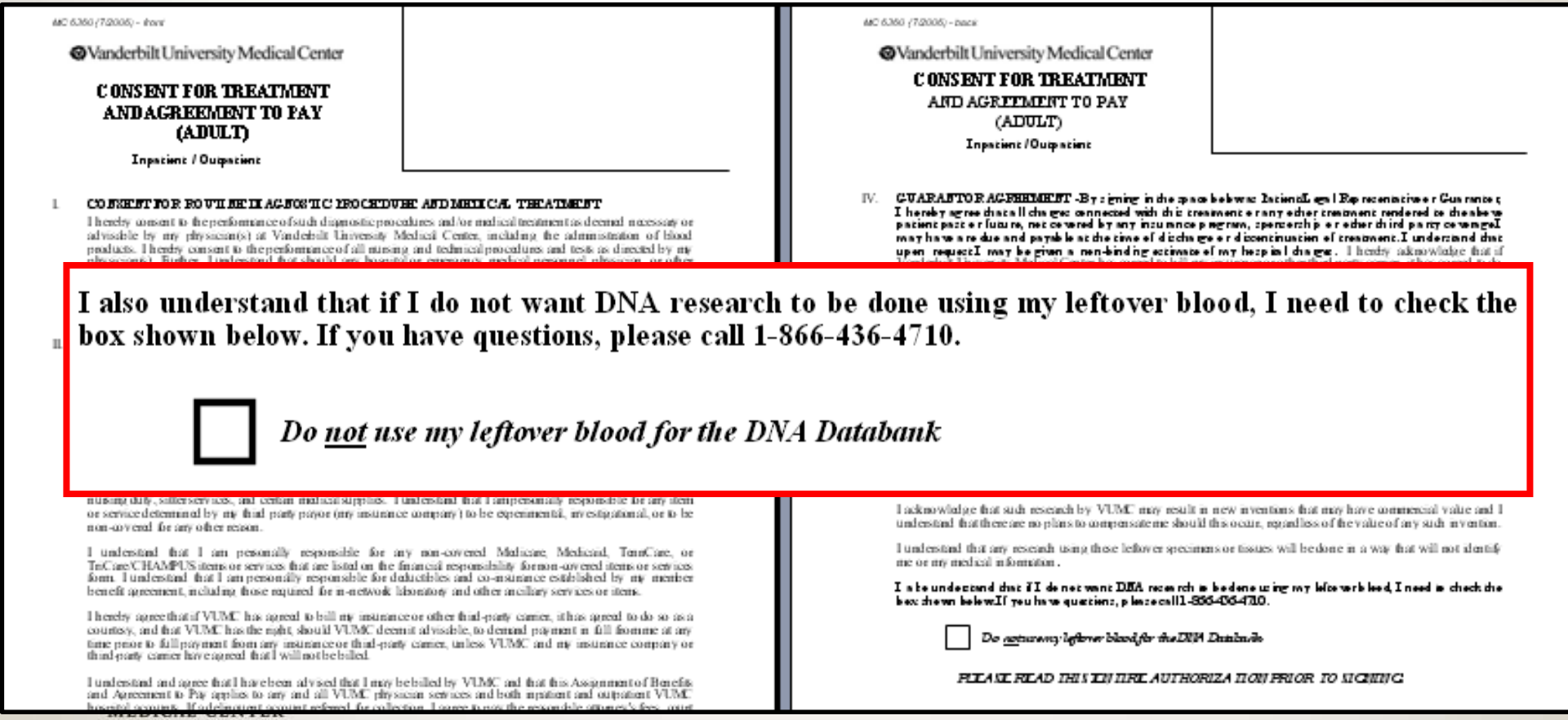
I also understand that if I do not want DNA research to be done using my leftover blood, I need to check the box shown below. If you have questions, please call 1-866-936-4710.

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

PLEASE READ THIS ENTIRE AUTHORIZATION PRIOR TO SIGNING

Vanderbilt BioVU: an Opt-Out DNA Biobank

Extracting DNA from left over blood samples



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Vanderbilt University Medical Center

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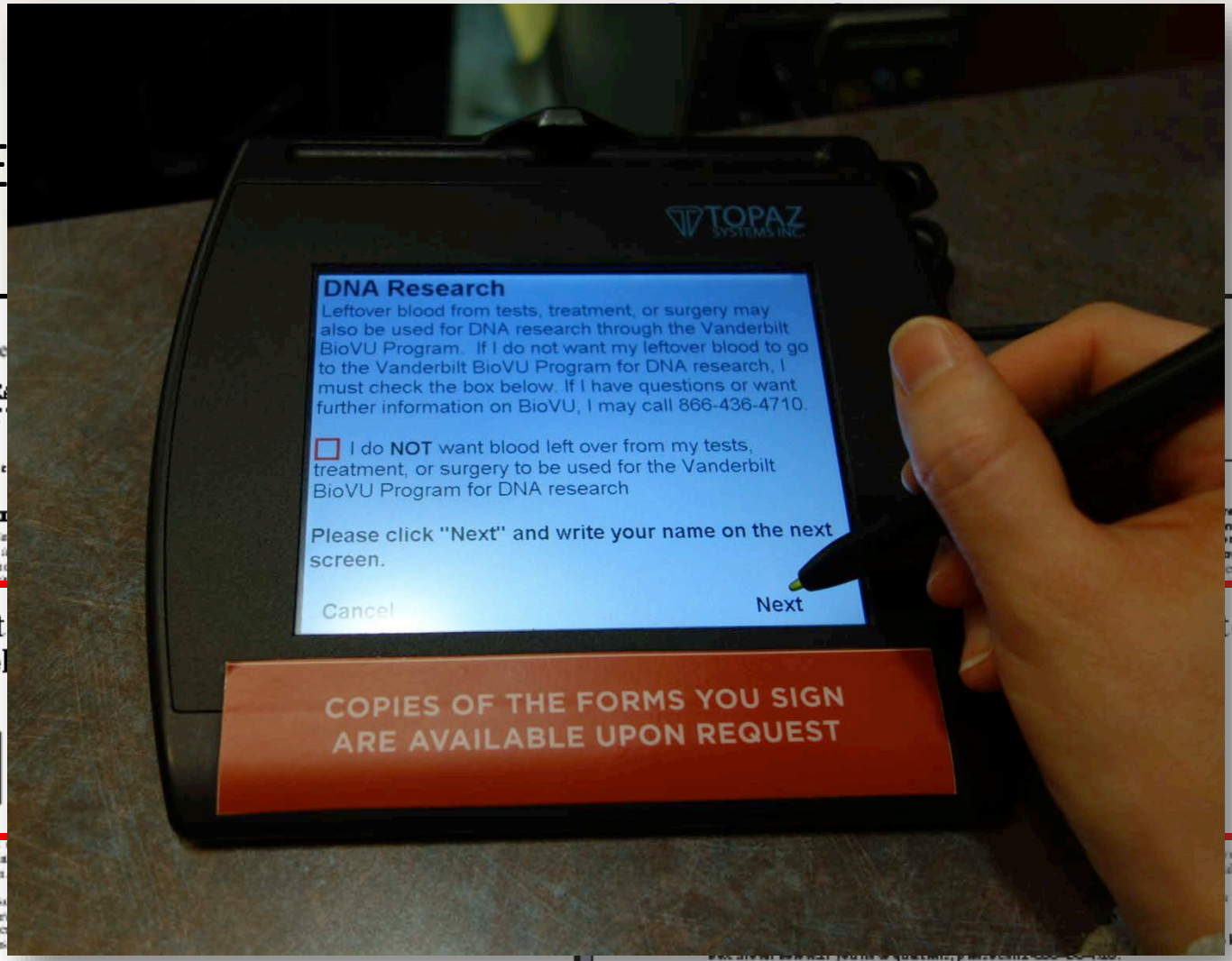
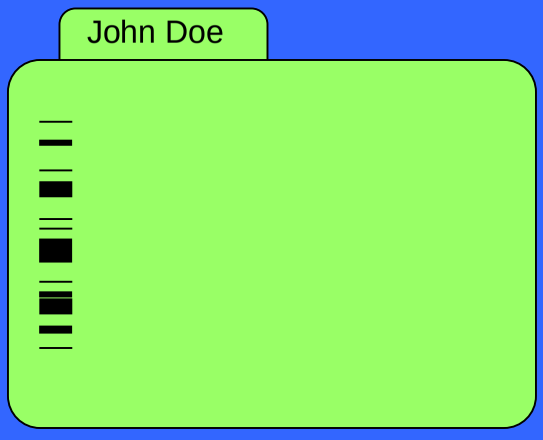
Vanderbilt BioVU: an Opt-Out

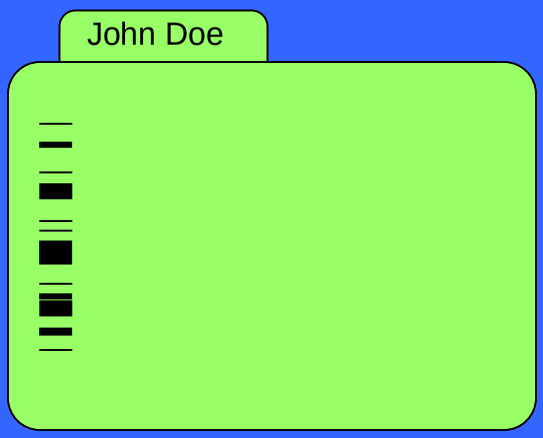


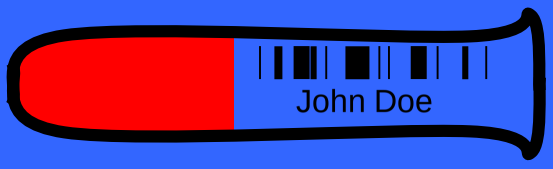

John Doe

One way hash

~2 million records

The Synthetic Derivative:
updated regularly





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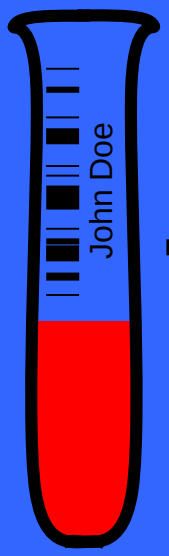
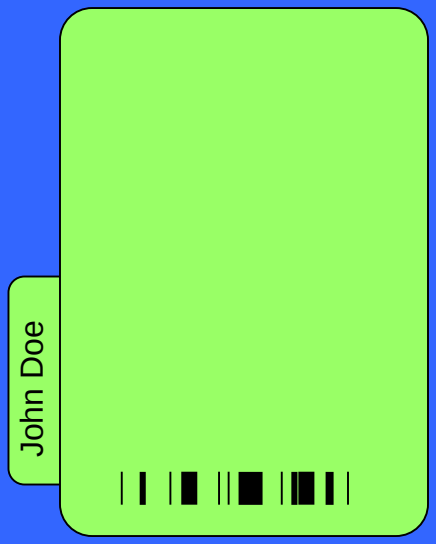


eligible?



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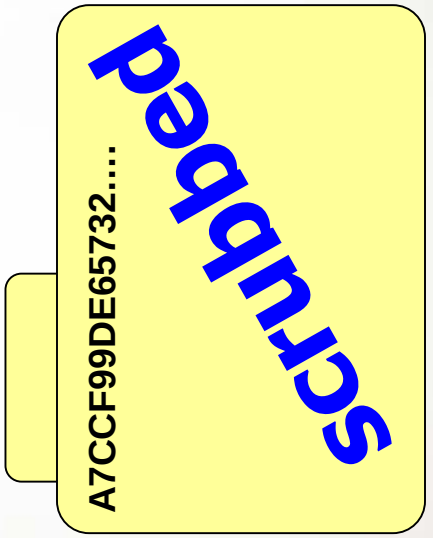

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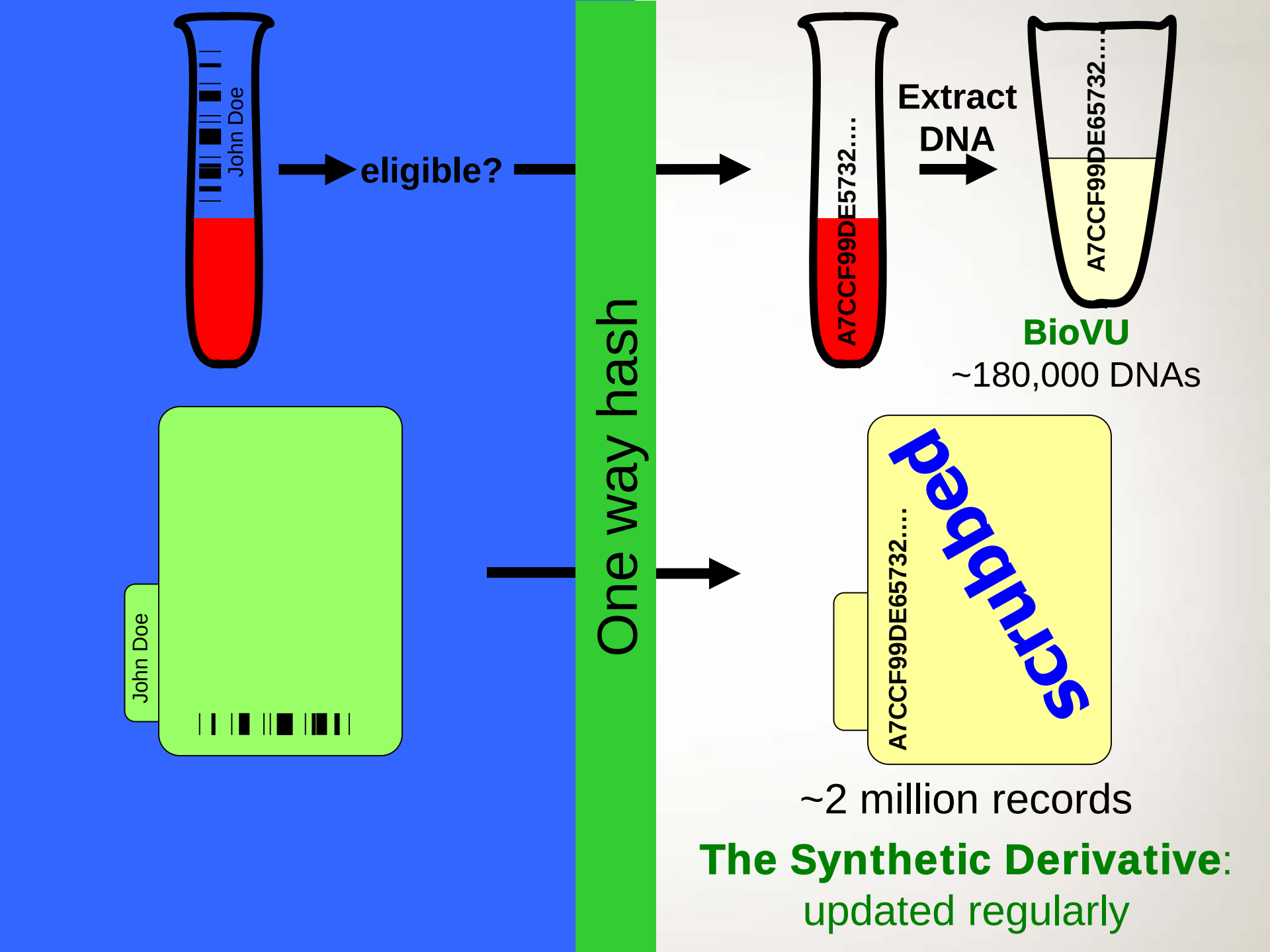
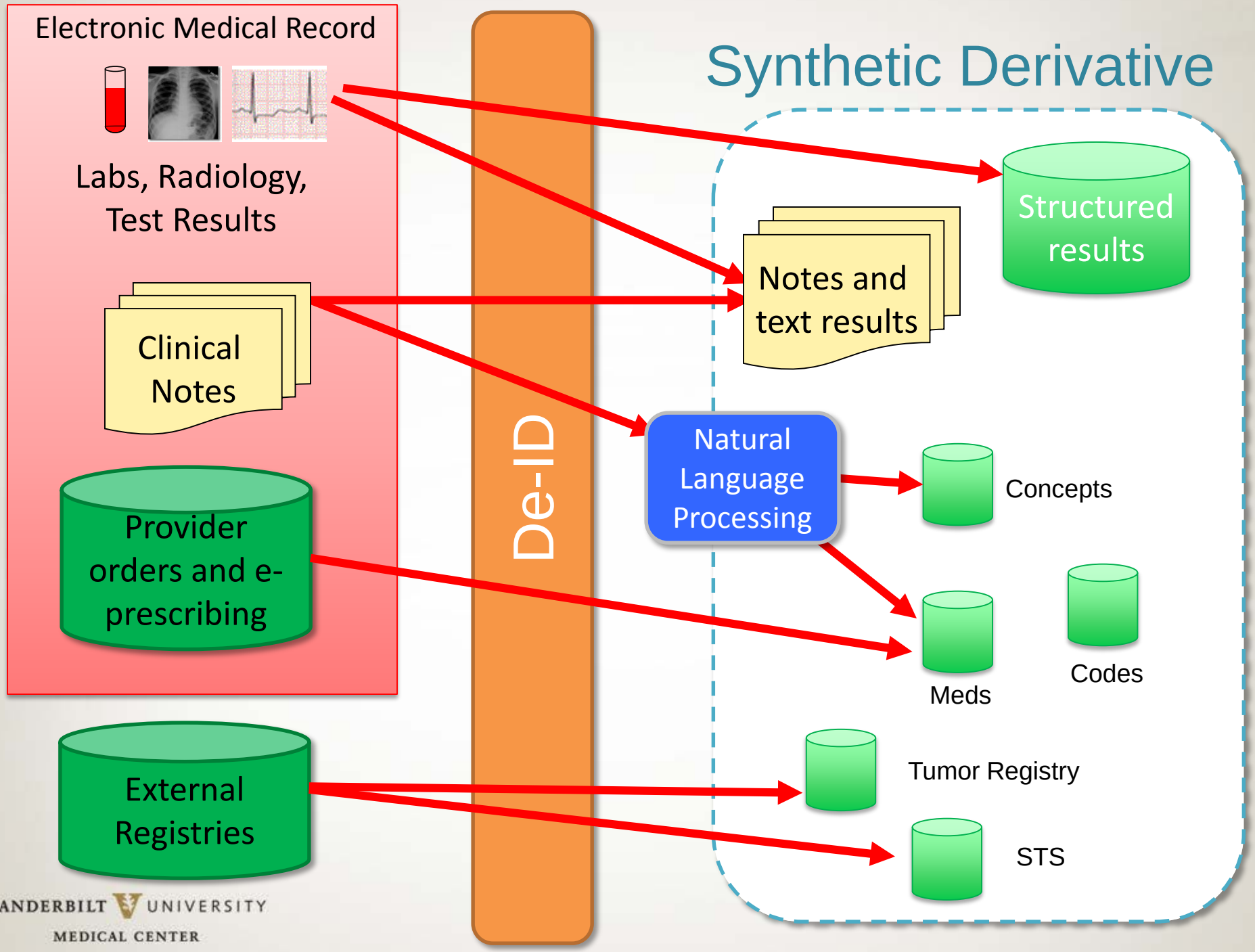

John Doe
eligible?
One way hash
A7CCF99DE5732....
Extract DNA
A7CCF99DE65732....
BioVU
~180,000 DNAs
John Doe
A7CCF99DE65732....
Scrubbed
~2 million records
The Synthetic Derivative:
updated regularly


Electronic Medical Record
Labs, Radiology, Test Results
Clinical Notes
Provider orders and e-prescribing
External Registries
De-ID
Synthetic Derivative
Structured results
Notes and text results
Natural Language Processing
Concepts
Meds
Codes
Tumor Registry
STS
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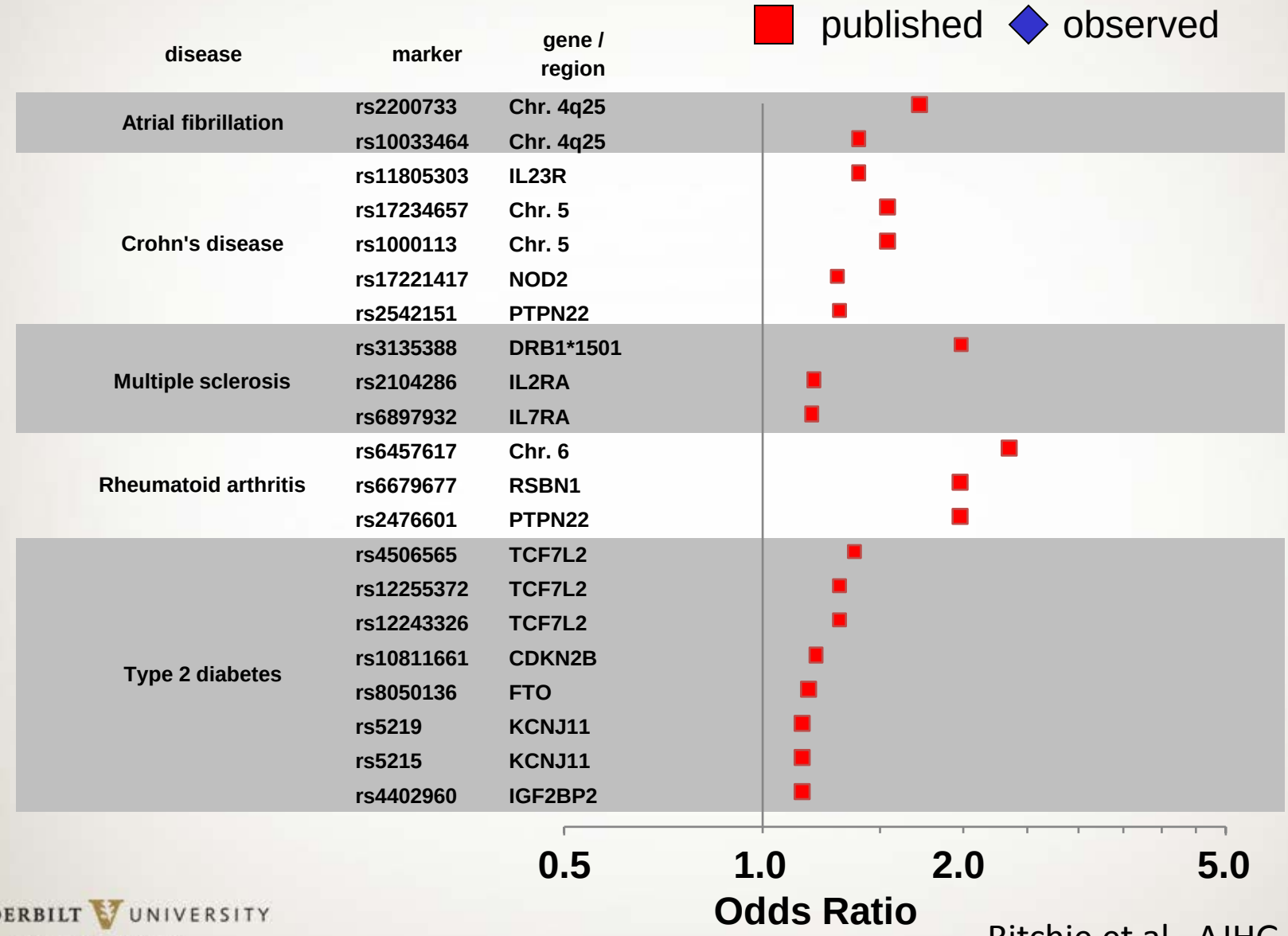
BioVU as a resource for discovery



Ritchie et al., AJHG 2010

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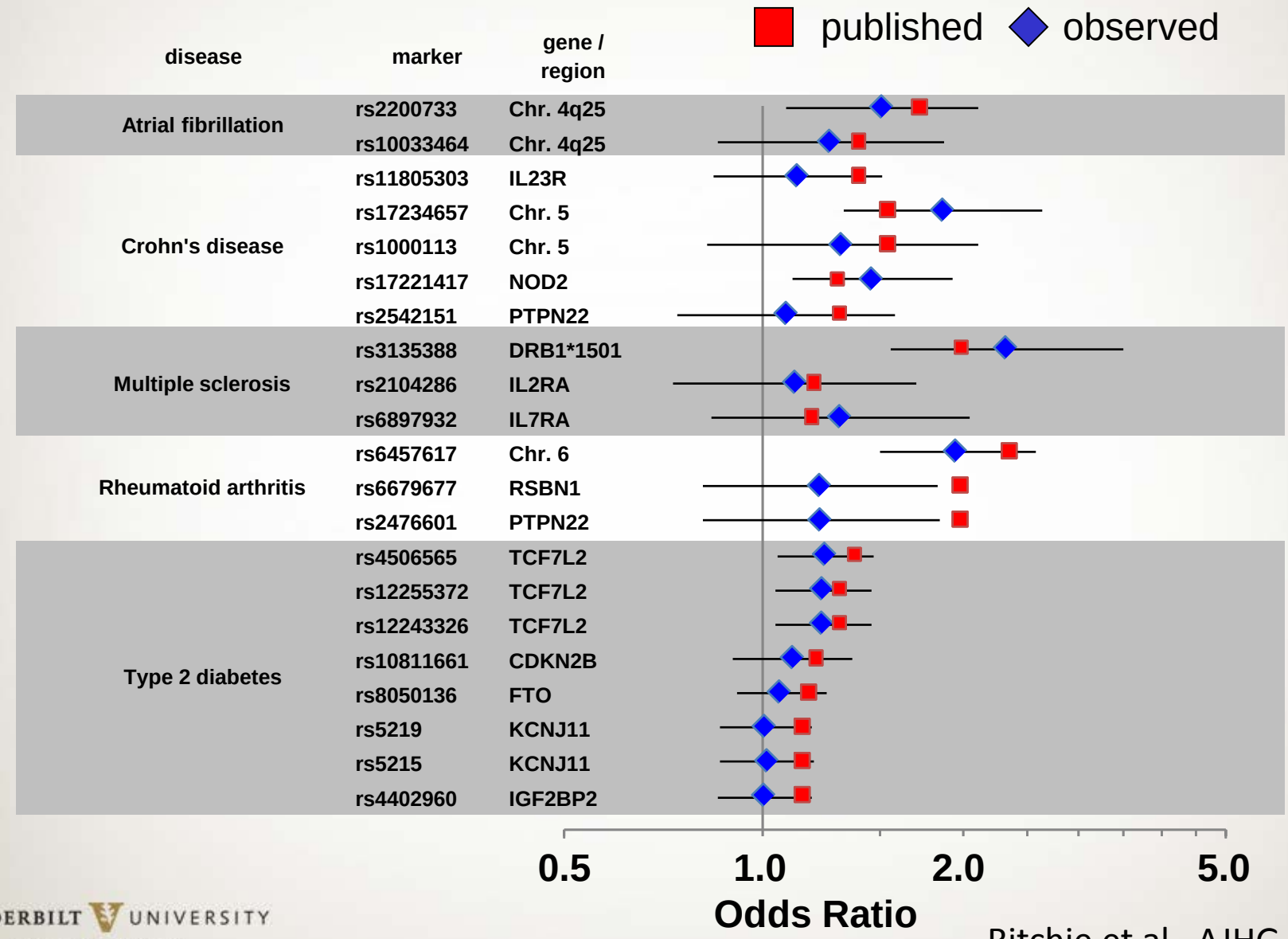

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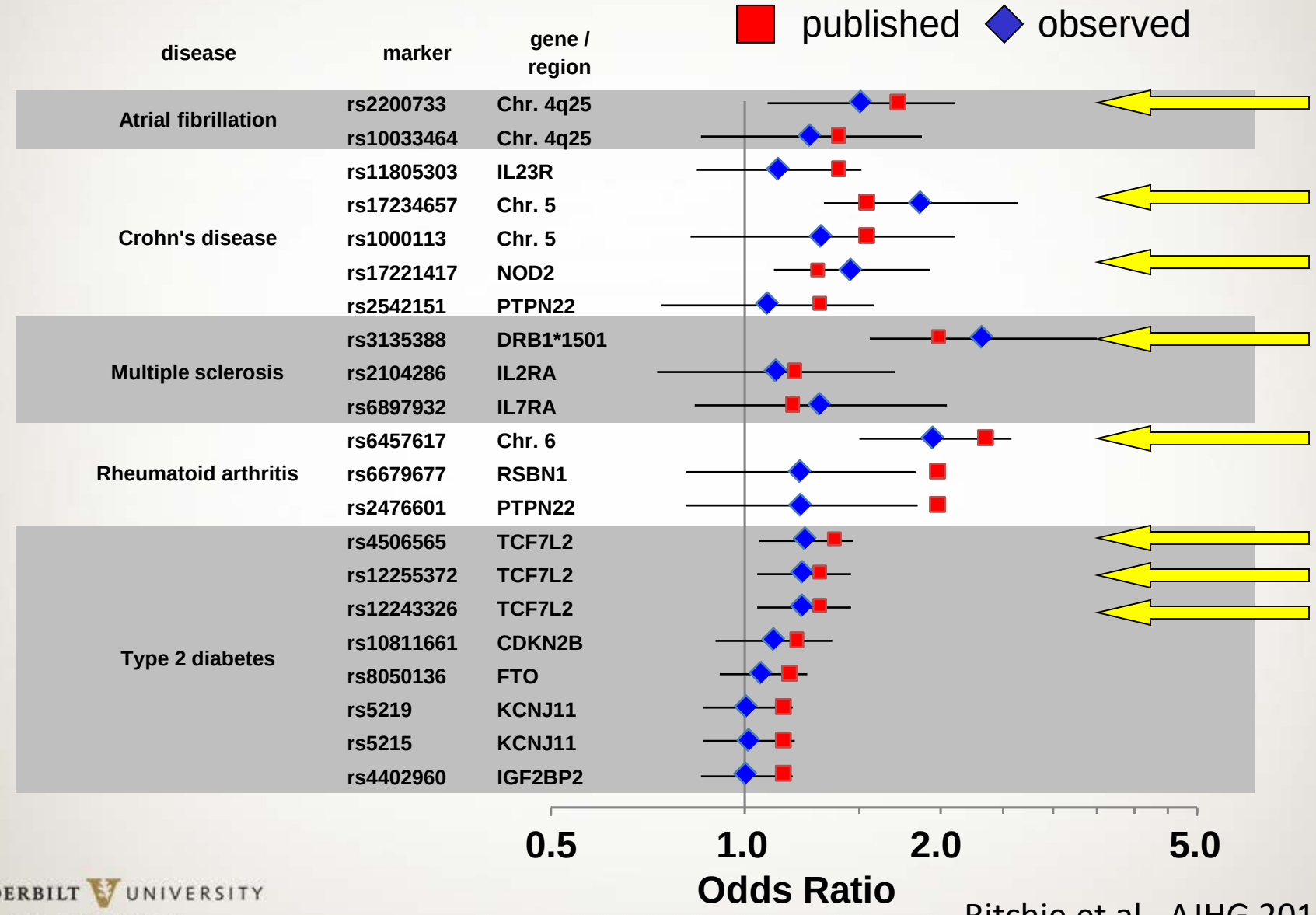
Ritchie et al., AJHG 2010

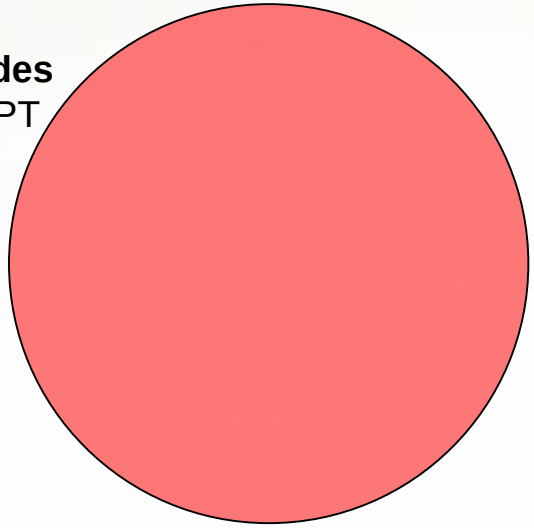
BioVU as a resource for discovery



Ritchie et al., AJHG 2010

What we learned - Finding phenotypes in the EMR

Billing codes
ICD9 & CPT



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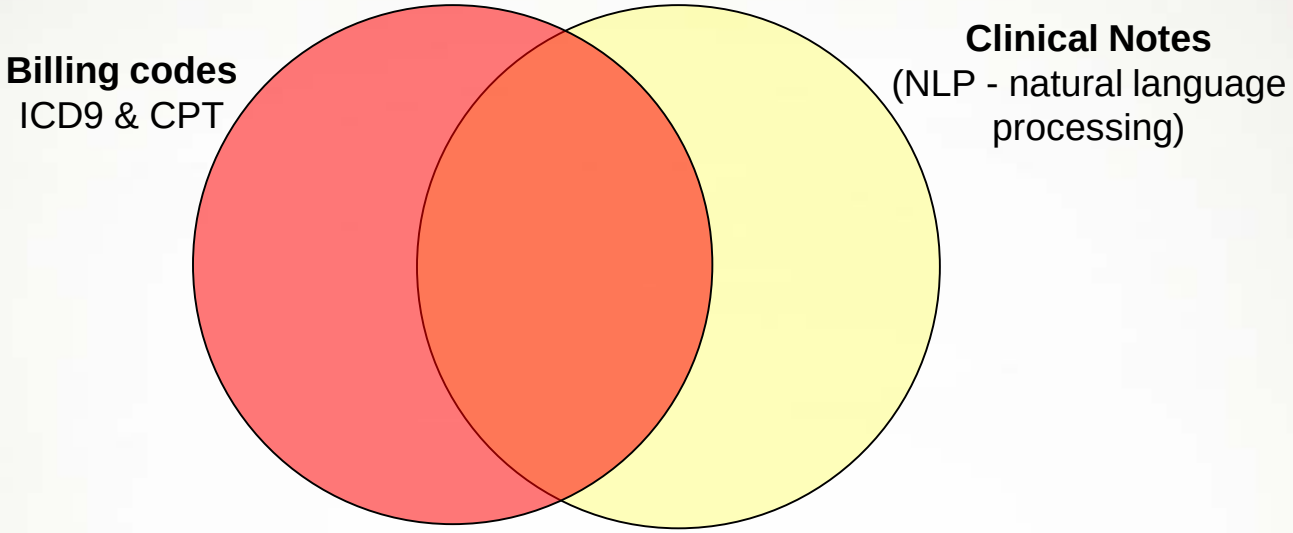

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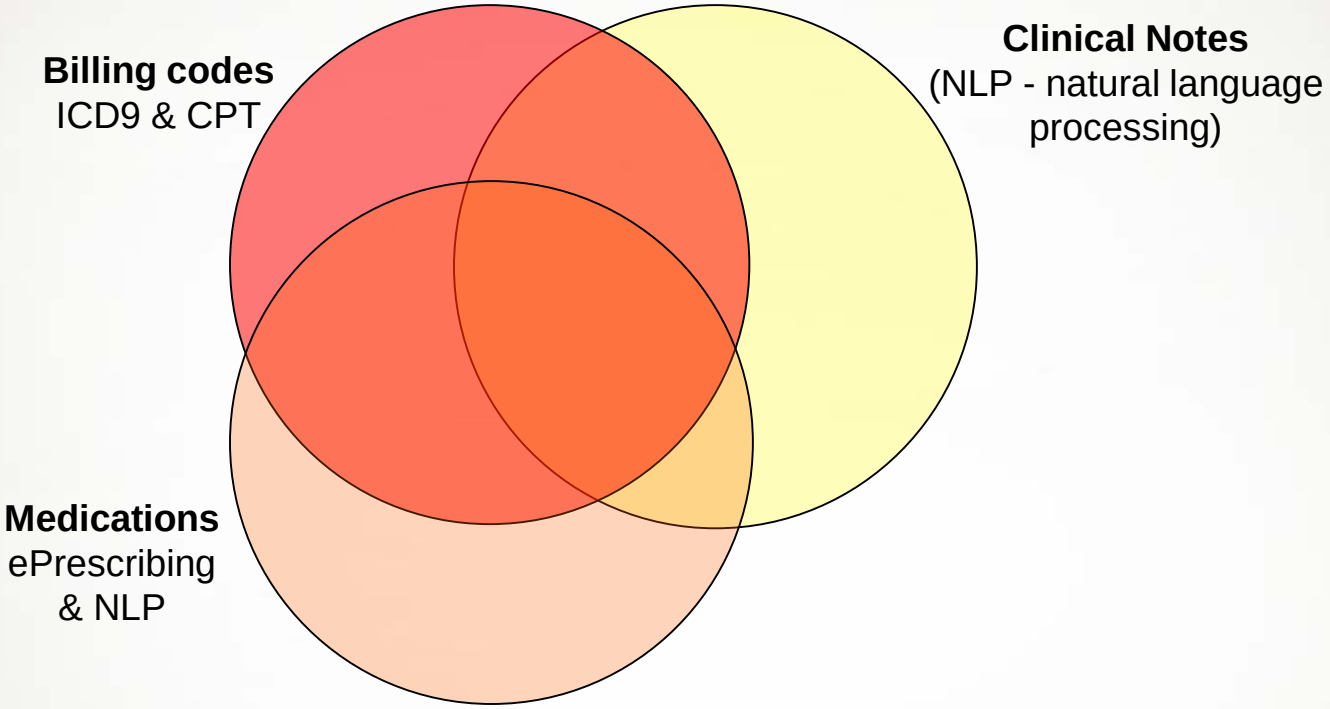

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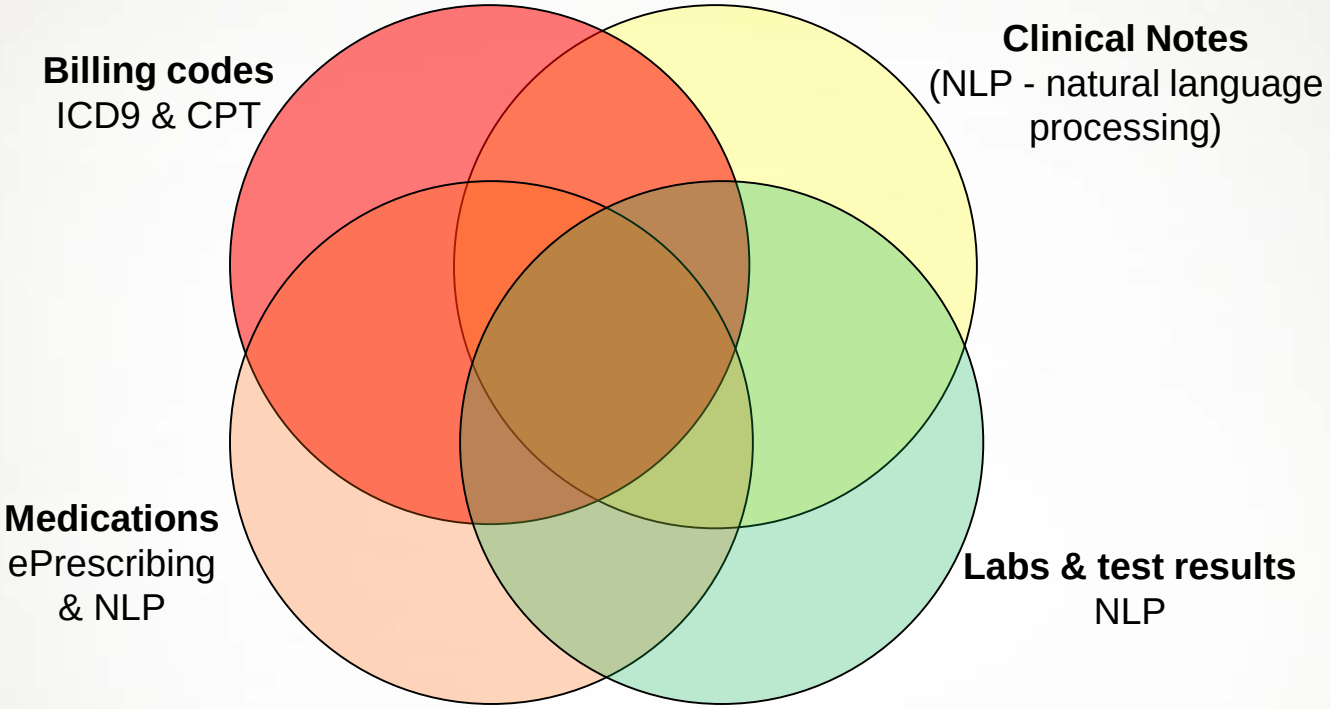

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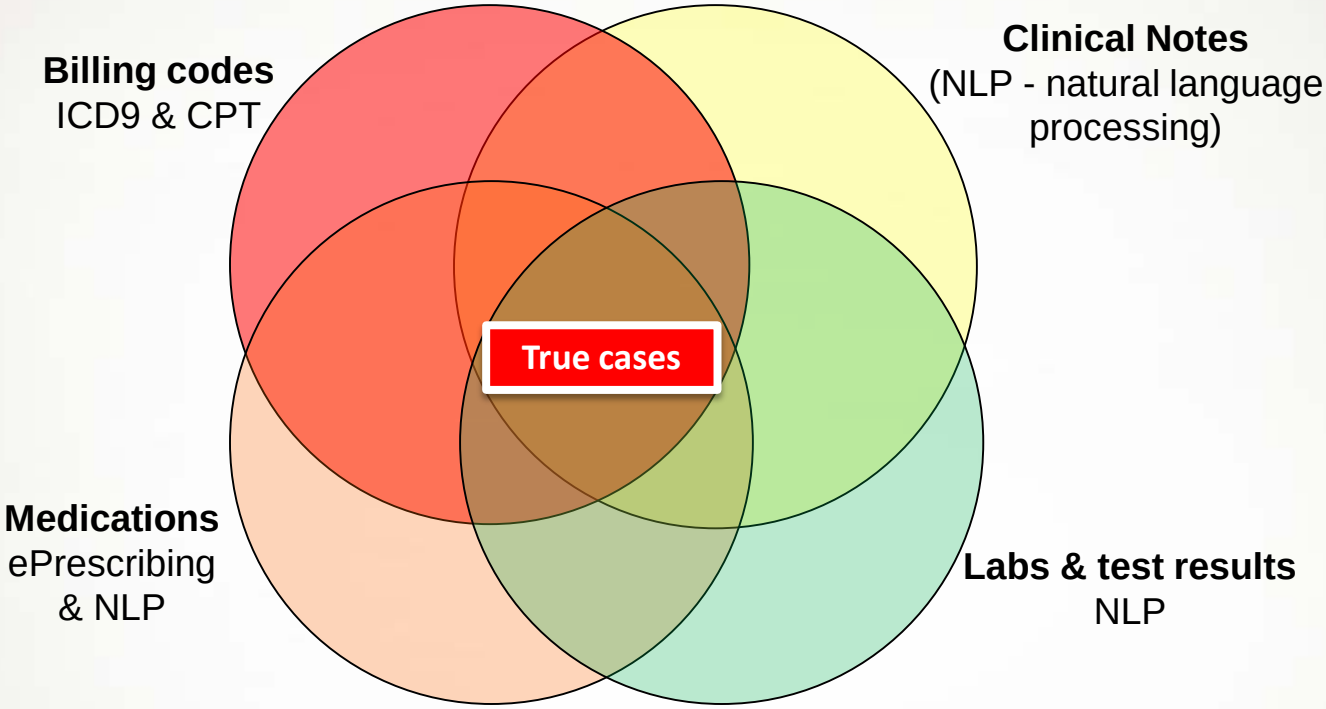

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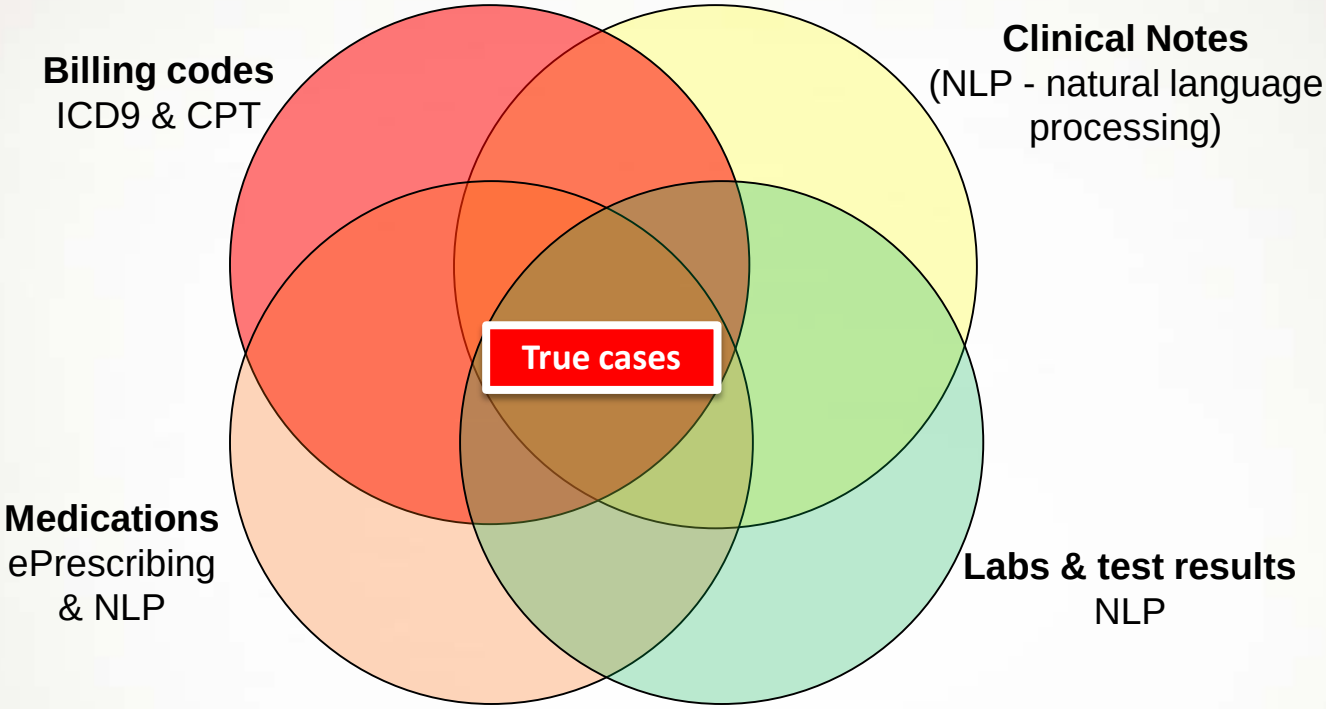
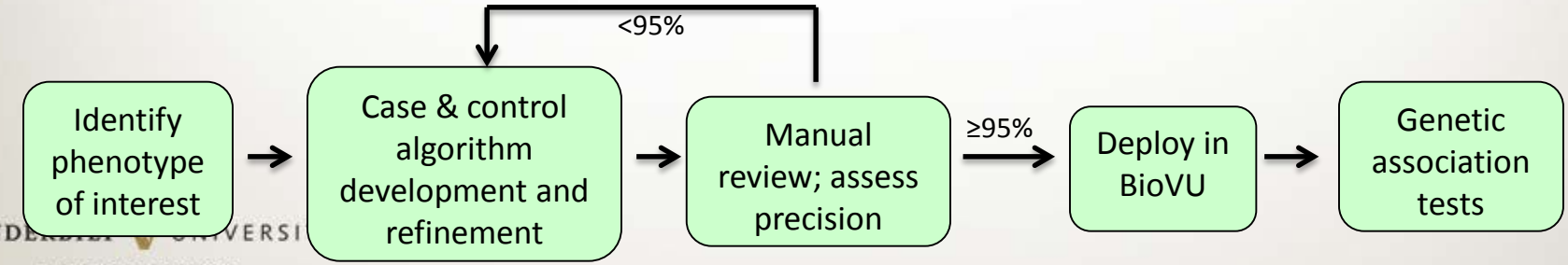


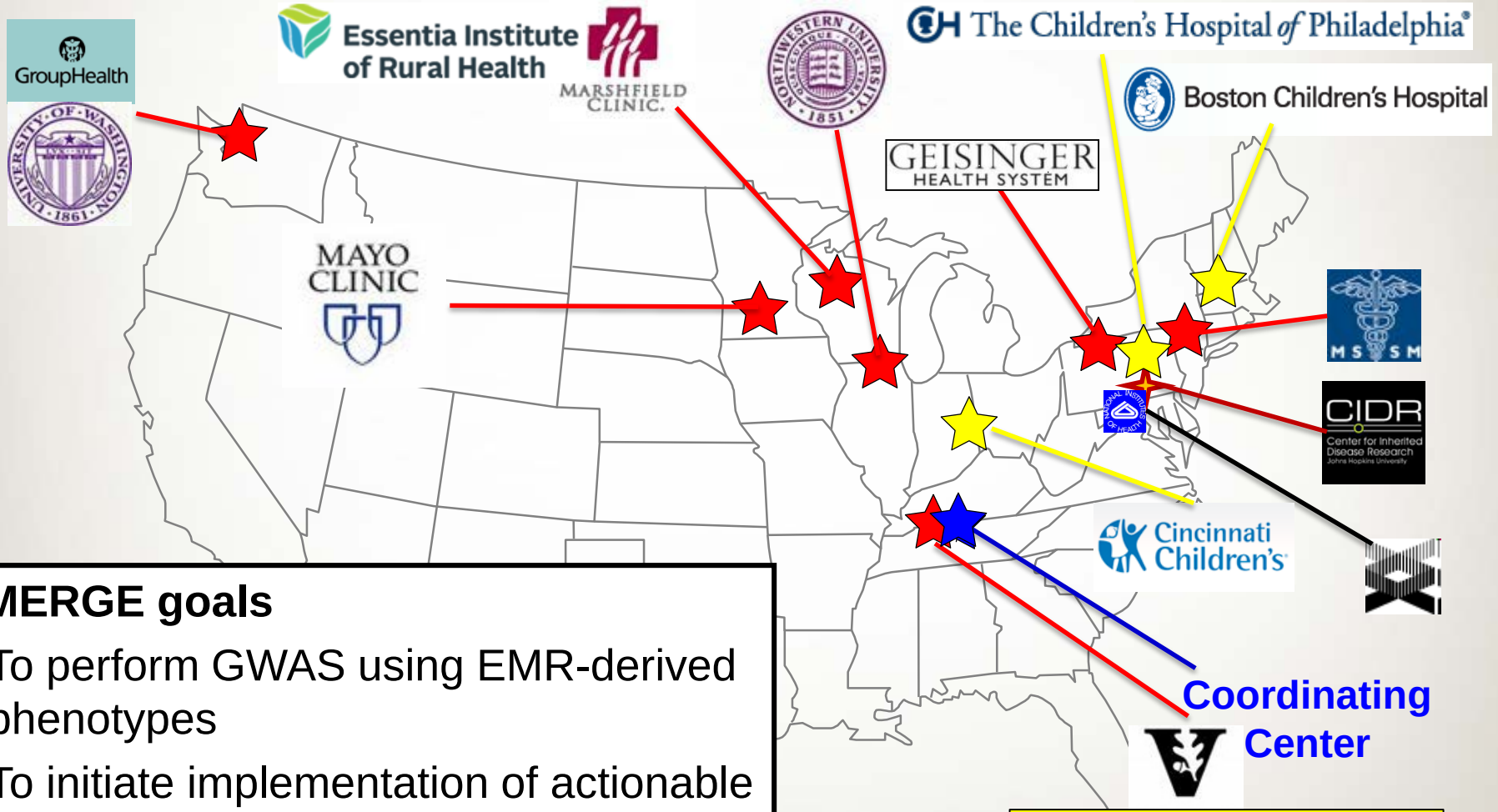
Algorithm Development and Implementation



The eMERGE Network

electronic Medical Records & Genomics

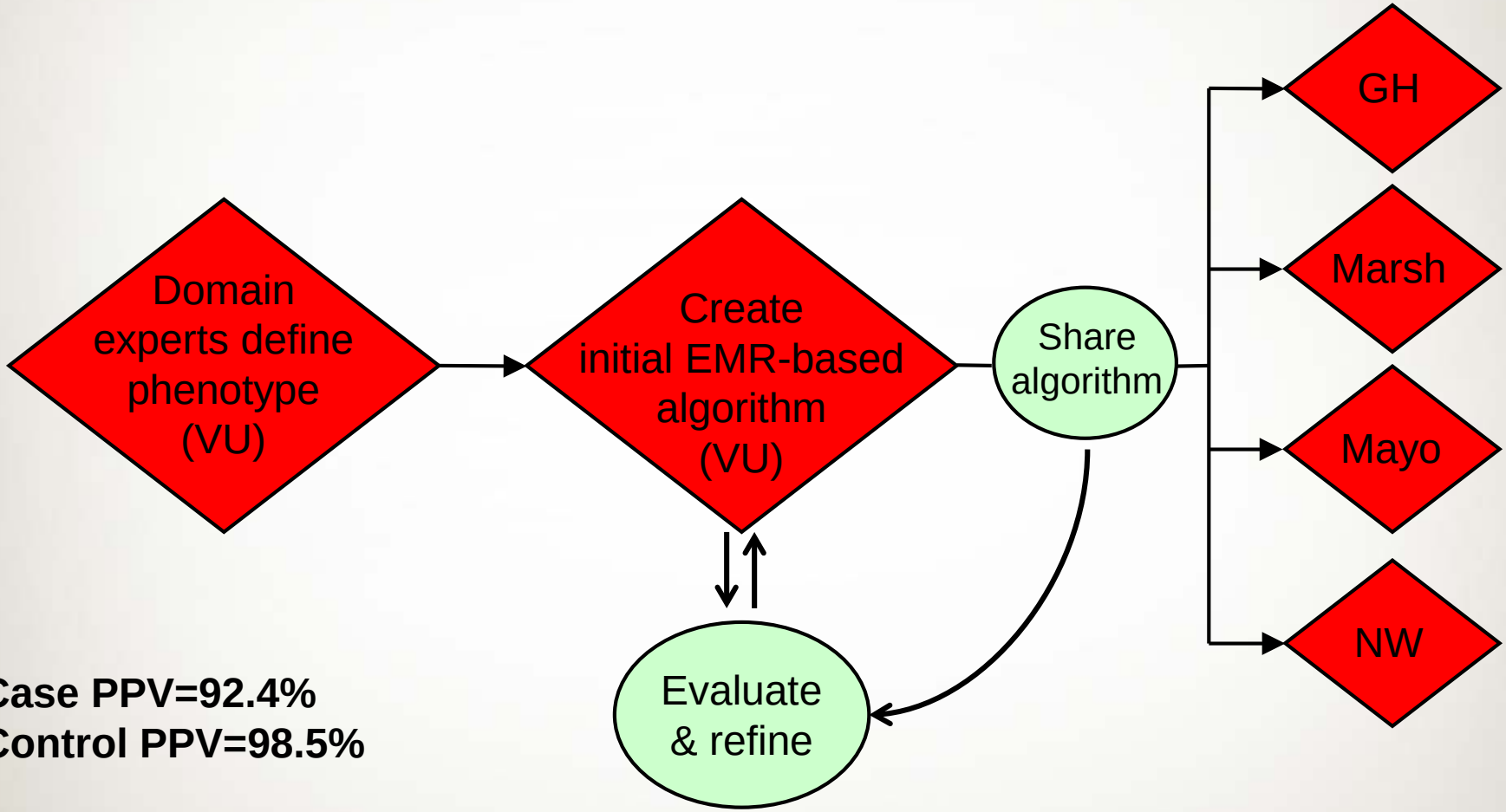
A consortium of biorepositories linked to electronic medical records data for conducting genomic studies



eMERGE goals

- To perform GWAS using EMR-derived phenotypes
- To initiate implementation of actionable variants into the EMR

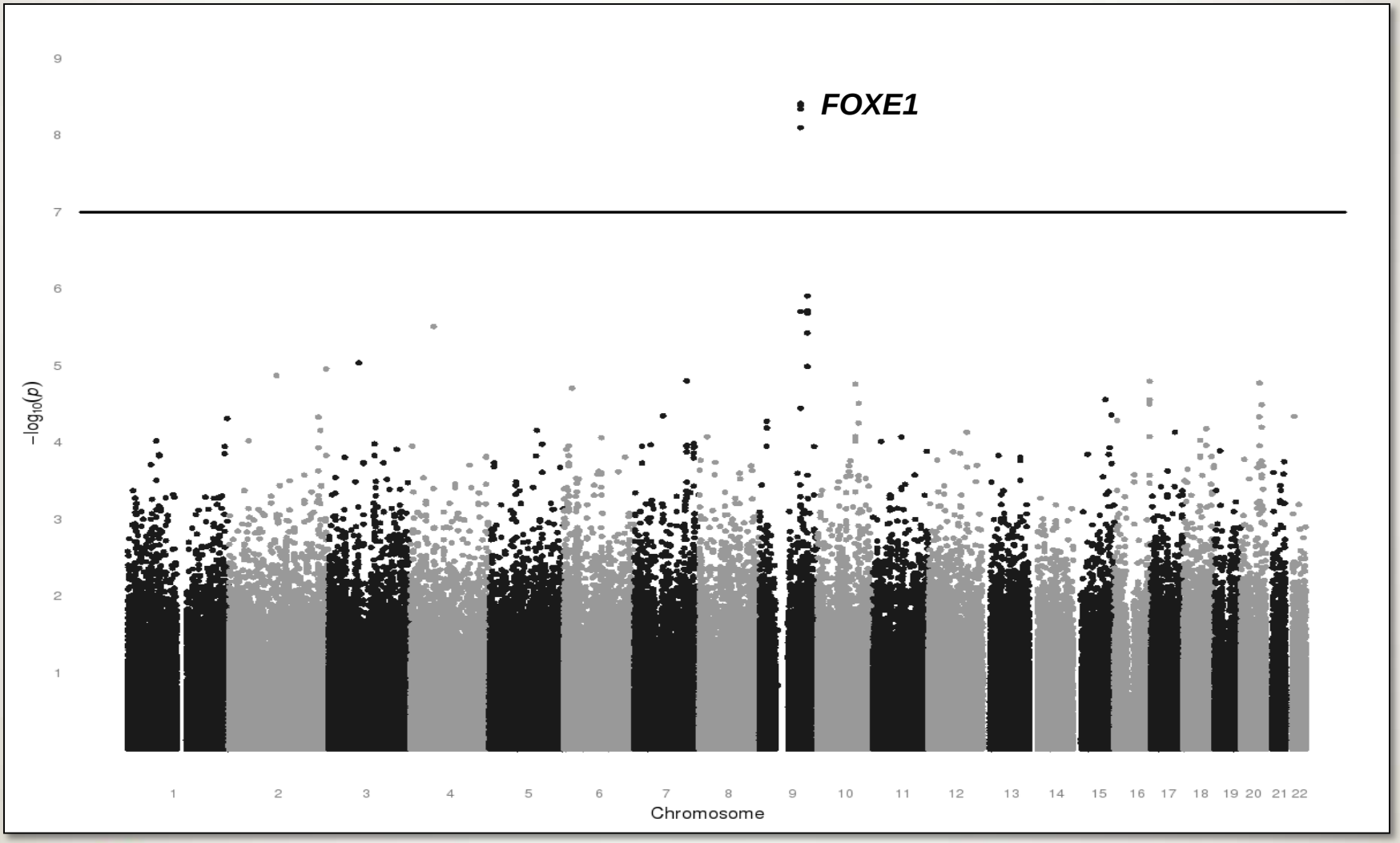
Hypothyroidism:
Can we do a "no genotyping" GWAS?



Case PPV=92.4%
Control PPV=98.5%

Denny et al., AJHG 2011

Hypothyroidism: "No-Genotyping" GWAS



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Denny et al., AJHG 2011

eMERGE GWAS completed

Site	Primary phenotype	Secondary Phenotypes
Group Health	**Dementia**	**white blood cell counts** **monocyte count** **herpes zoster** NEW
Marshfield	**Cataracts**	diabetic retinopathy
Mayo Clinic	Peripheral Arterial Disease	**red blood cell counts** NEW **ESR levels** NEW **Platelet levels**
Northwestern	**Type 2 Diabetes**	**HDL/LDL** **height**
Vanderbilt	**PR Duration** **QRS Duration** NEW	**PheWAS** NEW

Network Phenotypes
Autoimmune Hypothyroidism NEW
Resistant hypertension

bold=GWAS completed with significant results

NEW=first description or new findings

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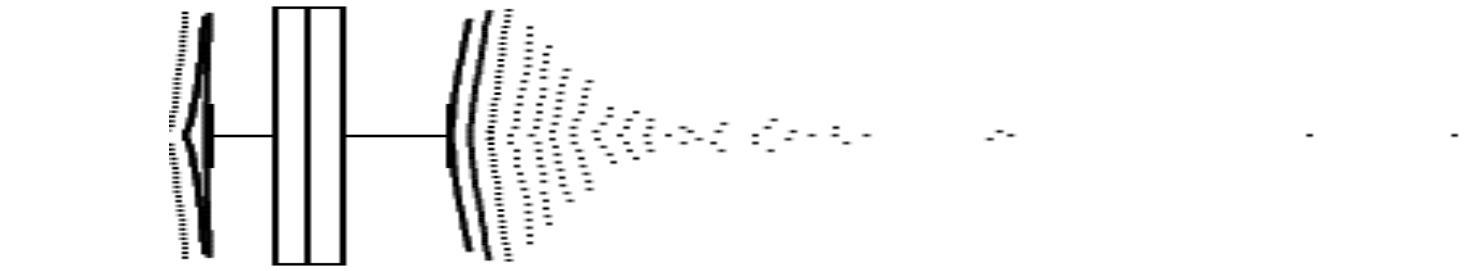
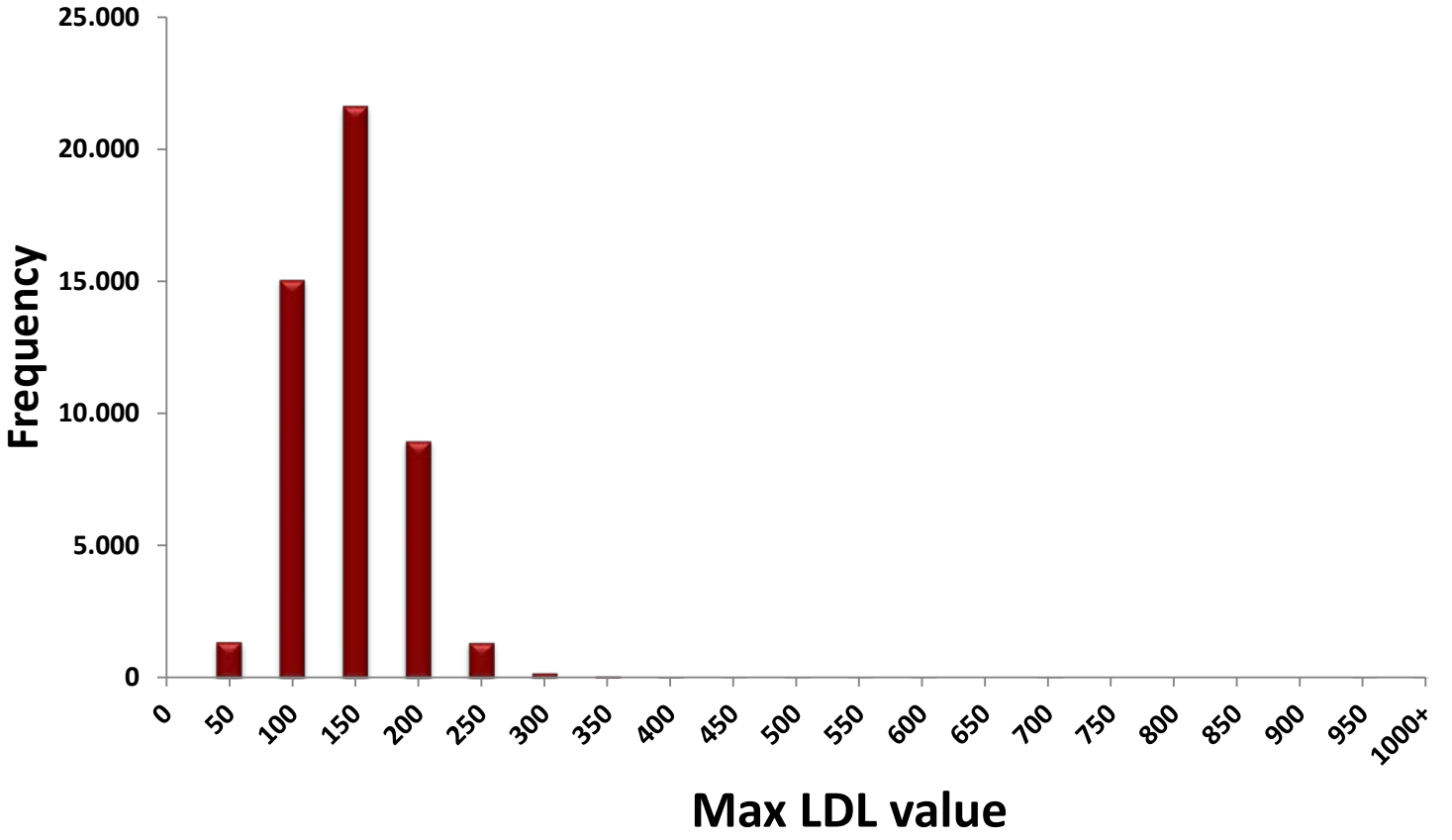
… another ~30 in progress as part of eMERGE II…

Extreme Phenotypes: LDL values in BioVU





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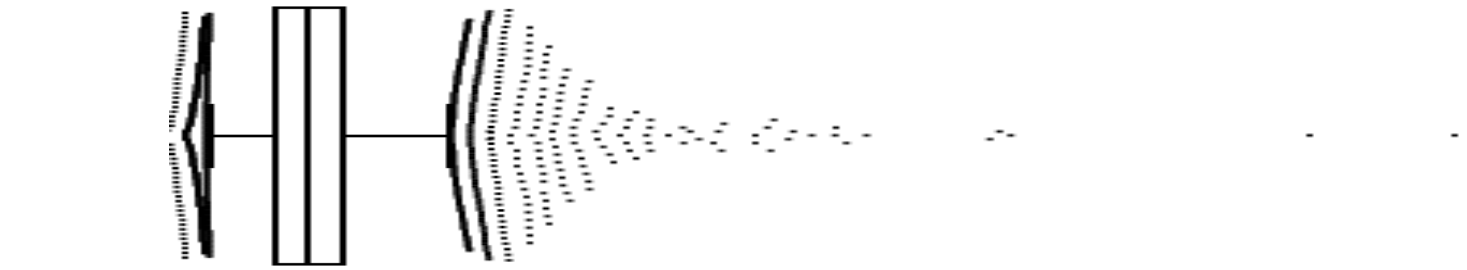

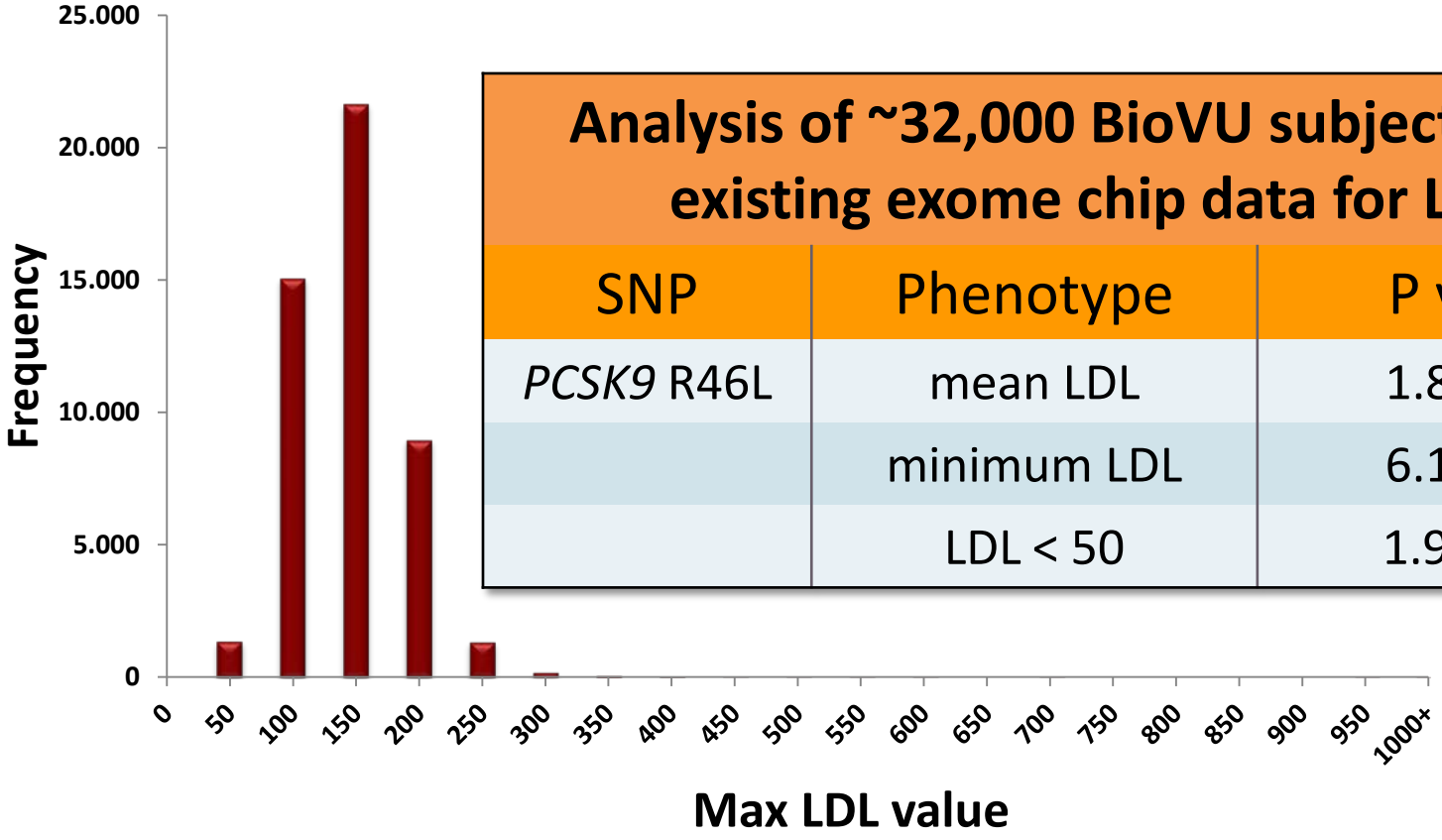

Analysis of ~32,000 BioVU subjects with existing exome chip data for LDL

SNP	Phenotype	P value
PCSK9 R46L	mean LDL	1.8×10^{-18}
	minimum LDL	6.1×10^{-13}
	LDL < 50	1.9×10^{-6}

Large scale GWAS for drug response discovery: the VESPA project

Vanderbilt Electronic Systems for Pharmacogenomic Assessment

Phenotype	Cases	Controls	% Reuse
Clopidogrel in CV disease	225	468	27%
Warfarin stable dose	1,167	N/A	47%
Early Repolarization	544	2,609	89%
Vancomycin stable dose	1,067	N/A	42%
C. difficile colitis	941	1,710	28%
Anthracycline cardiomyopathy	528	N/A	39%
Guillain-Barre Syndrome	97	6,536	99%
Heart Transplant	181	N/A	42%
Kidney transplant	1,078	N/A	32%
Clopidogrel in strokes/TIAs	6	123	22%
Statin-related myopathy	11	4,342	100%
Heparin-induced thrombocytopenia	73	2,300	99%
CV events with COX2 therapy	85	395	34%
Serious bleeding during warfarin	259	276	43%
Amiodarone toxicity (lung, thyroid)	97	343	34%
Chronic inflammatory polyneuropathy	12	14,000*	100%
Rheumatic Heart Disease	108	3,464	98%
ACEi cough	1,174	978	52%
Fluoroquinolones and tenopathy	87	537	90%
Warfarin stable dose in children	92	N/A	28%
Metformin efficacy	80	N/A	35%
Metformin and cancer	619	421	83%
Bisphosphonates and Atypical Fracture/Jaw Osteonecrosis	16	1,454	99%
Wolff-Parkinson-White	197	5,551	97%
Steroid-induced Osteonecrosis	83	352	57%
Shellfish Anaphylaxis	157	14,000*	99%
Aspirin Anaphylaxis	101	4,334	98%
Bell's Palsy[#]	577	14,000*	97%

Bowton et al., *Sci Trans Med.* 2014

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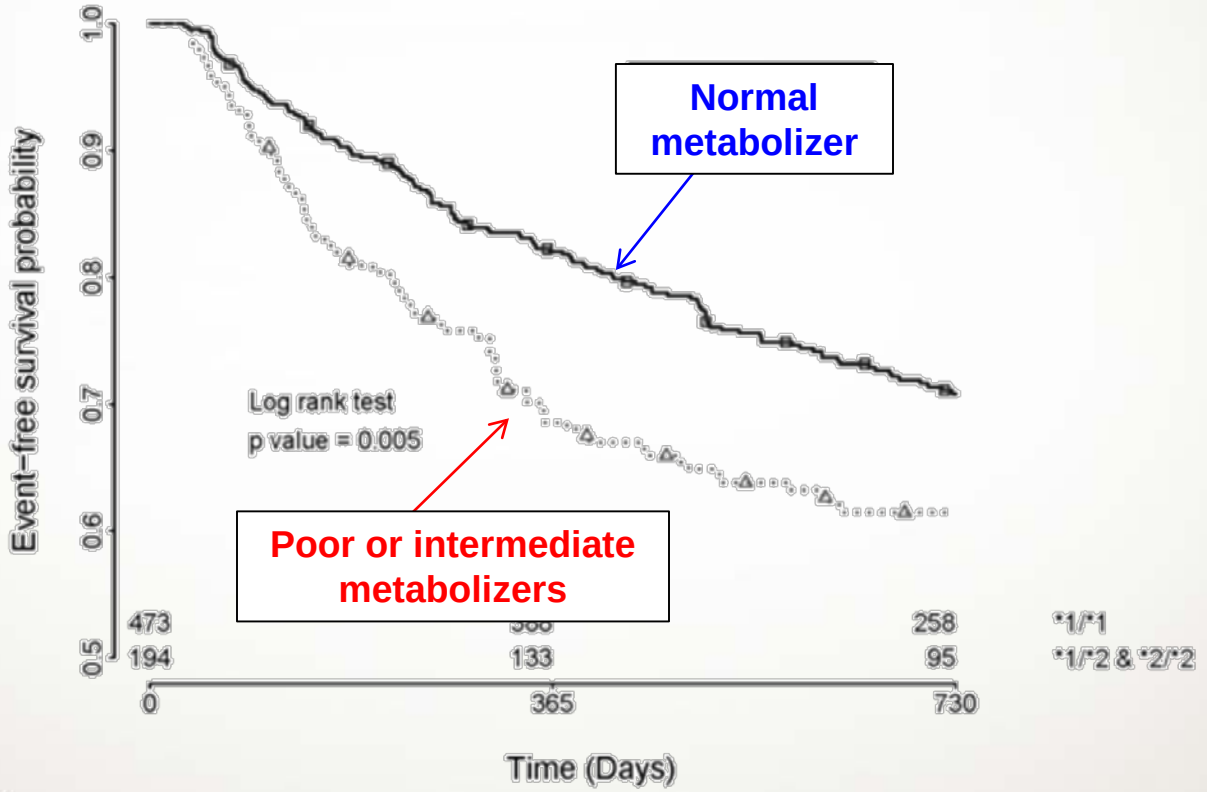
clopidogrel $\xrightarrow{CYP2C19}$ 2-oxoclopidogrel

clopidogrel failure=MI, stroke, revascularization, death following MI or PCI
Semi-automated Methods: Algorithms + Manual Review
n=225 cases / 468 controls



Delaney et al. *Clin Pharm Ther.* 2012

Predicting Warfarin Dose

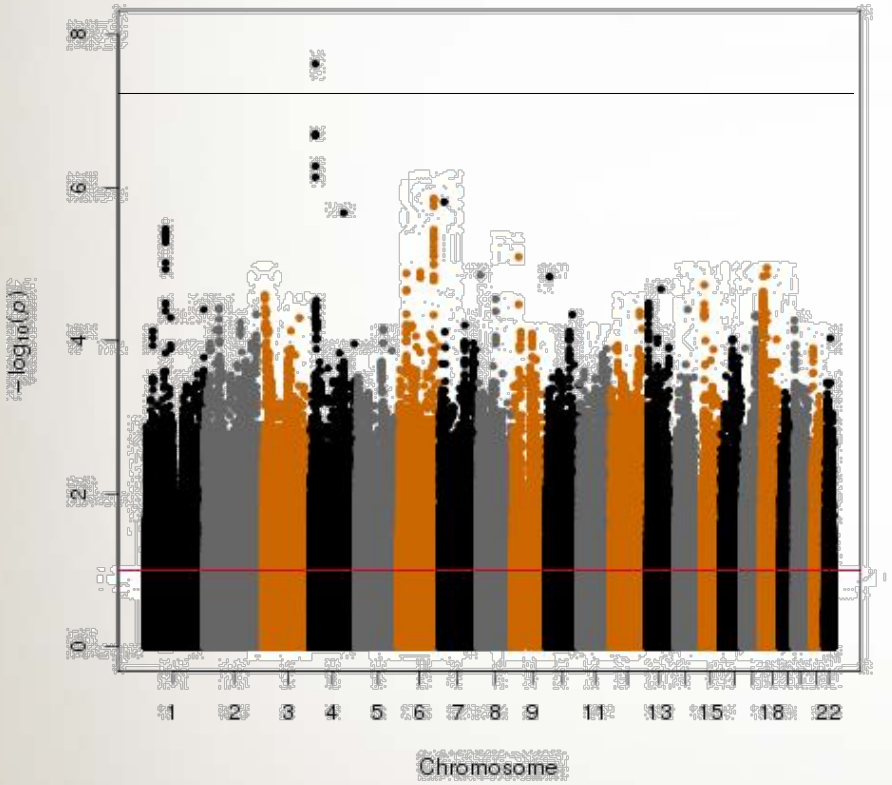
Trained from the stable doses in the EMR

SNP (Gene)	Beta	P
rs1057910 (CYP2C9*3)	0.83	2.70×10^{-26}
rs9934438 (VKORC1)	0.87	4.48×10^{-61}

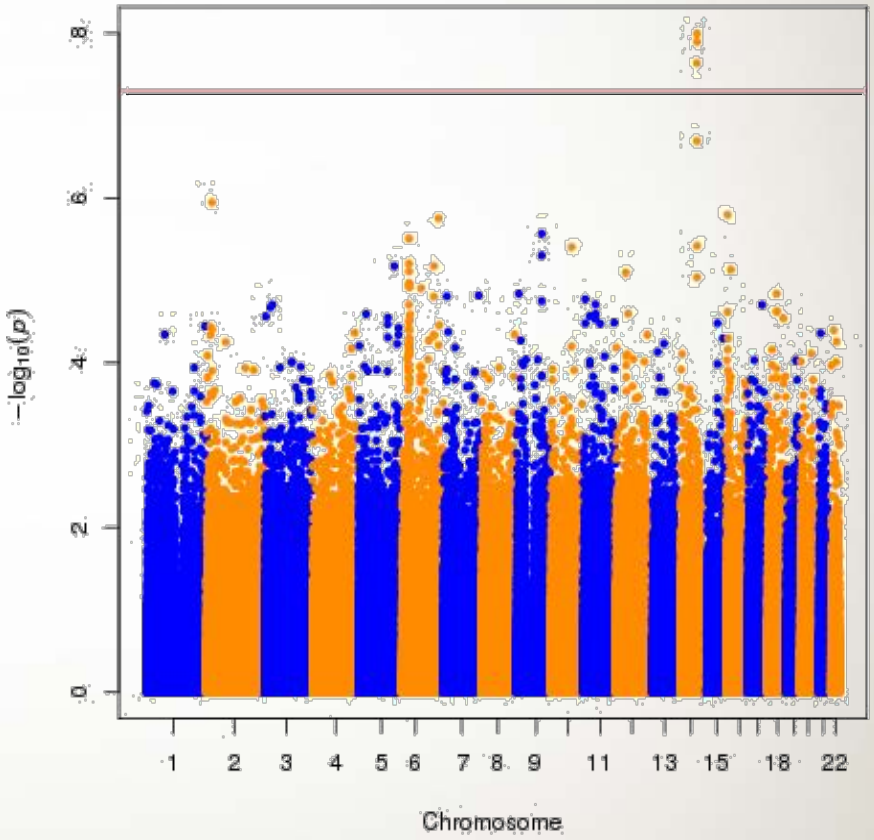
Ramirez et al. *Pharmacogenomics.* 2012

Two in-progress GWAS of Drug-ADEs from the EHR

ACEI-cough
(NLP of allergy sections, automated)



Heparin-induced thrombocytopenia
(automated+manual review)



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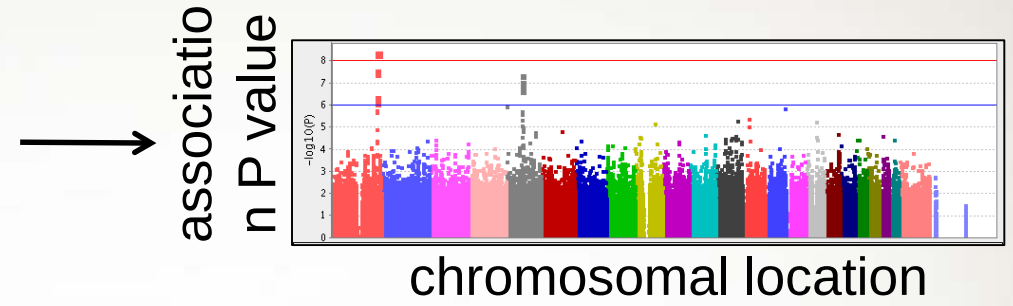
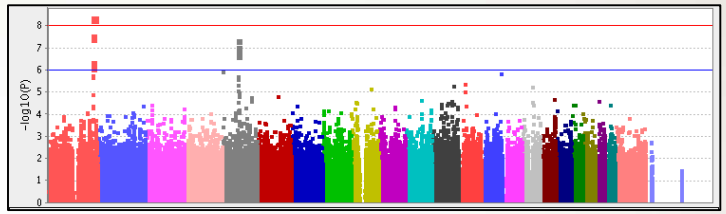
The genome-wide association study

Target phenotype



The genome-wide association study

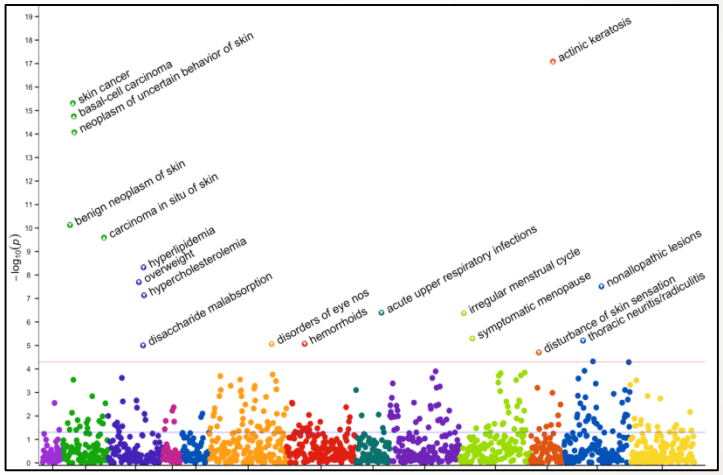
Target phenotype → association P value



chromosomal location

The phenome-wide association study

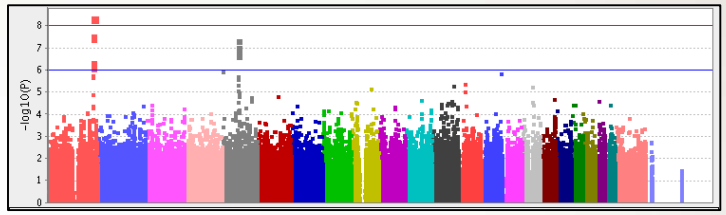
Target genotype → association P value



diagnosis code

The genome-wide association study

Target phenotype → association P value



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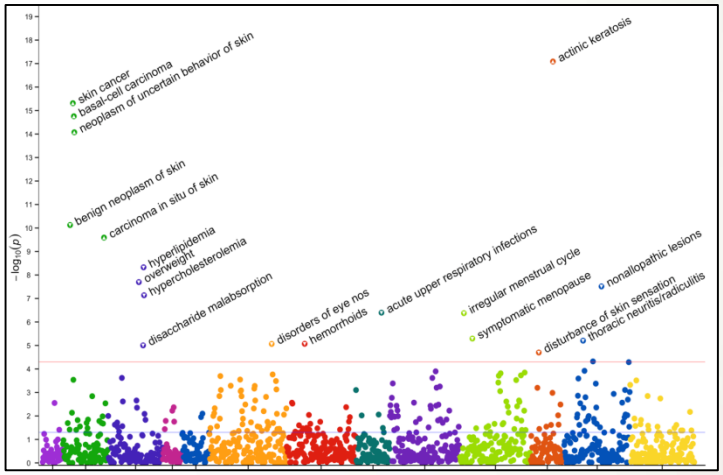
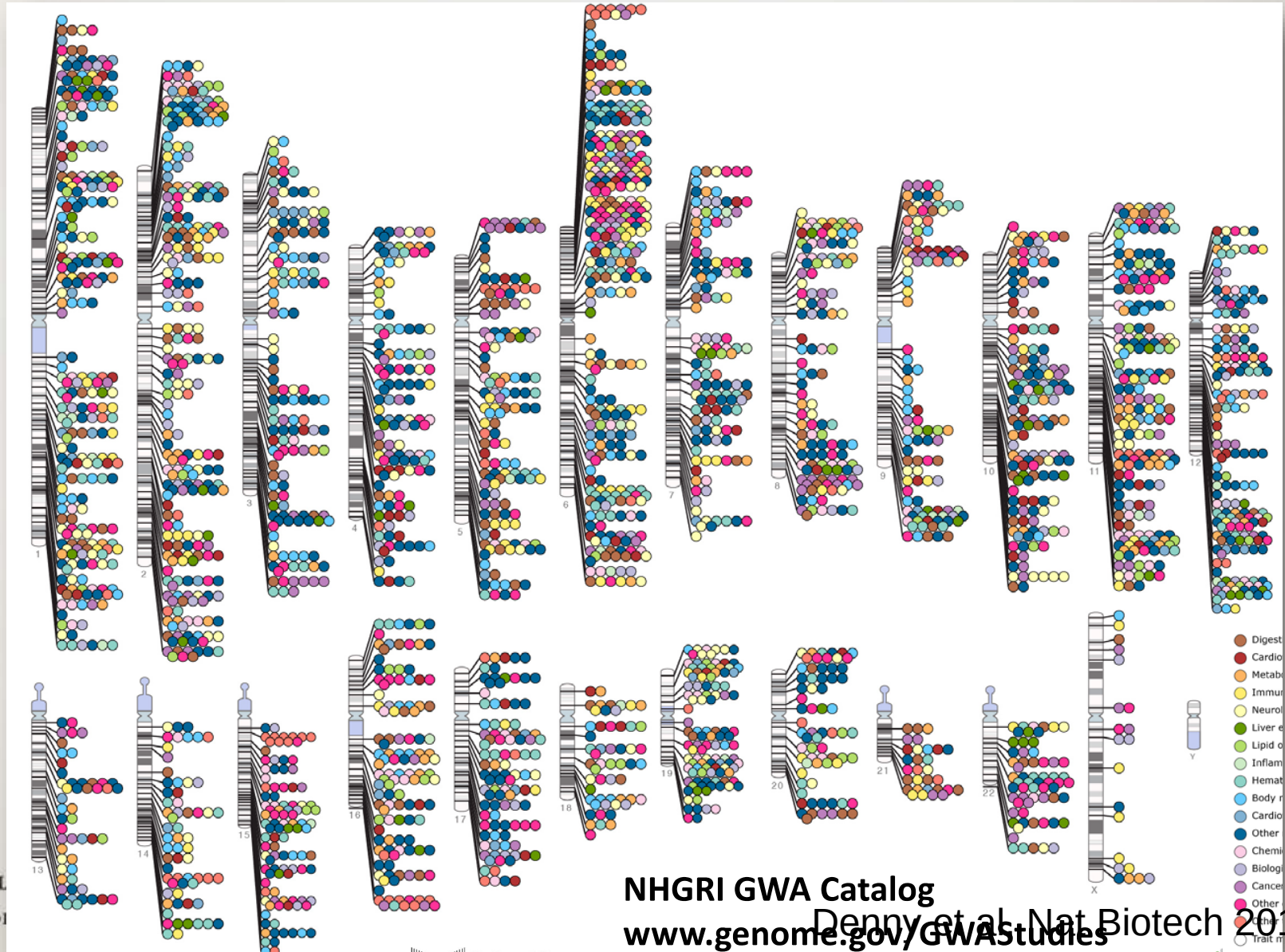


diagnosis code

PheWAS requirement: A large cohort of patients with genotype data and many diagnoses

PheWAS of “all” NHGRI GWAS Catalog SNPs



Denny et al. Nat Biotech 2013

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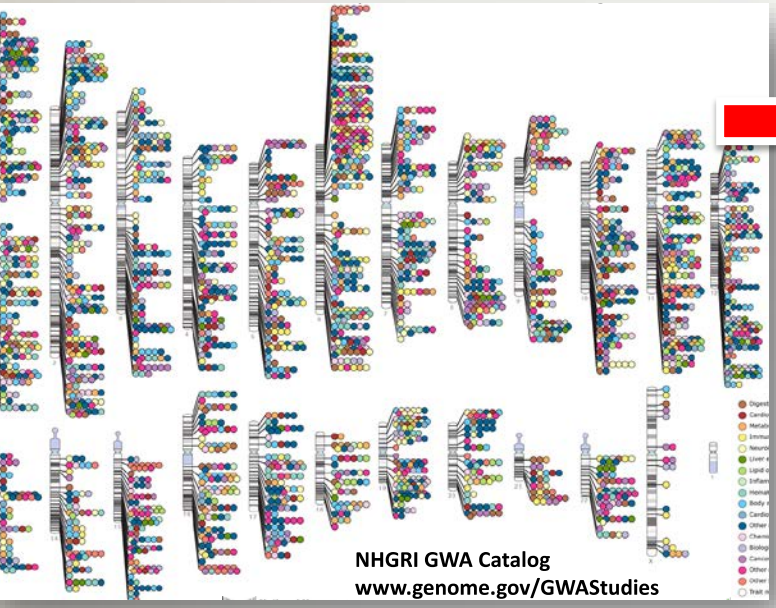

3,144 SNPs with prior GWAS-discovered associations

Denny et al, Nat Biotech 2013

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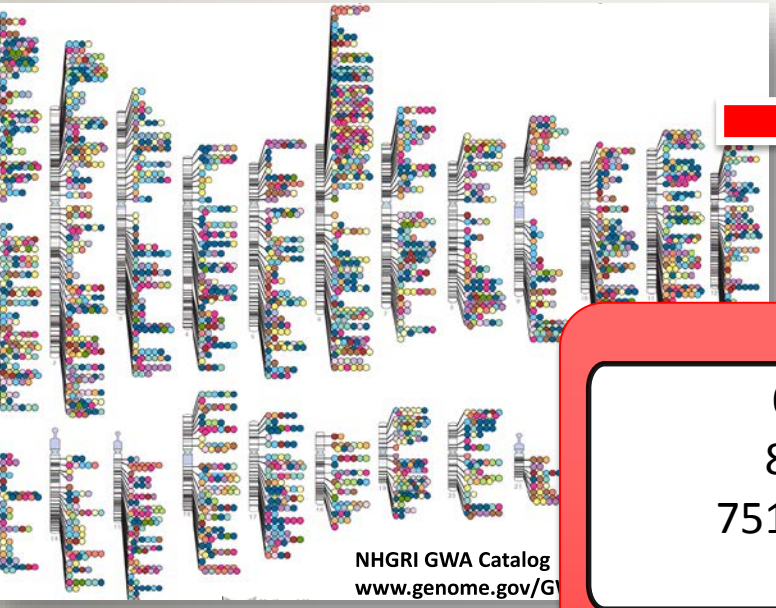

3,144 SNPs with prior GWAS-discovered associations

674 SNPs with
86 phenotypes
751 SNP-phenotype associations

Test for replication of 751 associations using PheWAS

Replication Arm

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Denny et al, Nat Biotech 2013

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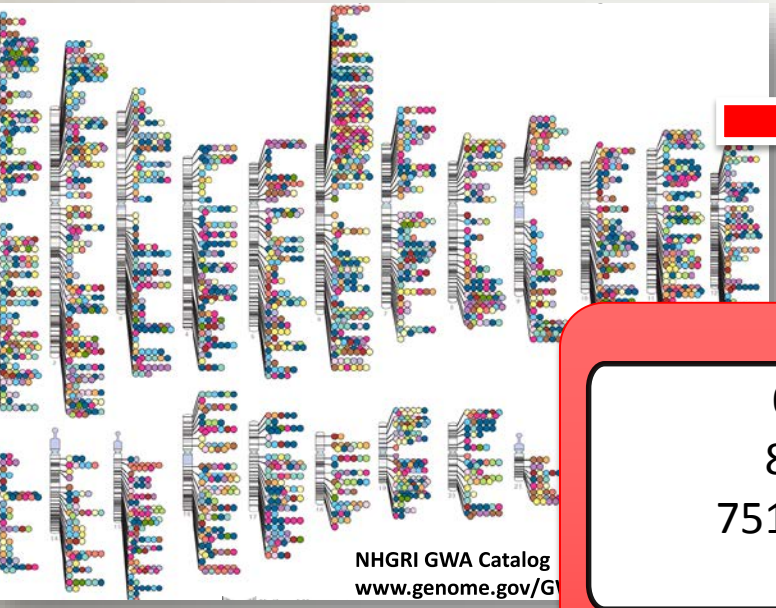

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Replication Arm

3,144 SNPs

PheWAS for each SNP to discovery pleiotropy

Replication of novel associations

Discovery Arm

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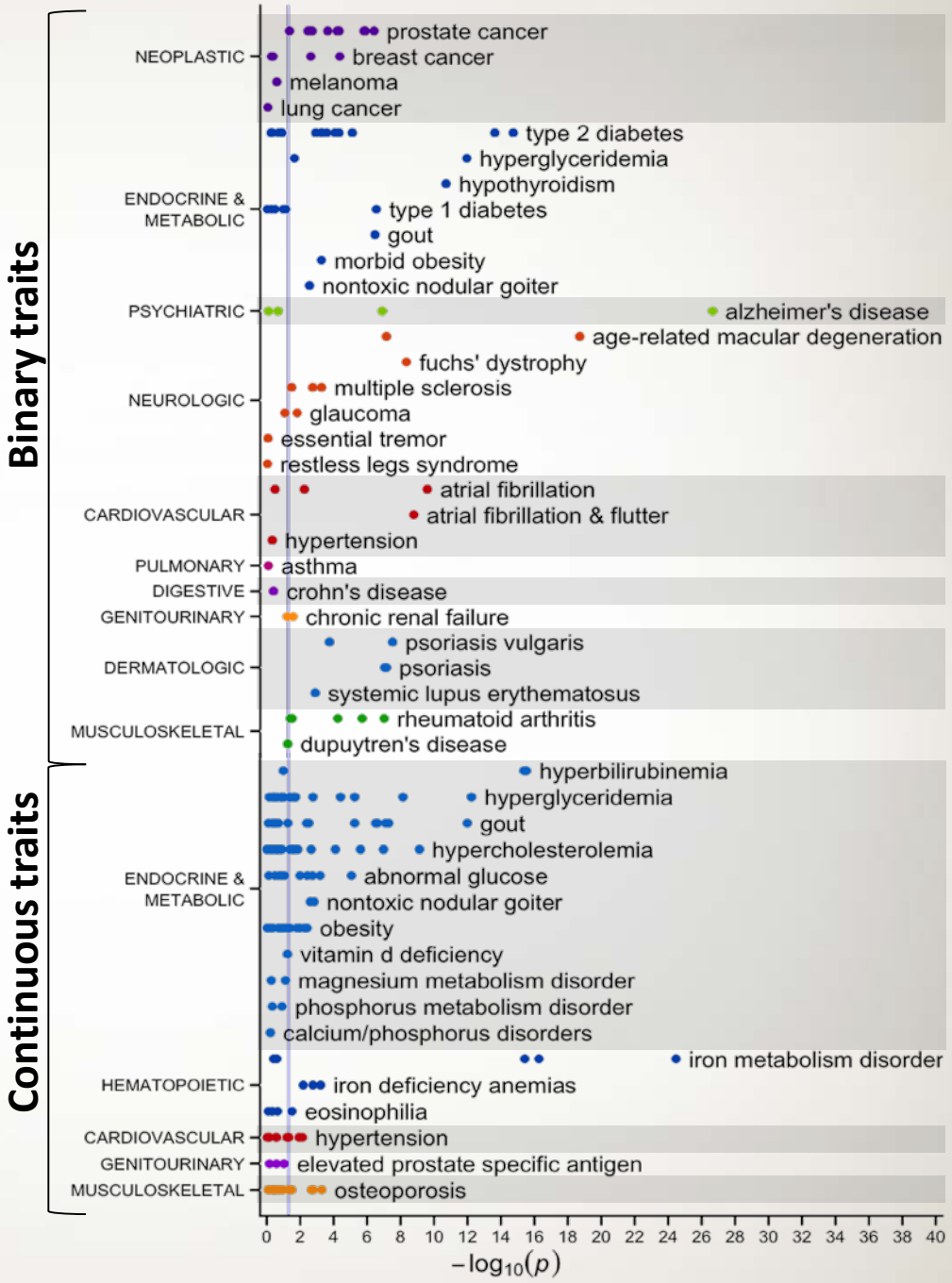
Denny et al, Nat Biotech 2013

Replications of NHGRI GWAS associations via PheWAS

P-value for replication:

- All - 210/751: $2x10^{-98}$
- Powered - 51/77: $3x10^{-47}$



Denny et al, Nat Biotech 2013

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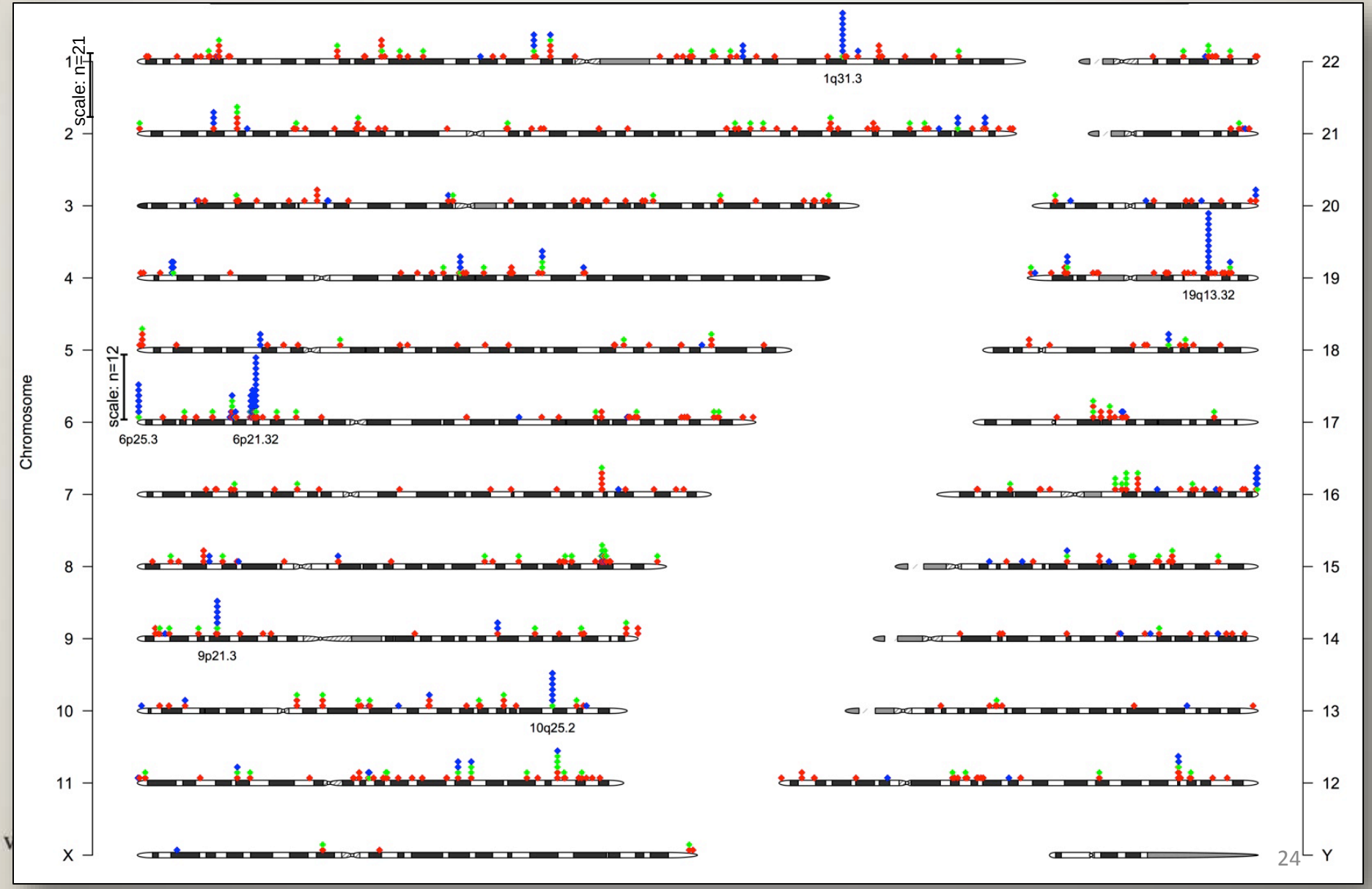
PheWAS of all GWAS "hits"

Each dot=one phenotype

- GWA catalog association only
- GWA catalog association replicated by PheWAS
- New association found by PheWAS



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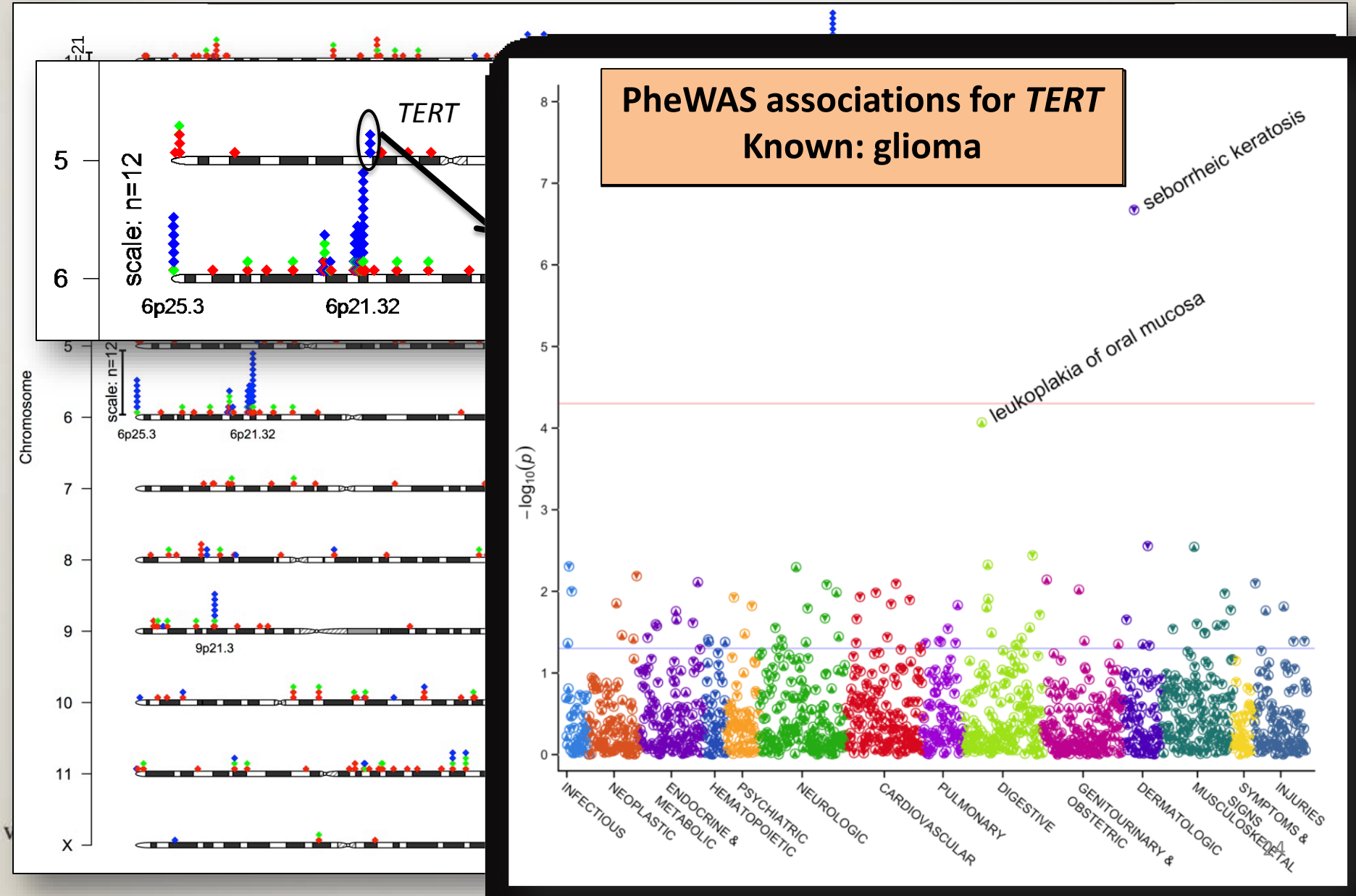

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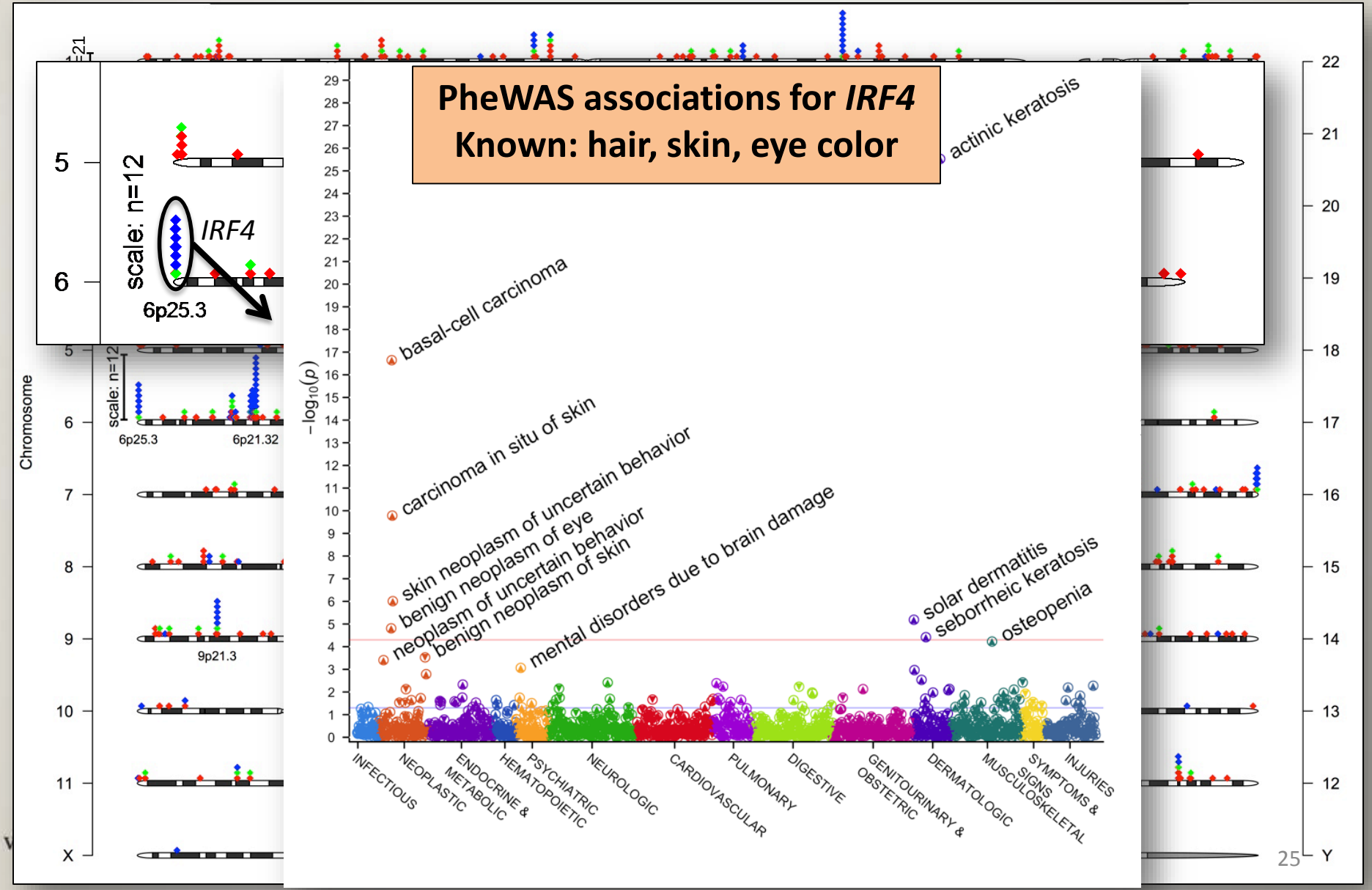
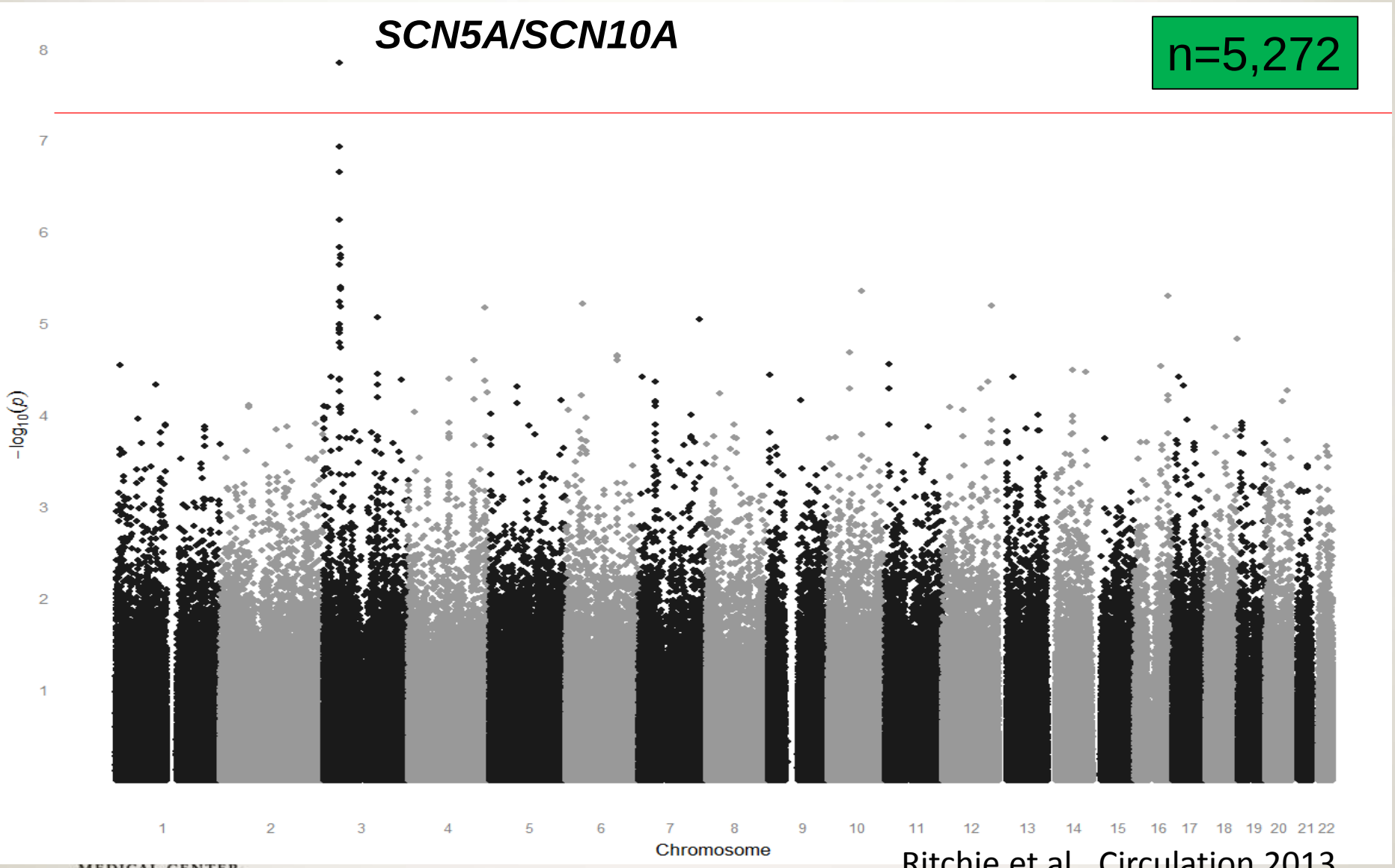


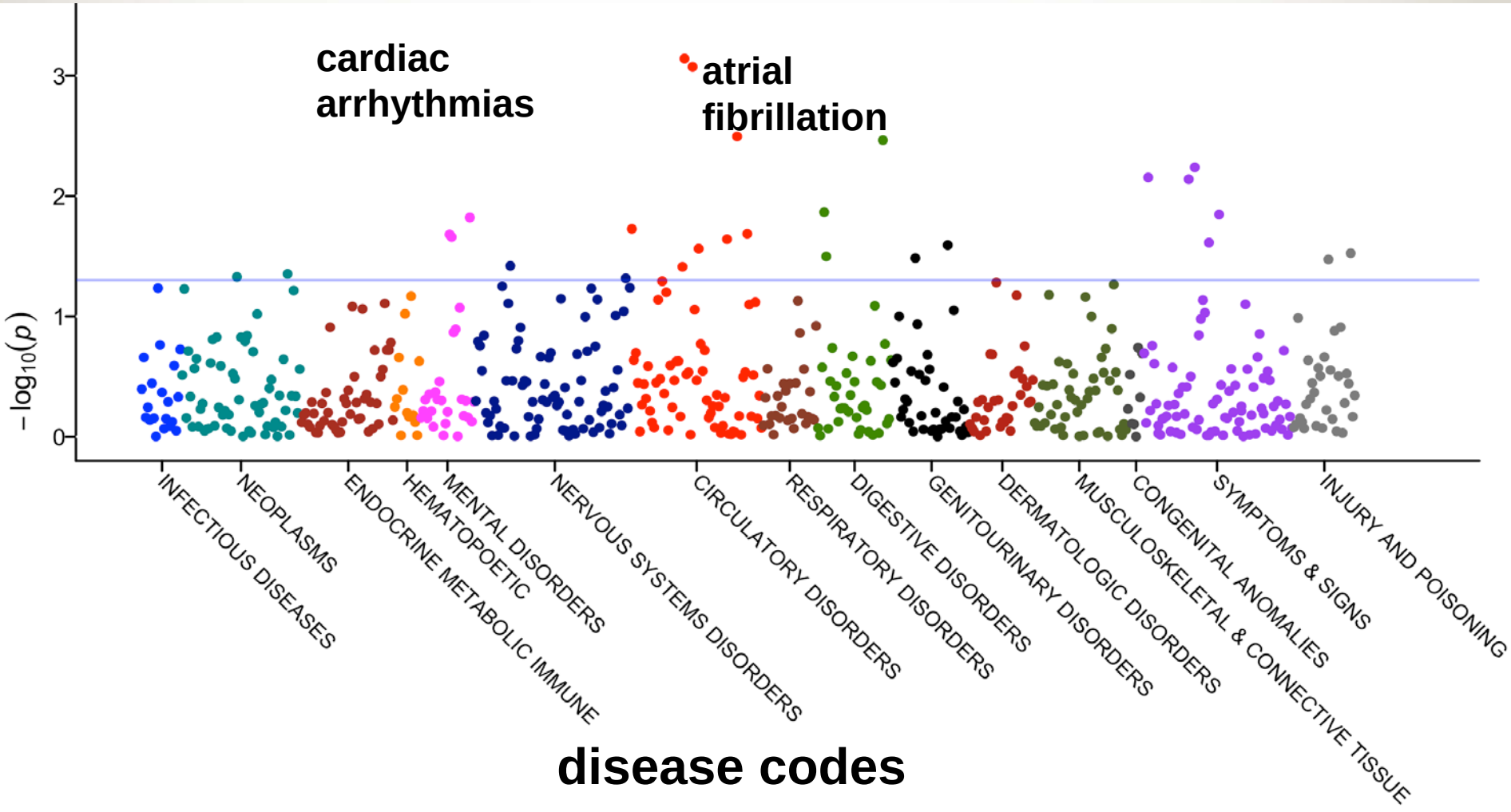
Using PheWAS to refine understanding of GWAS: normal cardiac conduction



Ritchie et al., Circulation 2013

"Phenome-wide association study" of rs6795970 (*SCN10A*)

N=13617 subjects with EHR data



Ritchie et al., Circulation 2013

What happens in the "heart healthy" population?

Examined 5272 "heart healthy" people

Followed for development of **atrial fibrillation** based on genotype

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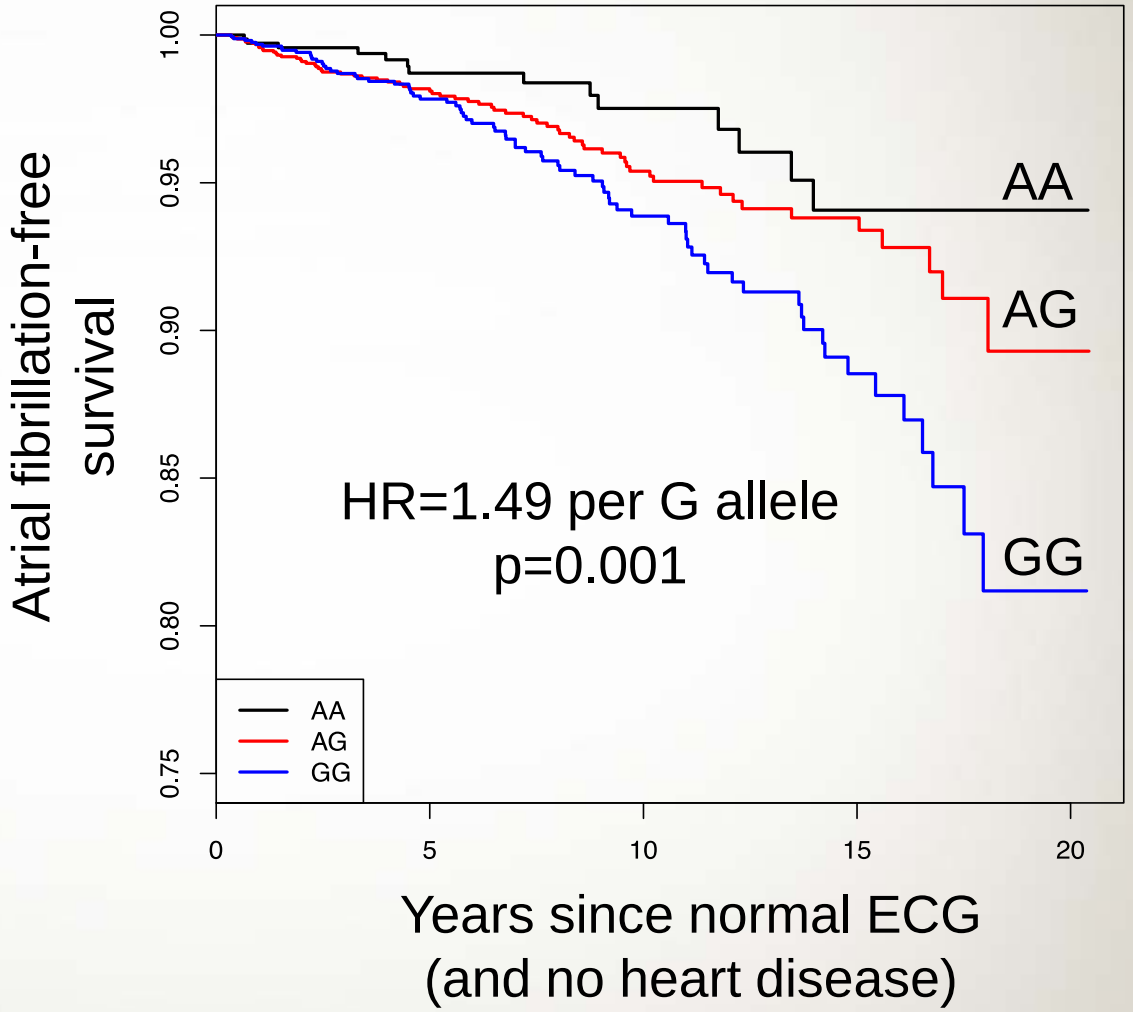

Ritchie et al., Circulation 2013

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The challenge of implementation

"Here's my sequence..."

New Yorker, 2000

PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

- Multiplexed genotyping of 184 variants in 34 pharmacogenes
- Prospective + indication based testing
- Coupled with EHR-based Decision Support
- 4 Drug Genome Interactions tested:
  - Clopidogrel/*CYP2C19*
  - Warfarin/*VKORC1+CYP2C9*
  - Tacrolimus/*CYP3A5*
  - Thiopurines/*TPMT*

"Here's my sequence..."

New Yorker, 2000

A Case for Prospective Genotyping:

identifying another high risk group

52,942 Vanderbilt "Medical Home" patients followed for up to 5 years….

How many patients received drug(s) that have a recognized pharmacogenetic story?

Schildcrout et al, CPT 2012

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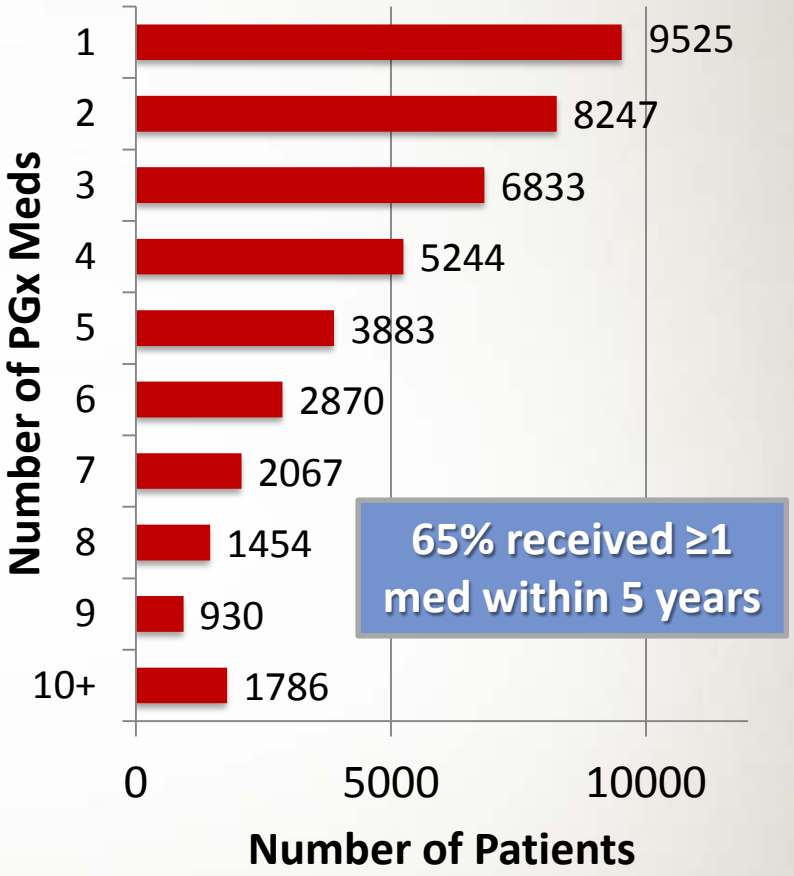

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Schildcrout et al, CPT 2012

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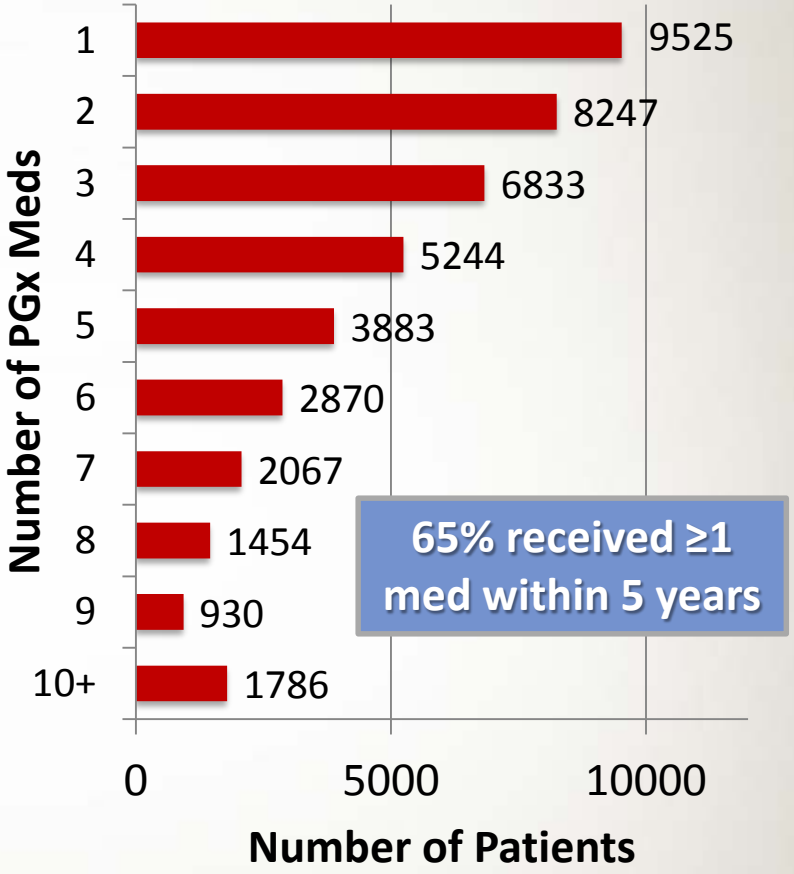

Estimated number of severe adverse events mitigated : 383
(~12-18 events for the average PCP over 5 years)

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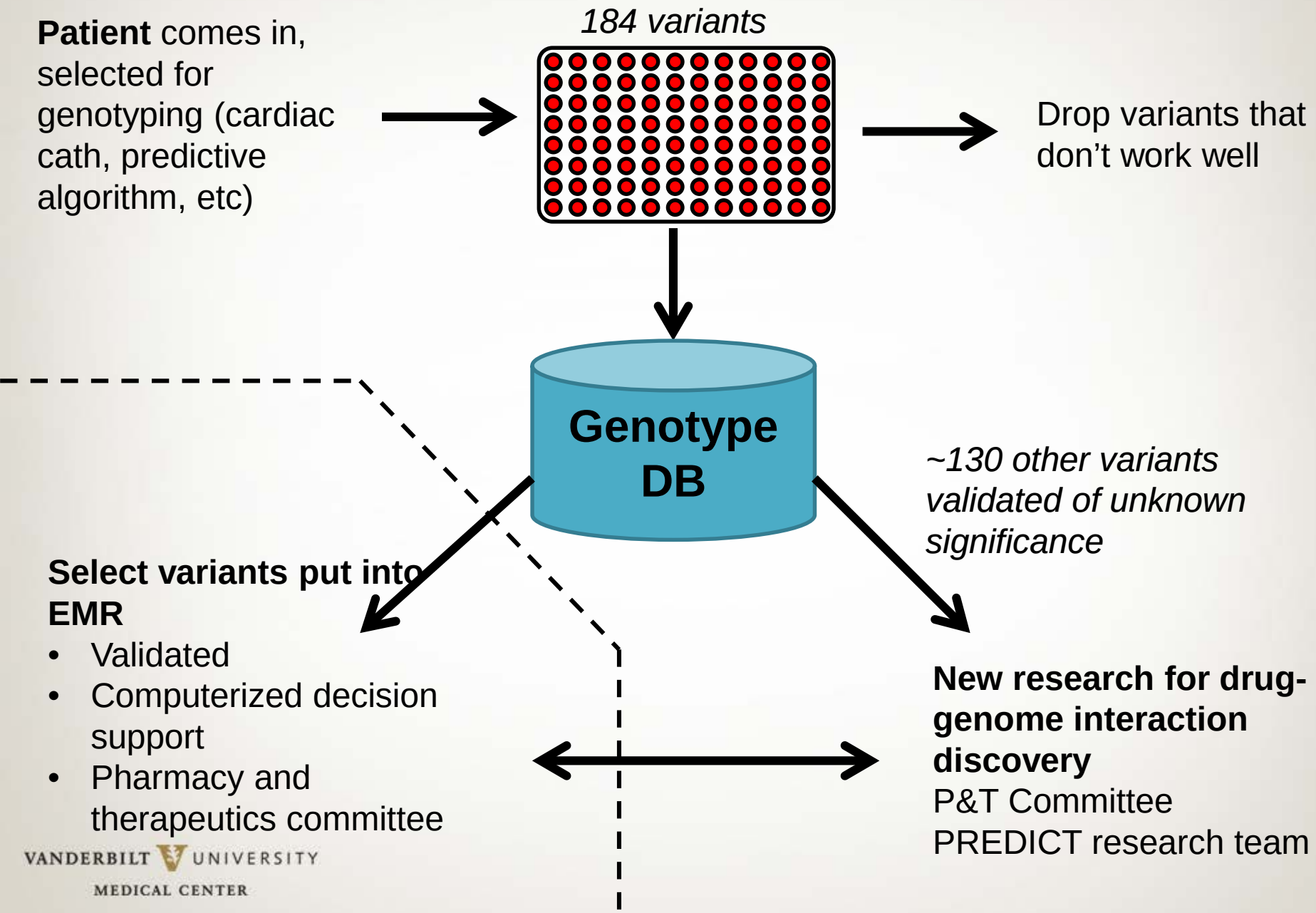
Schildcrout et al, CPT 2012



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Clinical Decision Support within E-Prescribing

Drug-Genome Advisor

Intermediate Metabolizer - clopidogrel (Plavix) - Rare Risk Allele

Substitution recommended due to increased cardiovascular risks

If not otherwise contraindicated:

- ☐ Prescribe prasugrel (Effient) 10 mg daily

  Prasugrel should not be given to patients:

  - history of stroke or transient ischemic attack
  - >= 75 years of age [Current patient age: 51]
  - with body weight < 60 kg [Current patient weight: 59.0 kg as of 10/12/2012]

- ☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily

  Ticagrelor should not be given to patients:

  - history of severe hepatic impairment
  - intracranial bleed

- ☑ Continue with clopidogrel (Plavix) prescription

  Primary override reason:

  - ☐ Contraindicated for prasugrel or ticagrelor
  - ☐ Potential side effects
  - ☐ Provider/Patient opts for clopidogrel
  - ☐ Cost

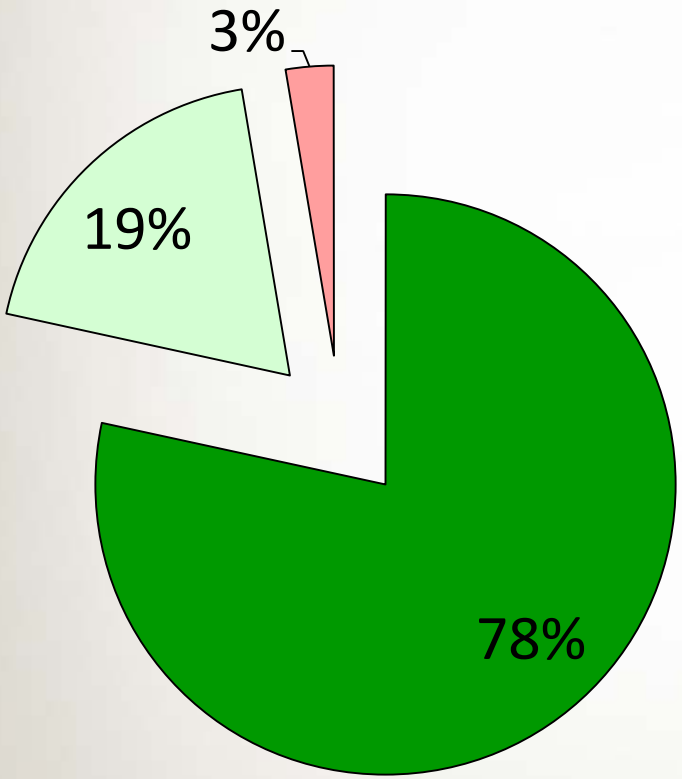
Evidence Link

This patient has been tested for CYP2C19 variants which has identified the presence of one copy of a rare risk allele which is associated with intermediate metabolism of clopidogrel. Intermediate metabolizers treated with clopidogrel at normal doses are associated with higher rates of stent thrombosis and other cardiovascular events. The Vanderbilt P&T Committee recommends that prasugrel or ticagelor replace clopidogrel for poor metabolizers unless contraindicated. If not feasible, maintain standard dose of clopidogrel. The guidelines above were developed based on the outcome studies of patients who received a drug-eluting stent into a coronary artery. However, there is not a national consensus on drug/dose guidance particularly associated with the population possessing extremely rare genetic variants.

Continue Cancel

Testing for clopidogrel efficacy

clopidogrel (inactive) —*CYP2C19*→ 2-oxoclopidogrel (active)



2.7% homozygous
18.9% heterozygous
} ↑ risk of MI
78.4% no common variant

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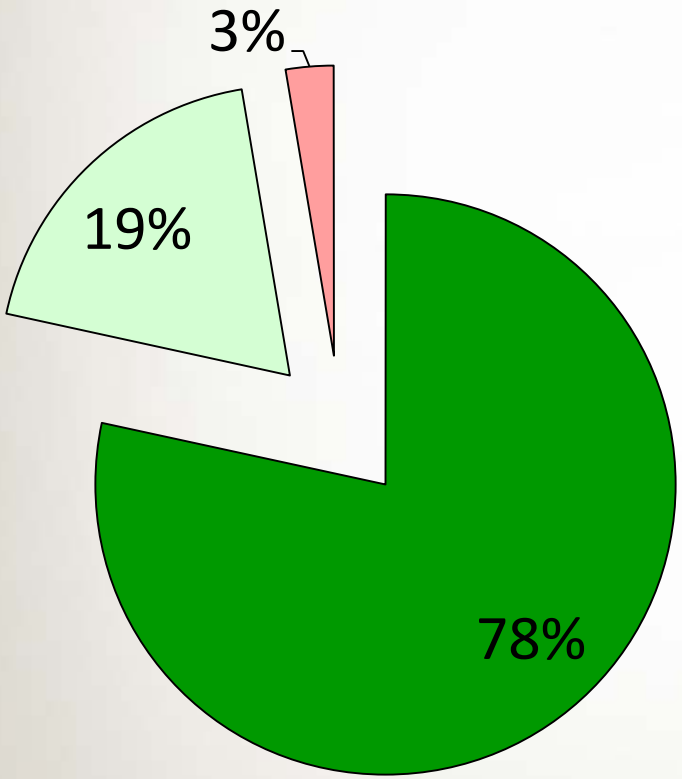

2.7% homozygous
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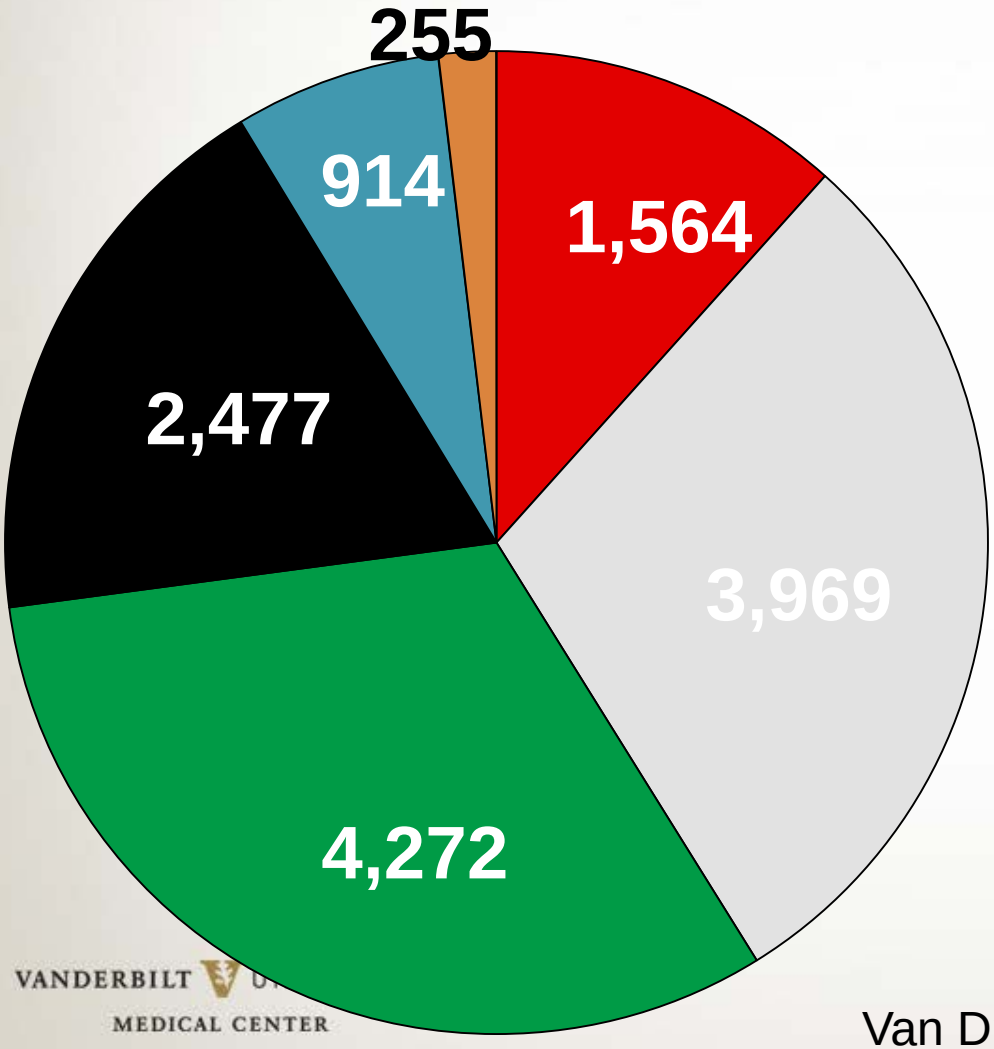
Multiplexed testing for pharmacogenetic variants

(after 5 drug-gene pairs…)



Total n=13,451
(9/10-6/13)

- 0 variants (11.7%)
- 1 variant (29.5%)
- 2 variants (31.7%)
- 3 variants (18.4%)
- 4 variants (6.8%)
- ≥5 variants (1.9%)

88% with risk variant

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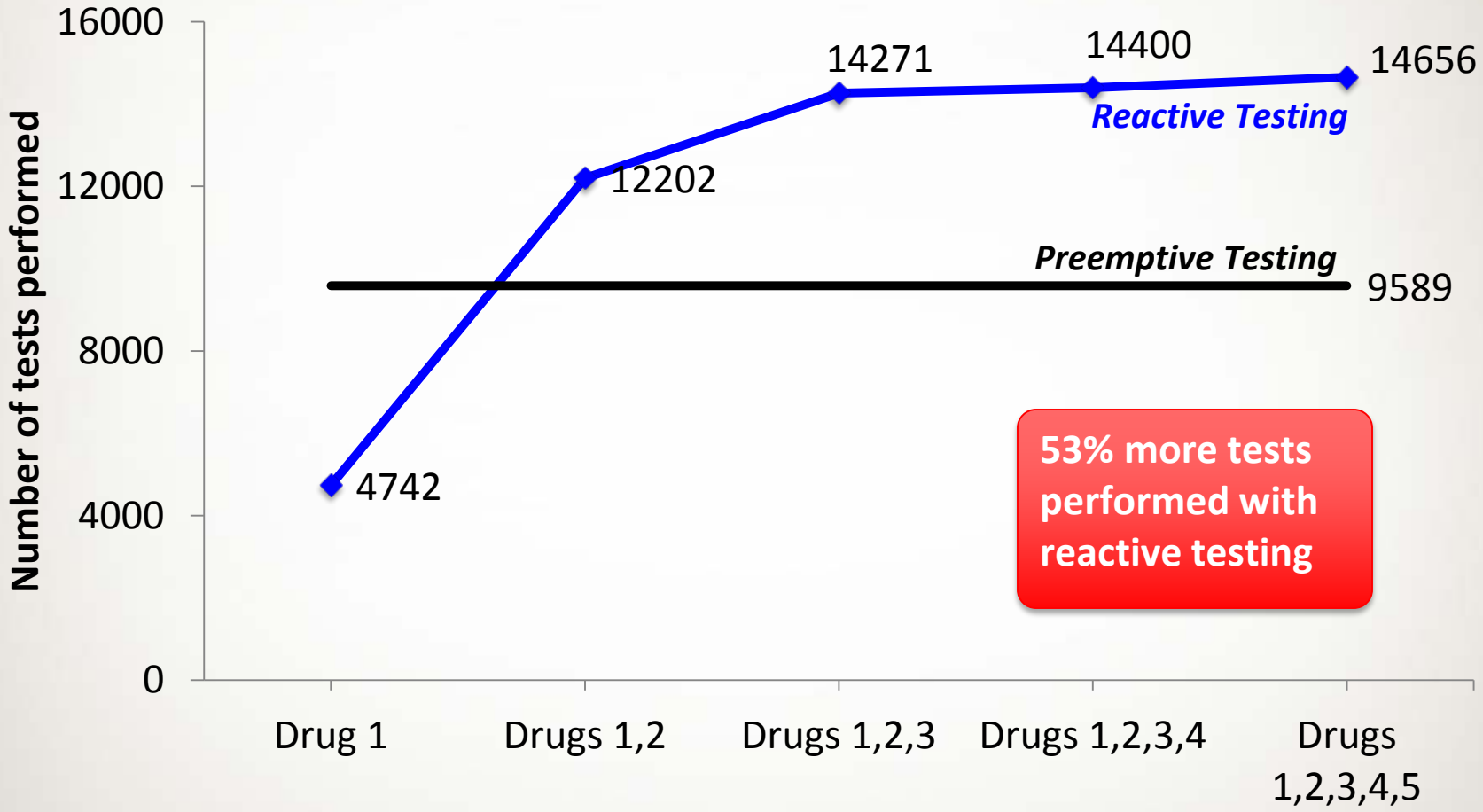
Van Driest et al, Clin Pharmacol Therap. 2013

Multiplexed Genetic Testing can reduce testing too



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Van Driest et al, Clin Pharmacol Therap. 2013

Initial analysis of Rx rates by *CYP2C19*

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

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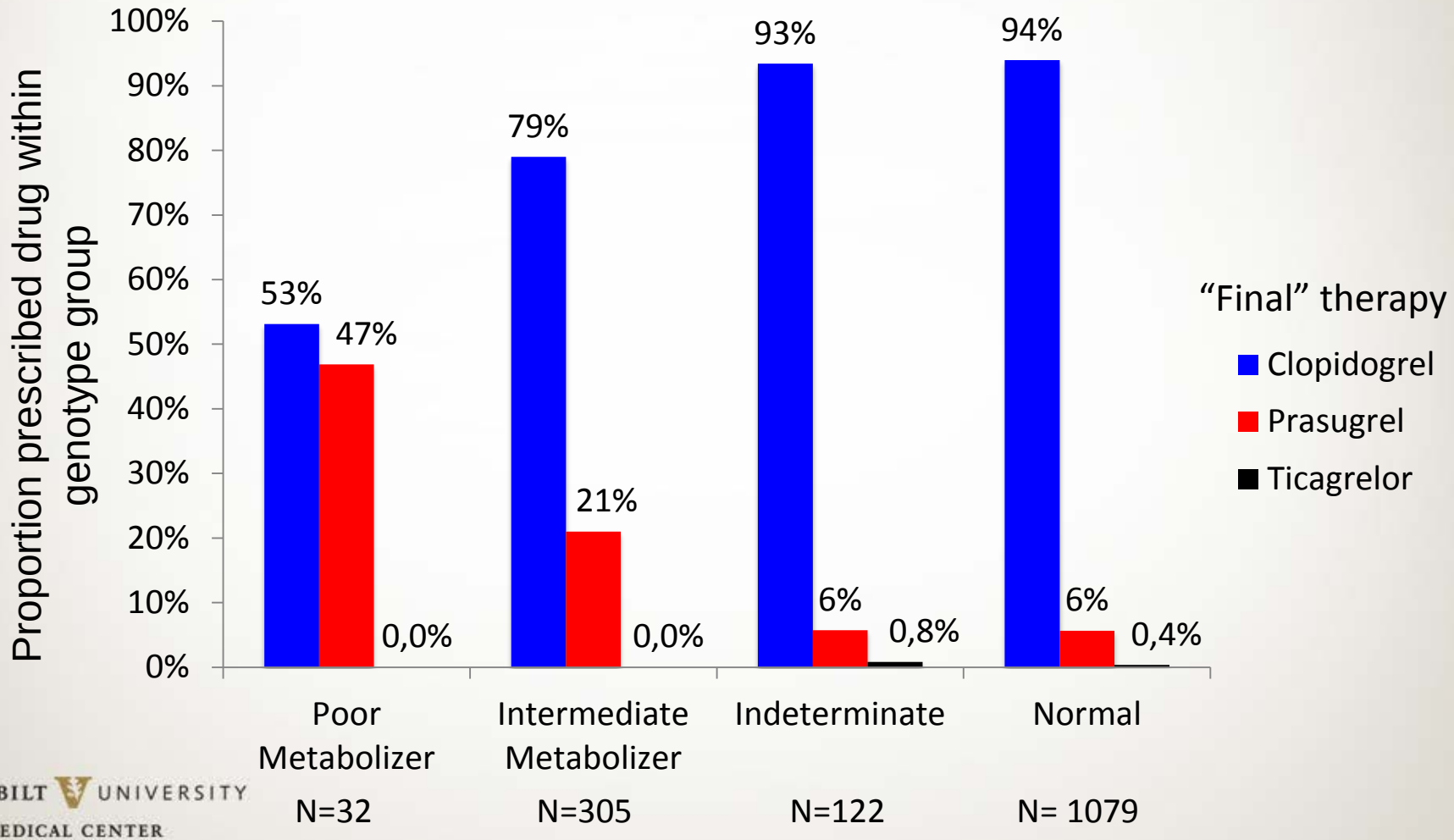

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PREDICT: Cost to Patient
Clopidogrel vs. Alternatives

Antiplatelet Drug	Dose	Avg. Annual Retail Price
Clopidogrel	75 mg qd	$480.53
Prasugrel	10 mg qd	$3365.52
Ticagrelor	90 mg qd	$1,736.79

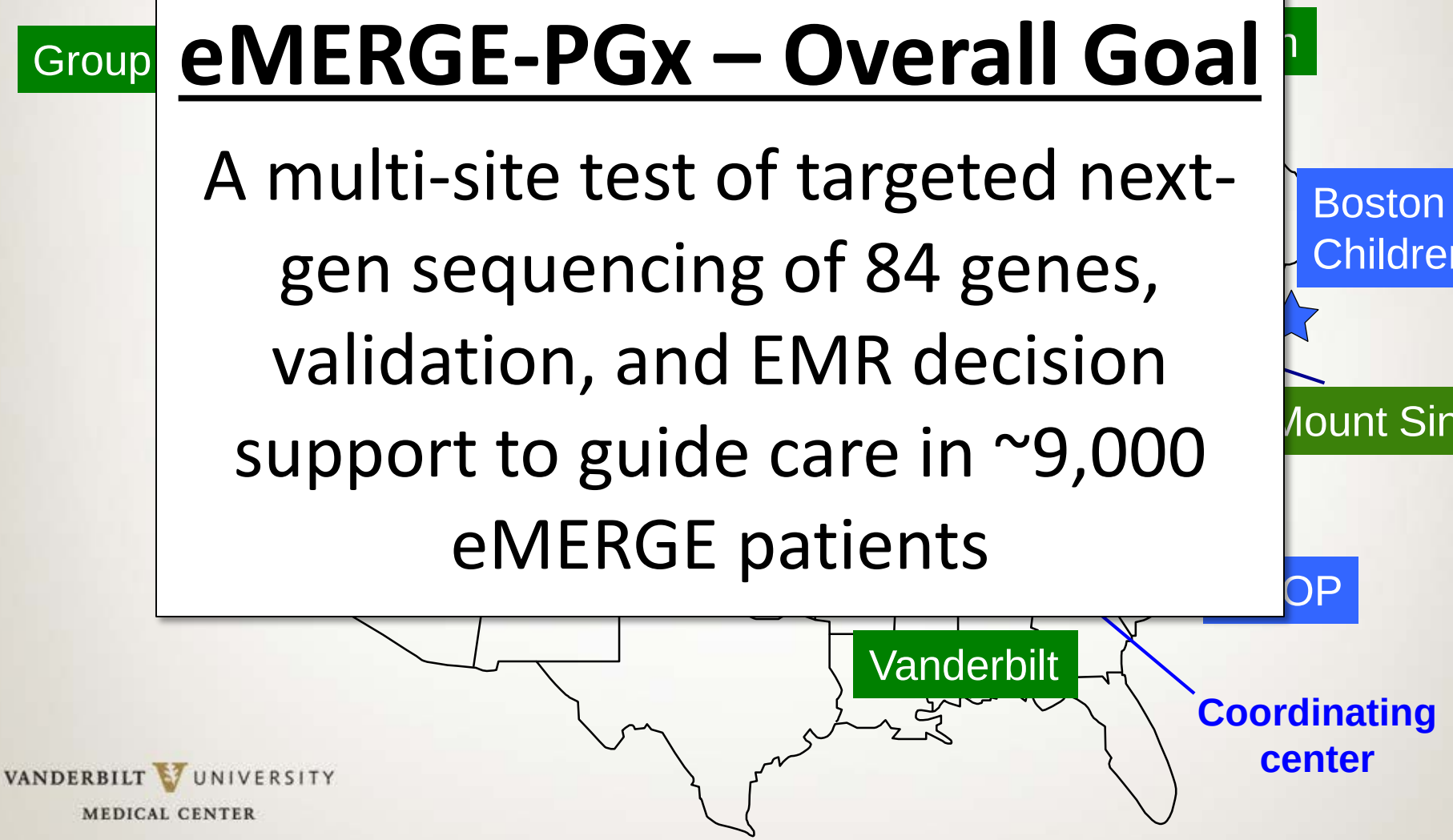
Maximum out-of-pocket cost of PREDICT test: $420

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

eMERGE-PGx – Overall Goal

A multi-site test of targeted next-gen sequencing of 84 genes, validation, and EMR decision support to guide care in ~9,000 eMERGE patients



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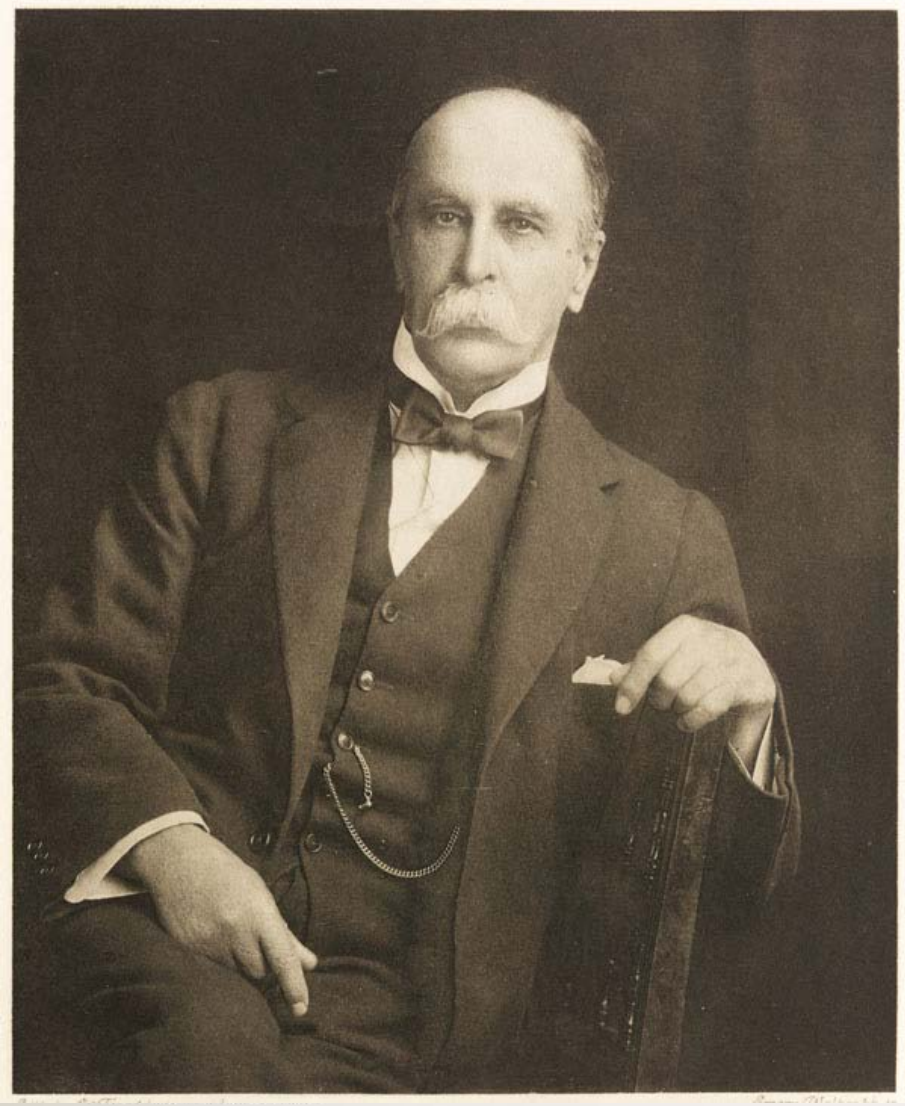
Personalized medicine – not a new idea



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

Sir William Osler

The Teams

Informatics

- Josh Peterson
- Lisa Bastarache
- Kevin Johnson
- Hua Xu
- Brad Malin
- Dan Masys
- Wei-Qi Wei

BioVU/SD

- Melissa Basford
- Jill Pulley
- Erica Bowton
- Jay Cowan
- Sunny Wang
- Jenny Madison
- Sue Bradeen

Medicine

- Dan Roden
- Ellen Clayton
- Jessica Delaney
- Sara Van Driest
- Jonathan Mosley
- Andrea Ramirez
- Peter Weeke

Genetics

- Dana Crawford
- Marylyn Ritchie
- Todd Edwards

Biostatistics

- Jonathan Schildcrout
- Yaping Shi

eMERGE Network

- Children's hospital of Philadelphia
- Boston Children's/Cincinnati Children's Hospitals
- Northwestern
- Marshfield Clinic
- Mayo Clinic
- Group Health/UW
- Mount Sinai
- Geisinger

Funding

- VICTR/NCATS
- NHGRI
- NLM
- NIGMS
- NCI