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The PREDICT program: Implementing prospective pharmacogenetics for inpatient and outpatient clinical care

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5/29/2014

Disclaimers

I receive funding from:

- NIH: NLM, NHGRI, NIGMS, NCI, NCATS
- Reynolds Foundation (Geriatrics Education)
- National Board of Medical Examiners

The vision

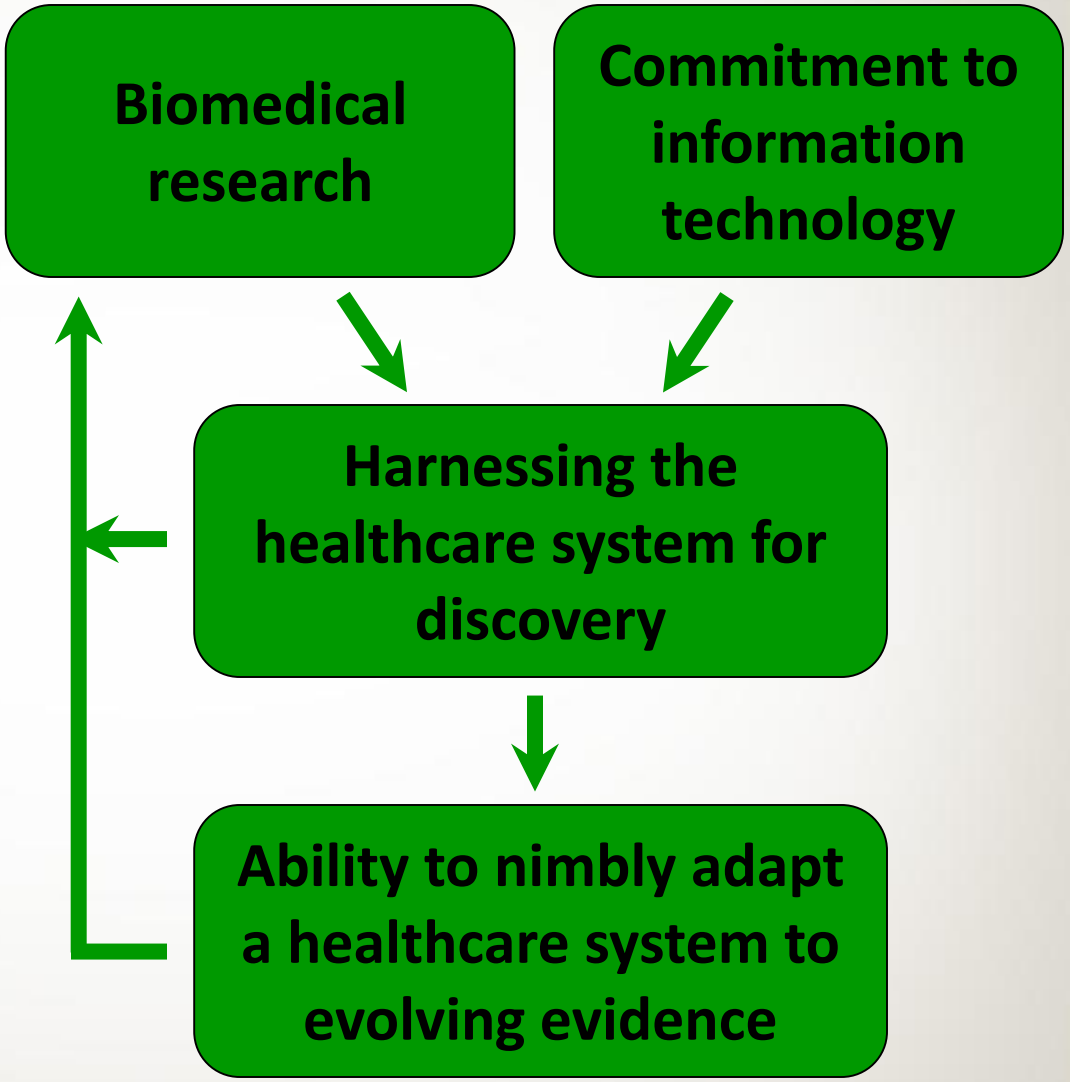
"Here's my sequence..."

New Yorker, 2000

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

"Here's my sequence..."

New Yorker, 2000



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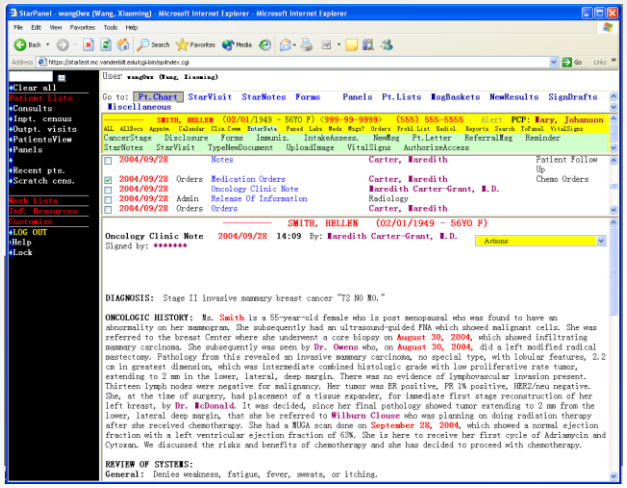

EHR feeds both discovery and implementation

Discovery

VanderbiltBioVU

De-identified DNA repository

>180k 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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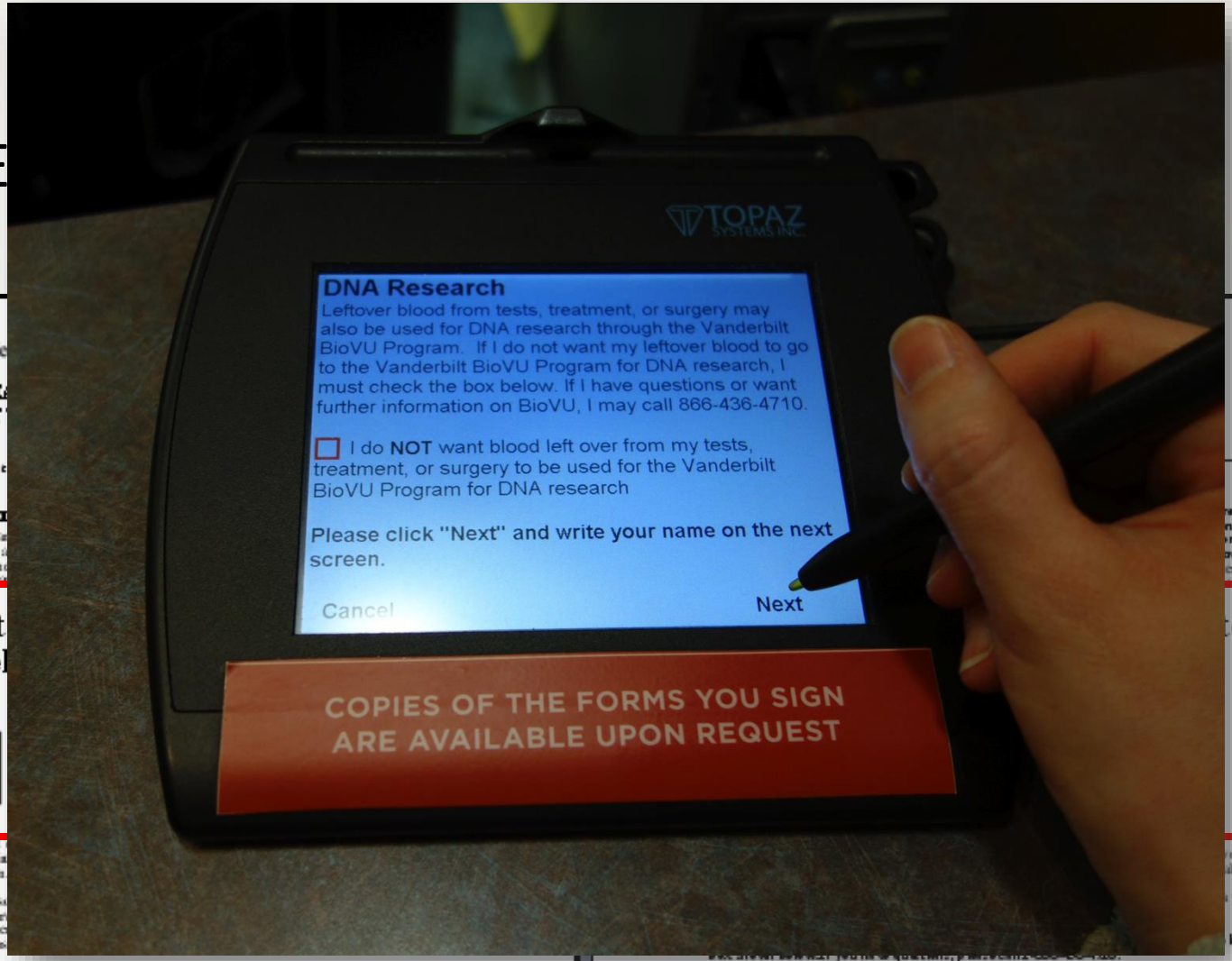
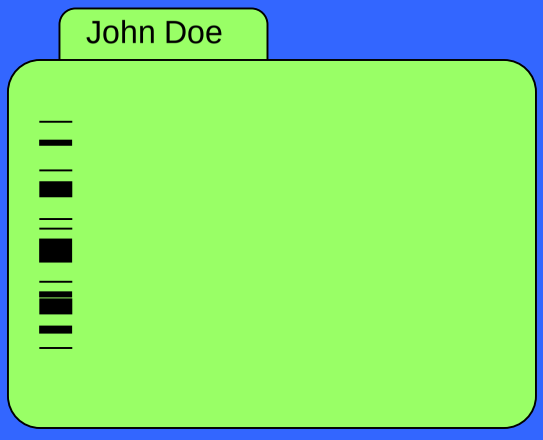
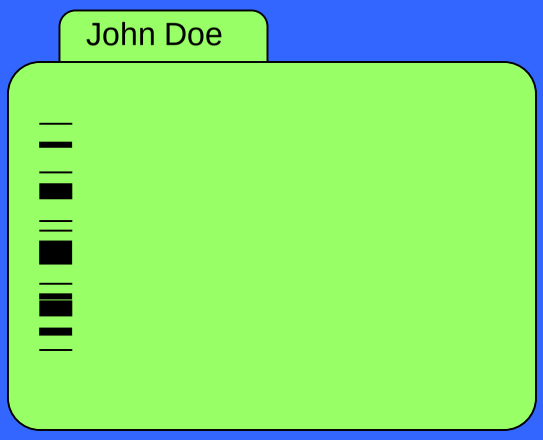
Vanderbilt BioVU: an Opt-Out




John Doe

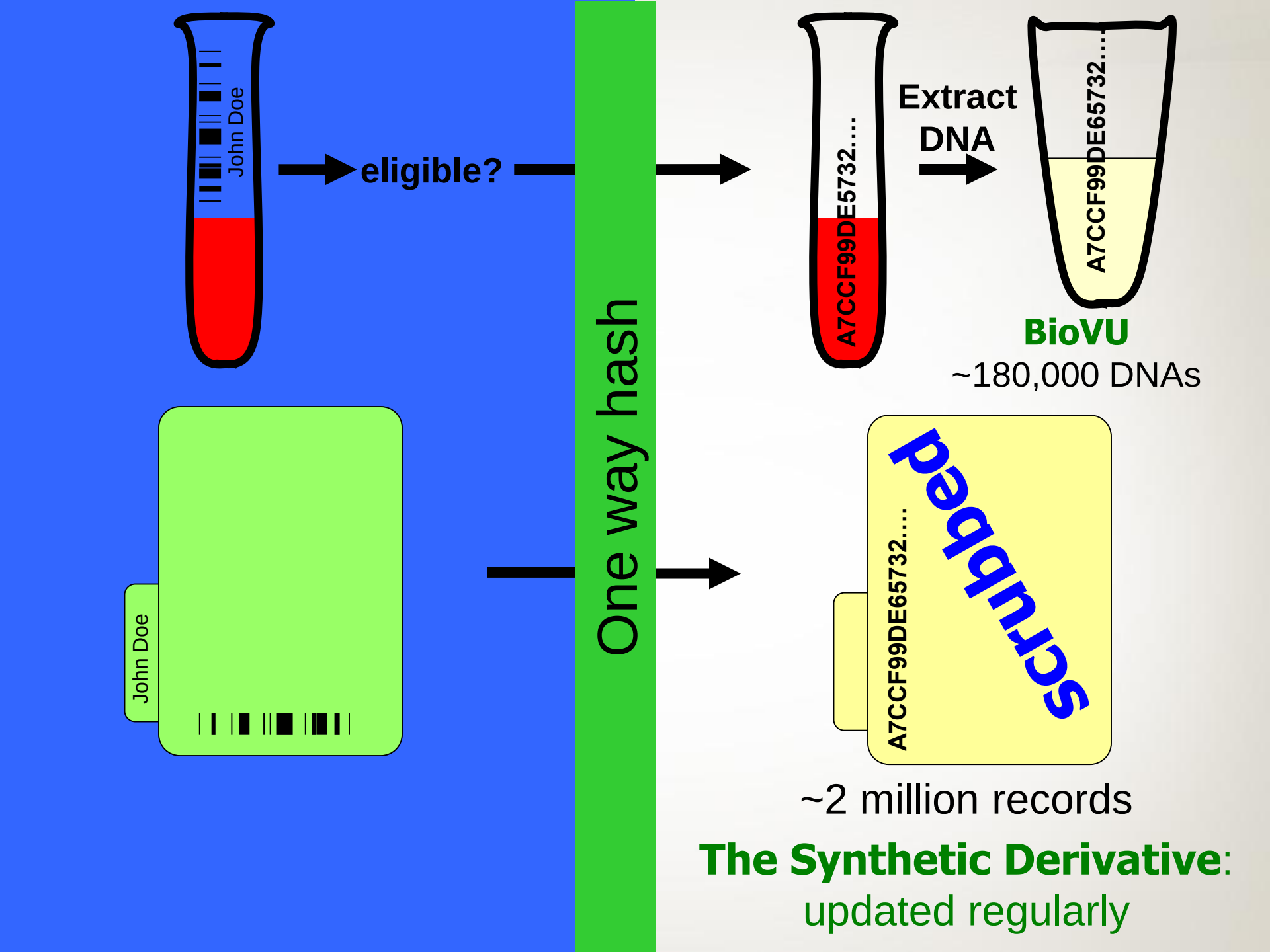


One way hash

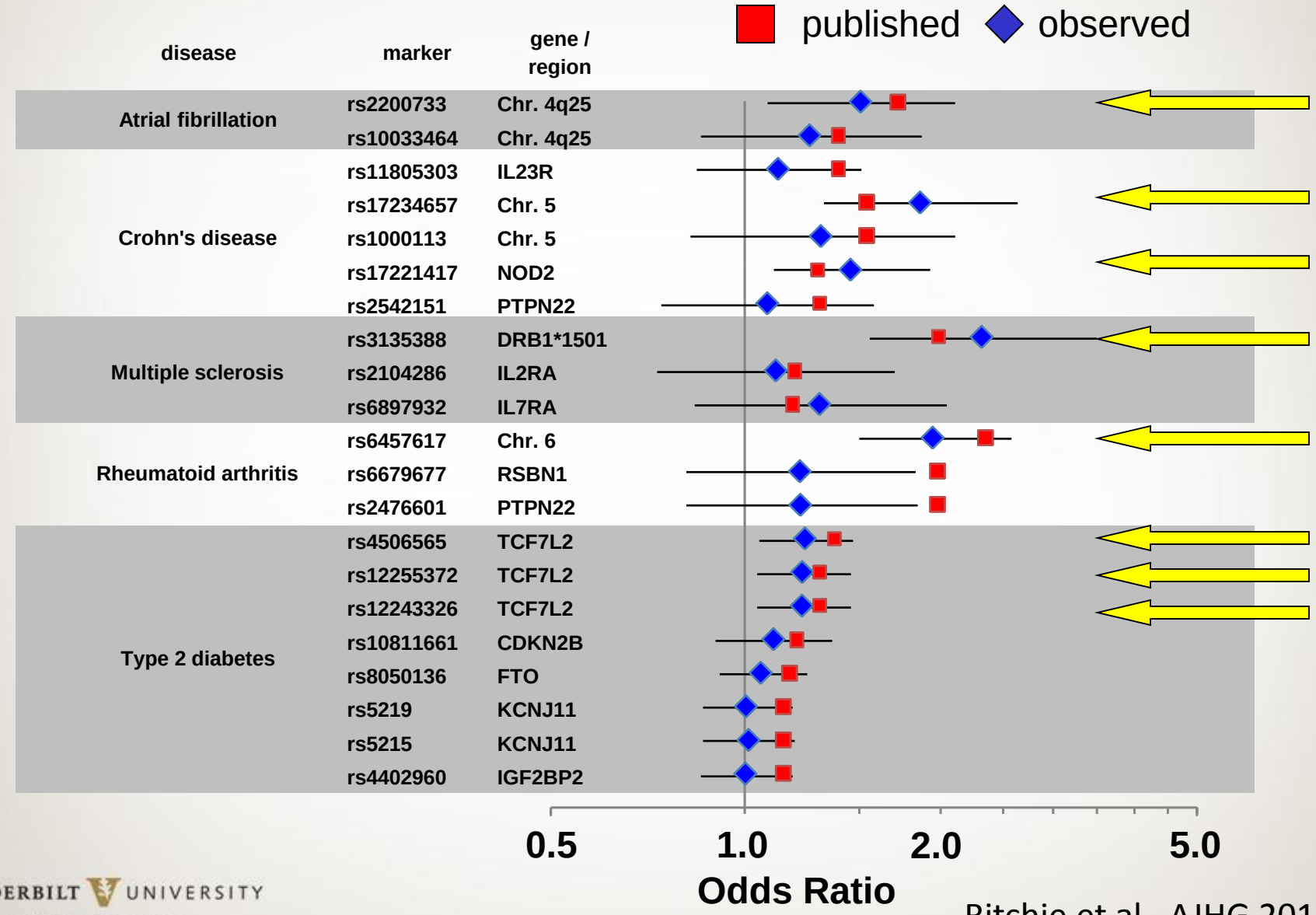
~2 million records

The Synthetic Derivative:

updated regularly


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

BioVU as a resource for discovery

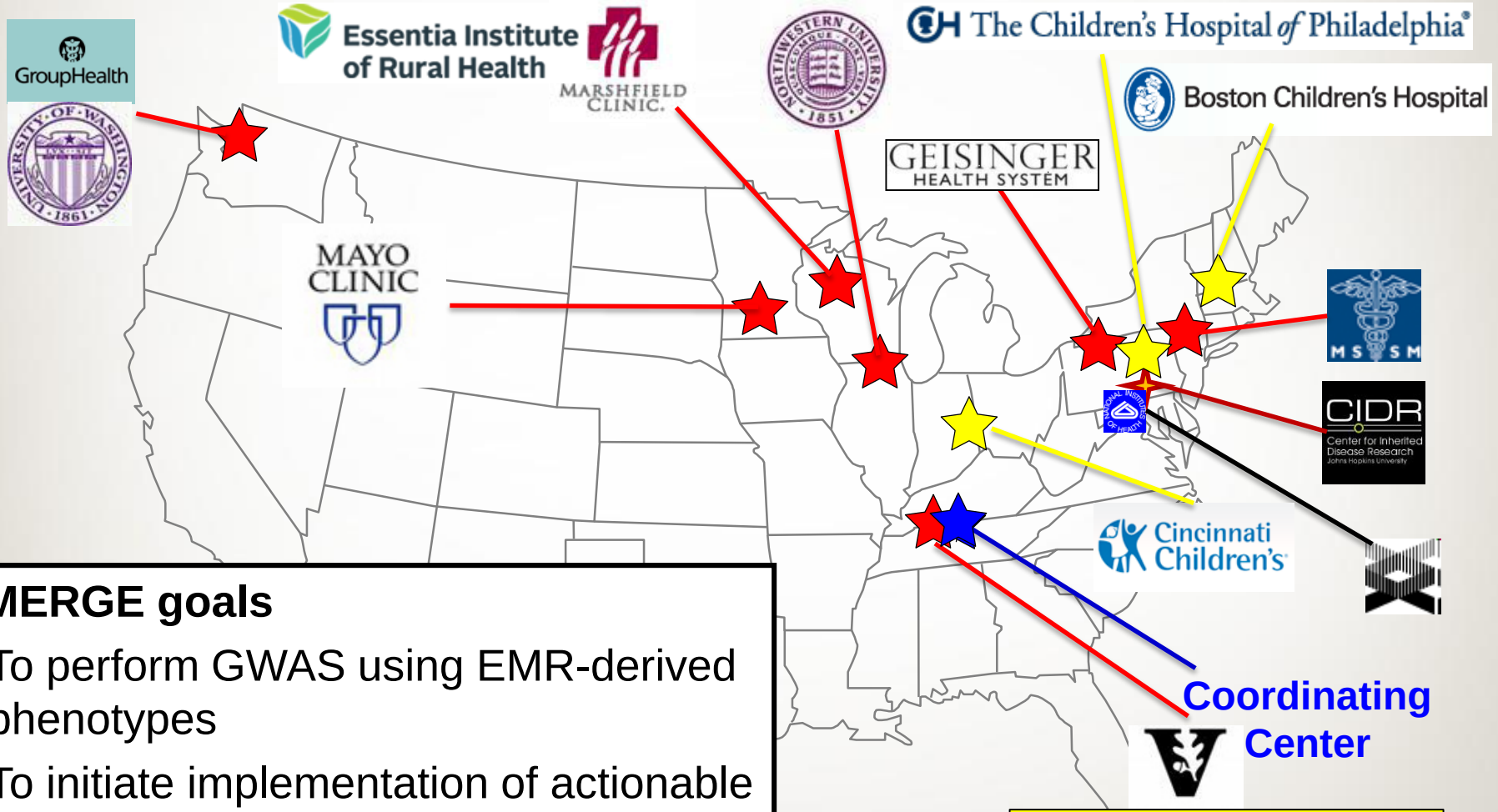


Ritchie et al., AJHG 2010

The eMERGE Network

electronic Medical Records & Genomics

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

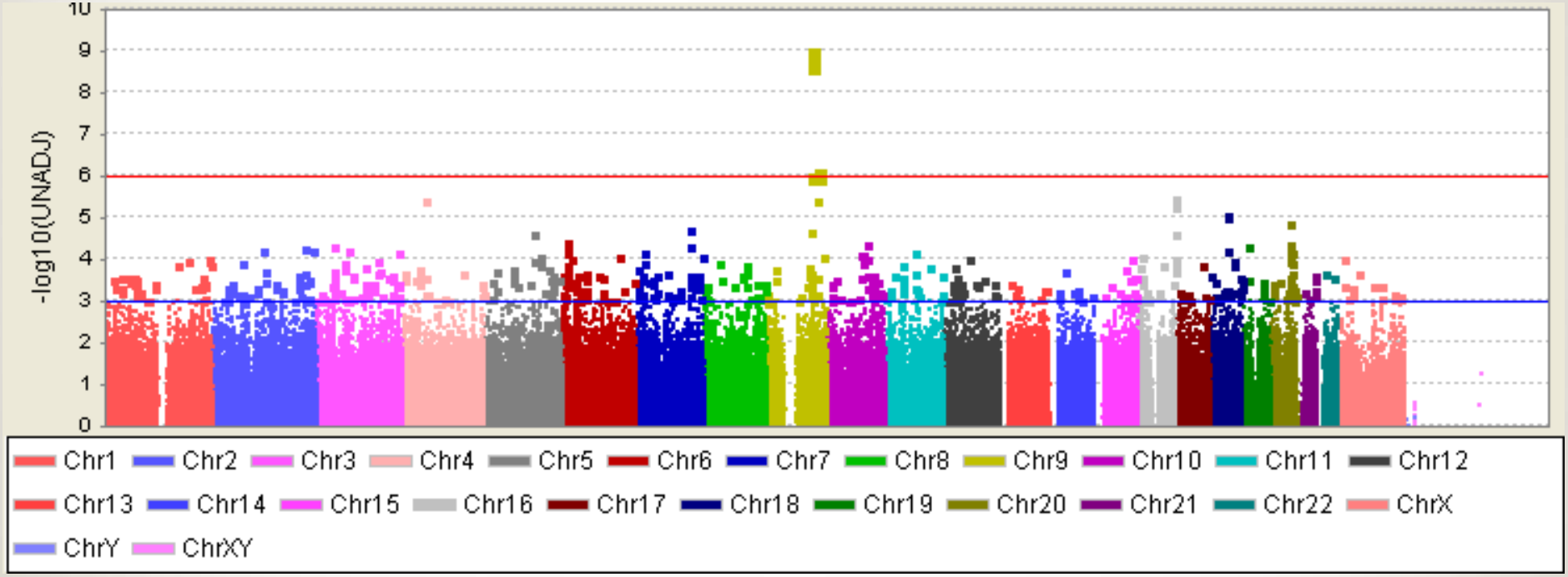


eMERGE goals

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

An eMERGE-wide phenotype analyzed with no extra genotyping: hypothyroidism

European Americans (1,306 cases and 5,013 controls)



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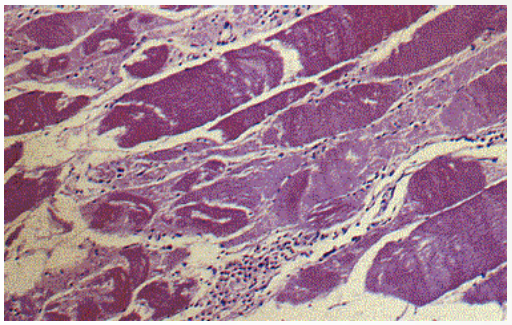
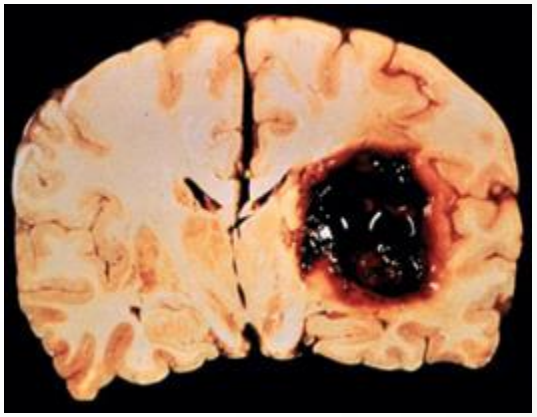
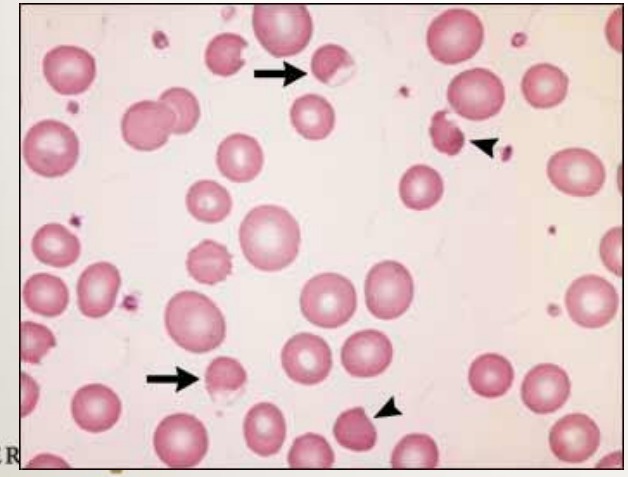
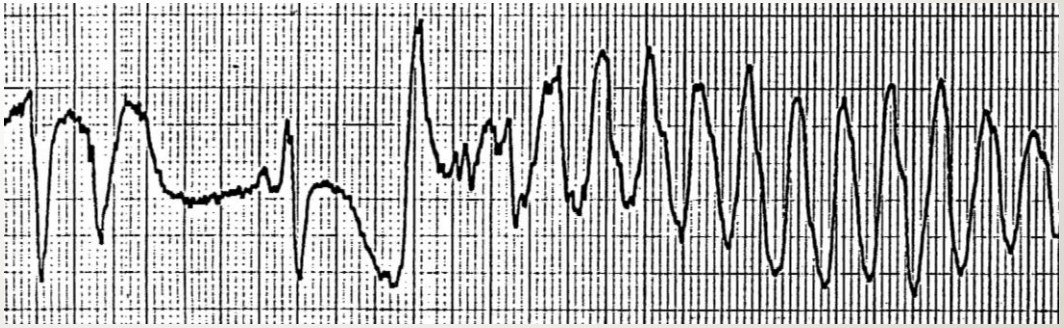
Denny et al.,AJHG 2011

Another perception of genomic medicine - pharmacogenomics









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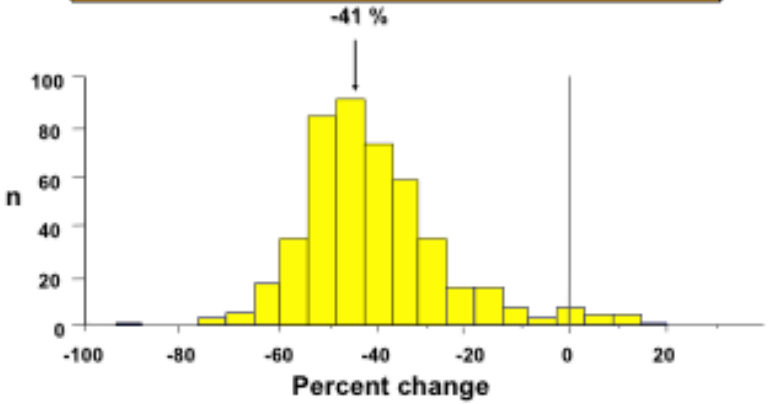
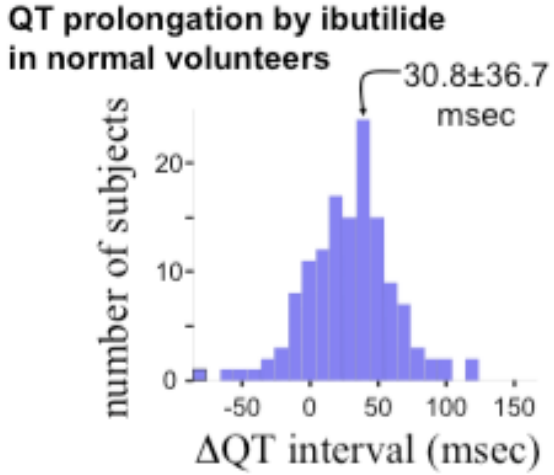
Variable drug response is common; Genetics may predict this too

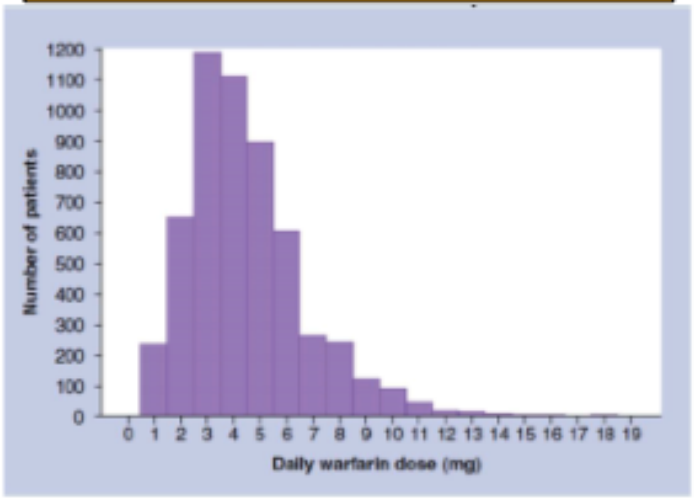
LDL cholesterol changes by simvastatin 40 mg



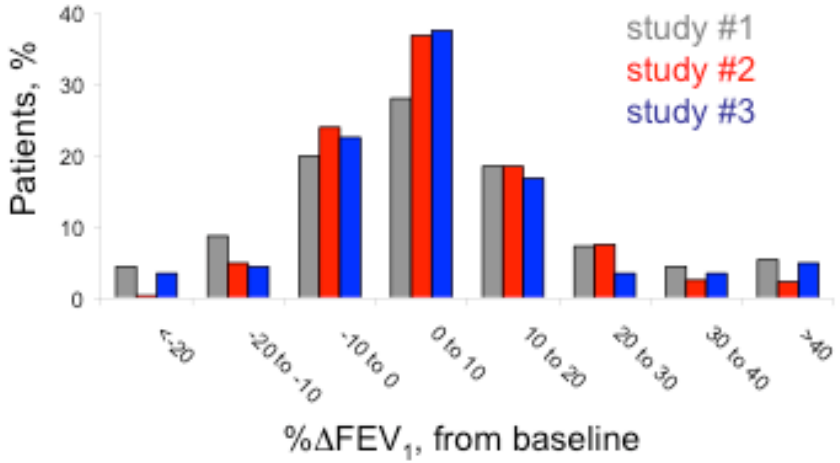
QT changes with ibutilide



Therapeutic Warfarin dose



Change in FEV_1 with inhaled corticosteroids in asthma



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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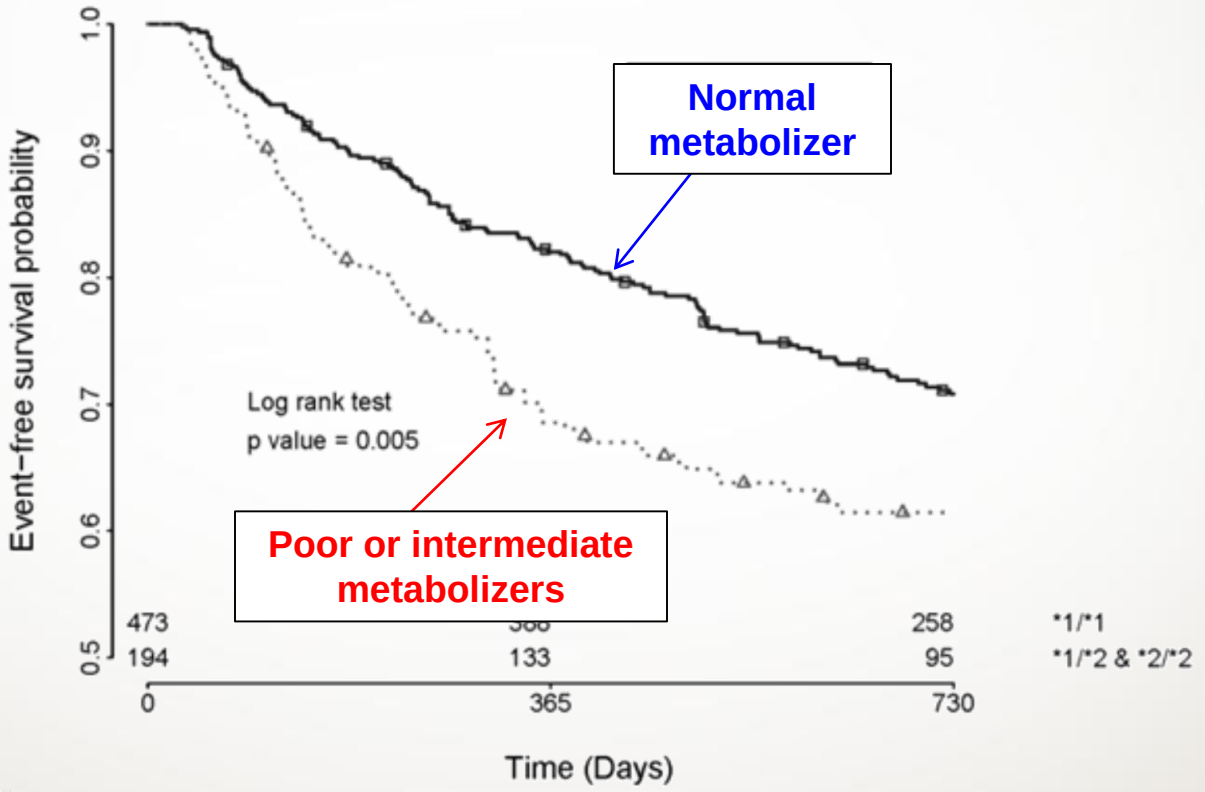
clopidogrel $\xrightarrow{CYP2C19}$ 2-oxoclopidogrel

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



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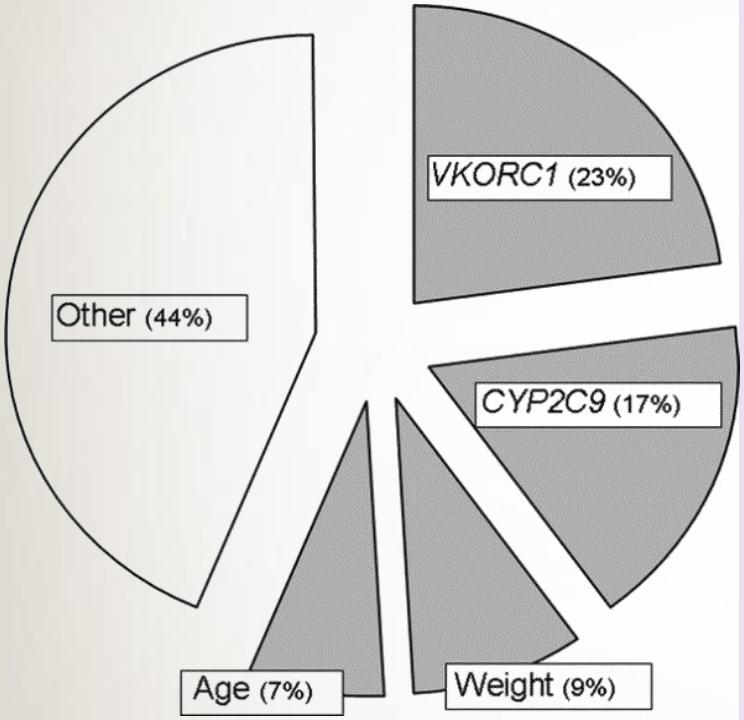
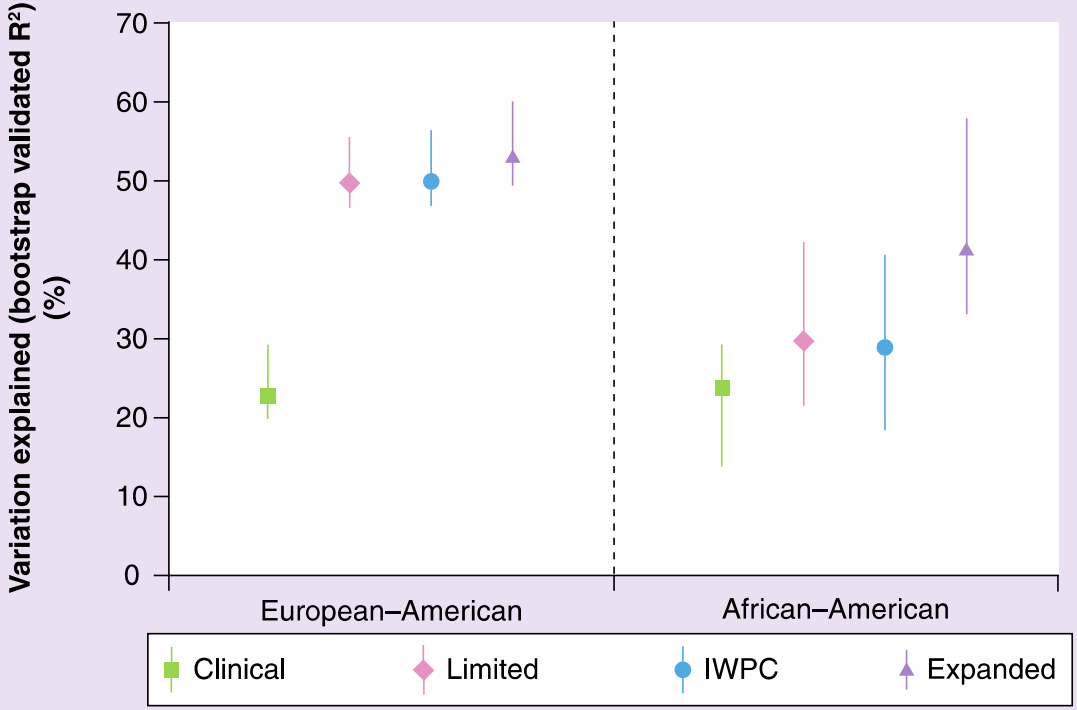
Delaney et al. *Clin Pharm Ther.* 2012

Warfarin Pharmacogenetics

Using genetics to predict effective dose



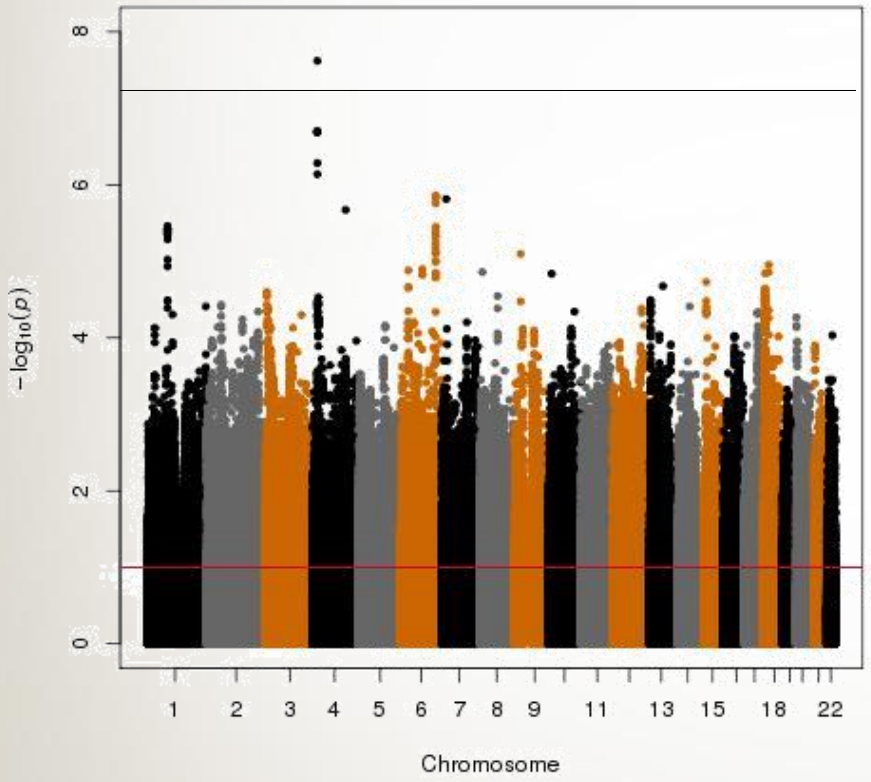


SNP (Gene)	Beta	P
rs1057910 (CYP2C9*3)	0.83	2.70×10^{-26}
rs9934438 (VKORC1)	0.87	4.48×10^{-61}

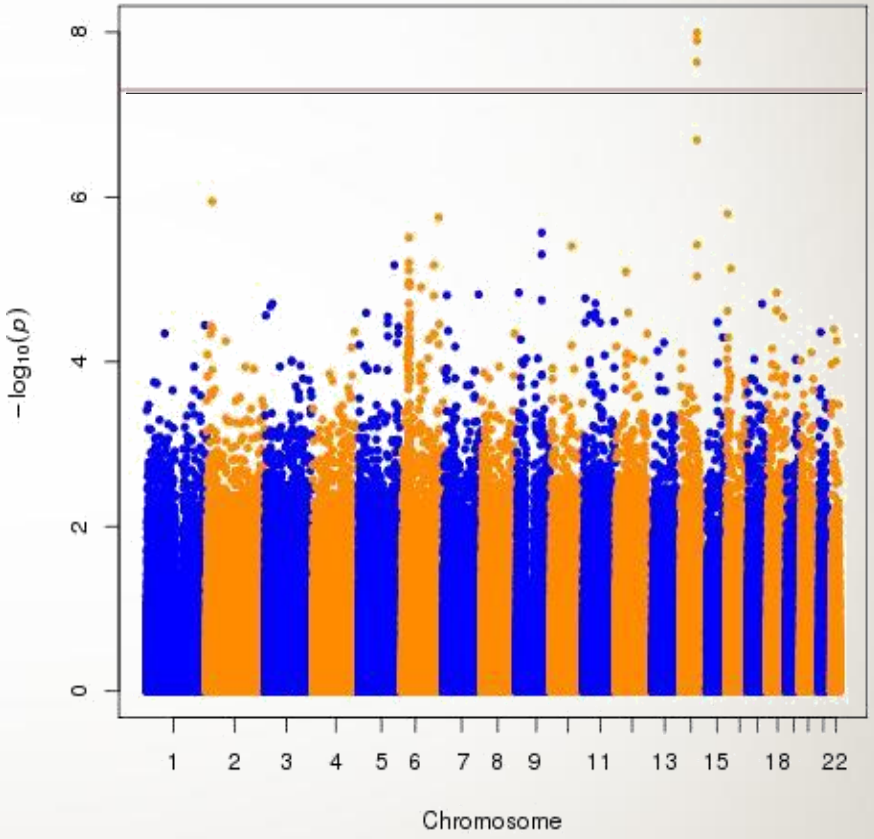
Ramirez et al. *Pharmacogenomics.* 2012

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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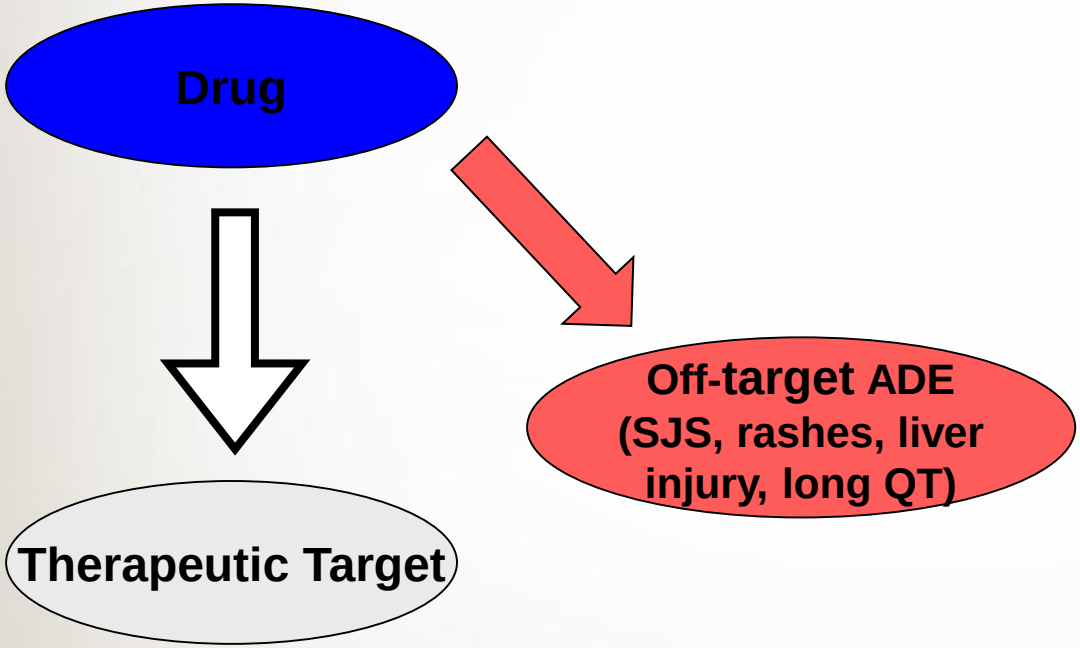
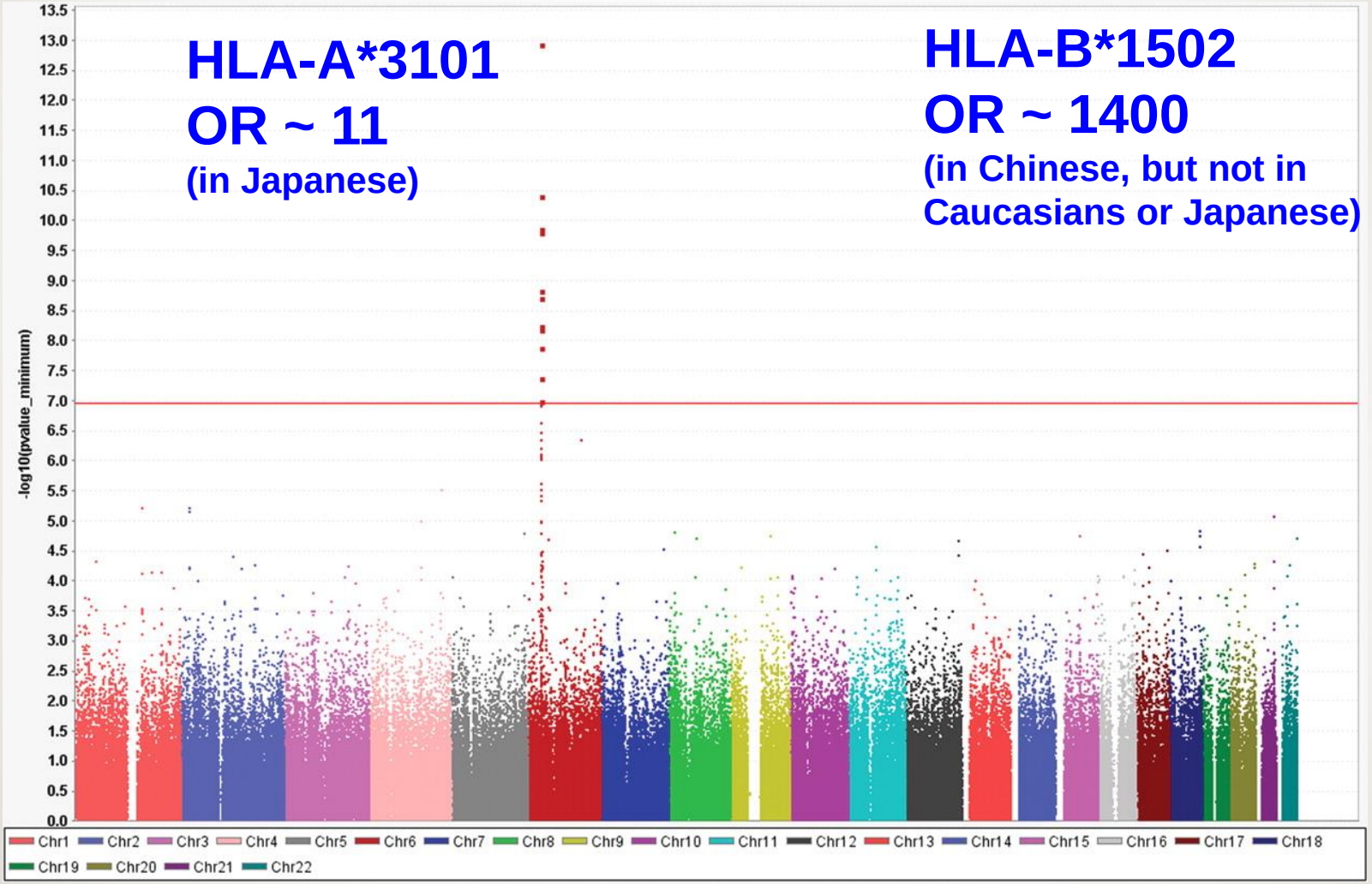
Another pathway of adverse effects: Off target effects



- carbamazepine
- clozapine
- haloperidol
- abacavir
- antibiotics

Ancestry matters… Carbamazepine-induced cutaneous adverse drug reactions



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Ozeki T et al. Hum. Mol. Genet. 2011;20:1034-1041

The challenge of implementation

"Here's my sequence..."

New Yorker, 2000

...the right drug, the first time.

FDA's role

- FDA began including pharmacogenomic (PGx) effects in labels in 2007
- Now lists >100 medications
  - Cancer (somatic mutations) becoming more common now

Gene	Drug
Drug Metabolism Pathways	
TPMT	azathioprine
UGT1A1	irinotecan, nilotinib
CYP2D6	atomoxetine, fluoxetine
CYP2C19	clopidogrel, proton pump inhibitors
CYP2C9	celecoxib, warfarin
N-acetyl transferase	rifampin, isoniazid, pyrazinamide
DPD	capecitabine

Gene	Drug
Other Germline Variants	
VKORC1	warfarin
HLA-B*1501	carbamazepine
HLA-B*5701	abacavir
CCR5	maraviroc
Familial hypercholesterolemia	atorvastatin
G6PD deficiency	rasburicase, primaquine
Protein C deficiency	warfarin
urea cycle disorder	valproate

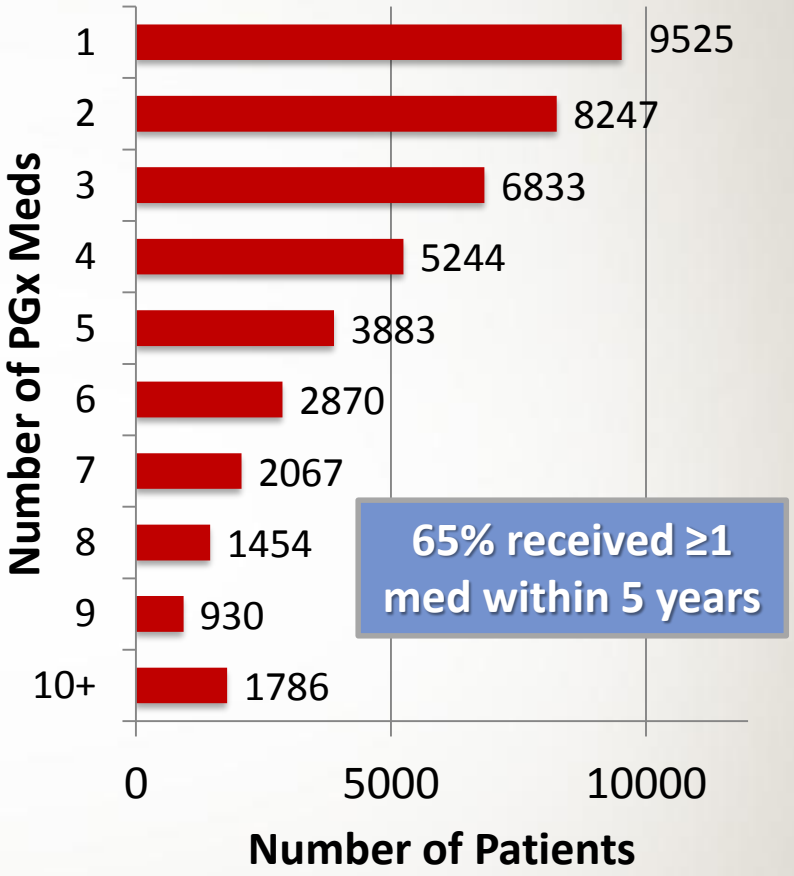
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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?



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

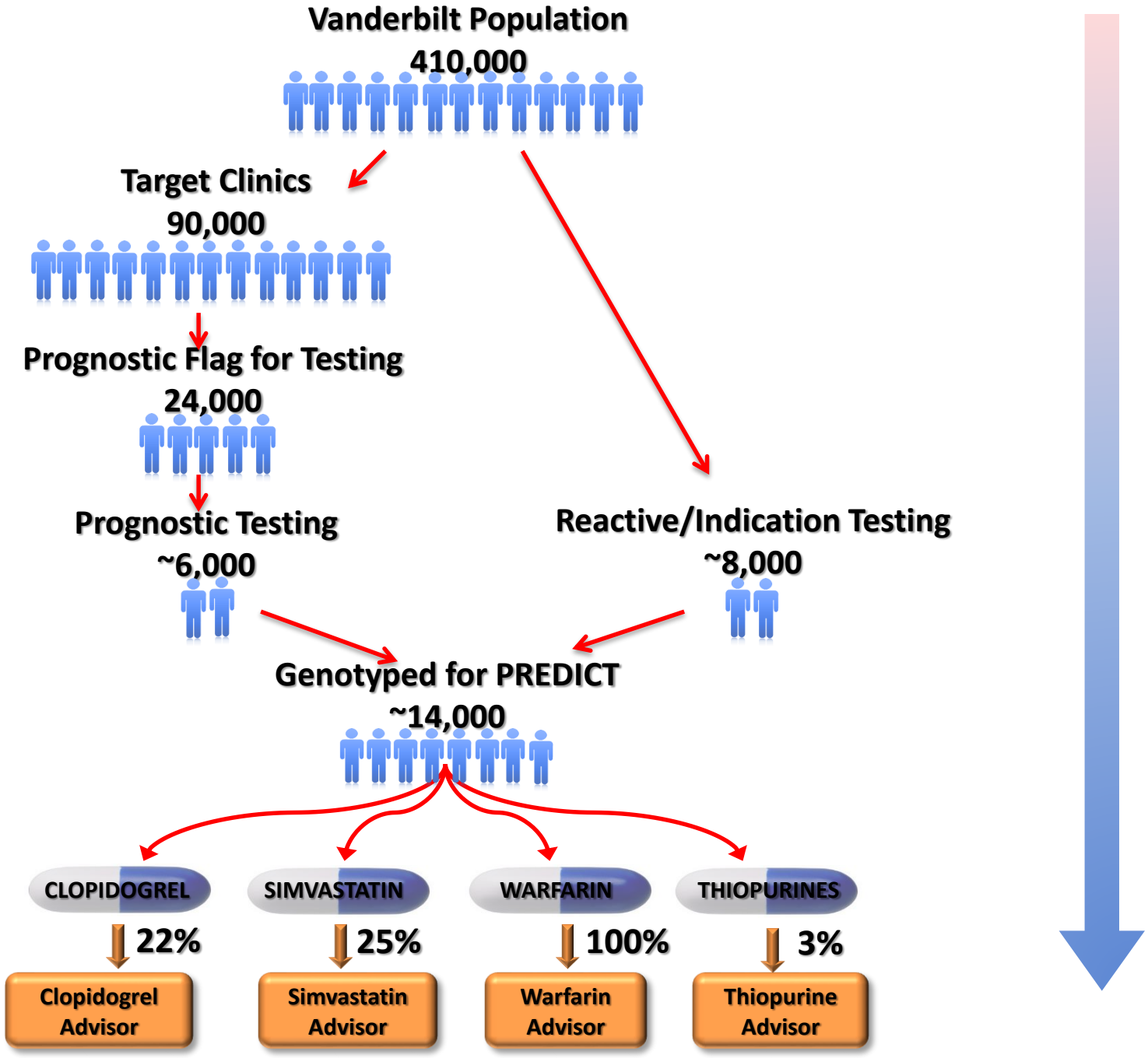
A first step to pharmacogenomic implementation

The Vanderbilt PREDICT project: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

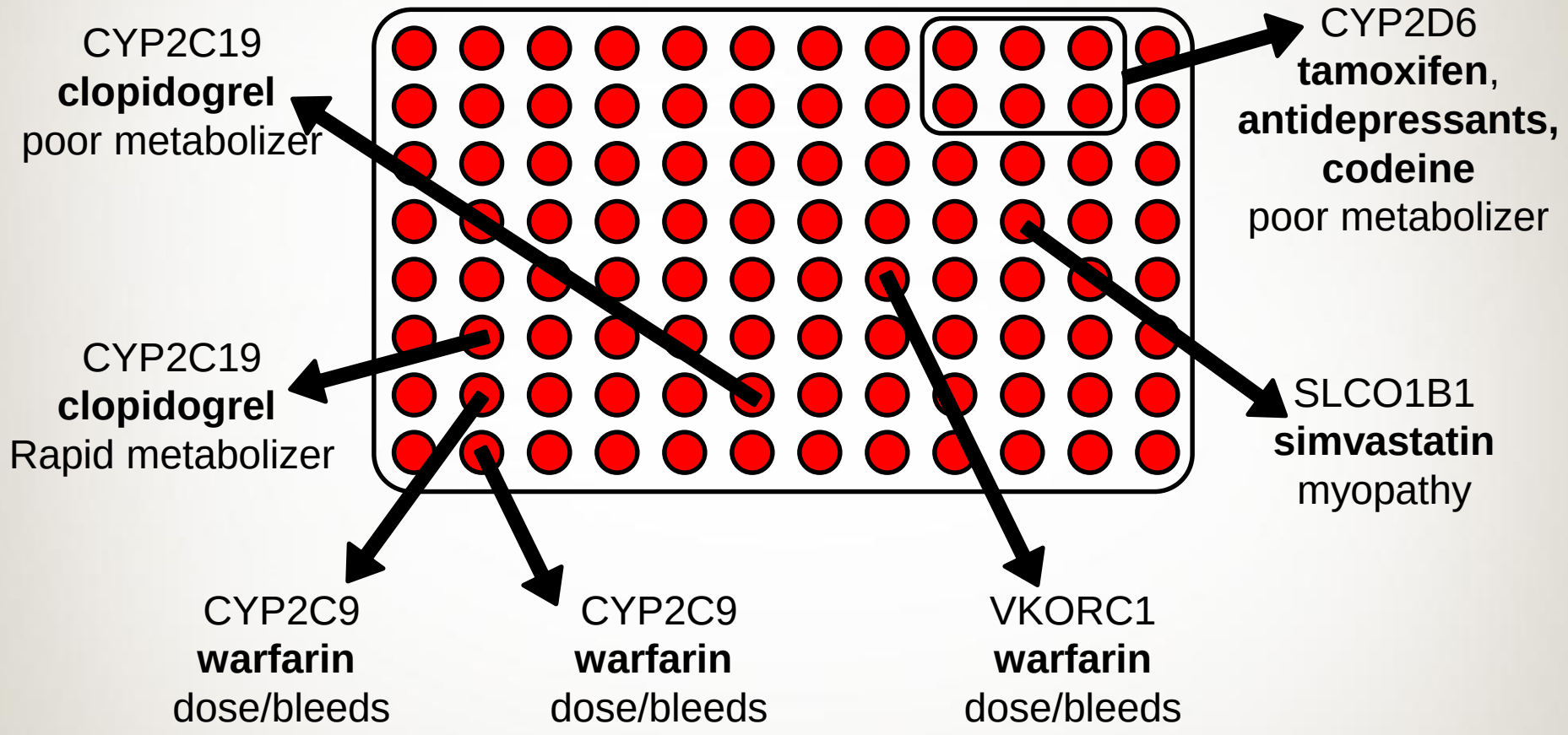
"Here's my sequence..."

New Yorker, 2000

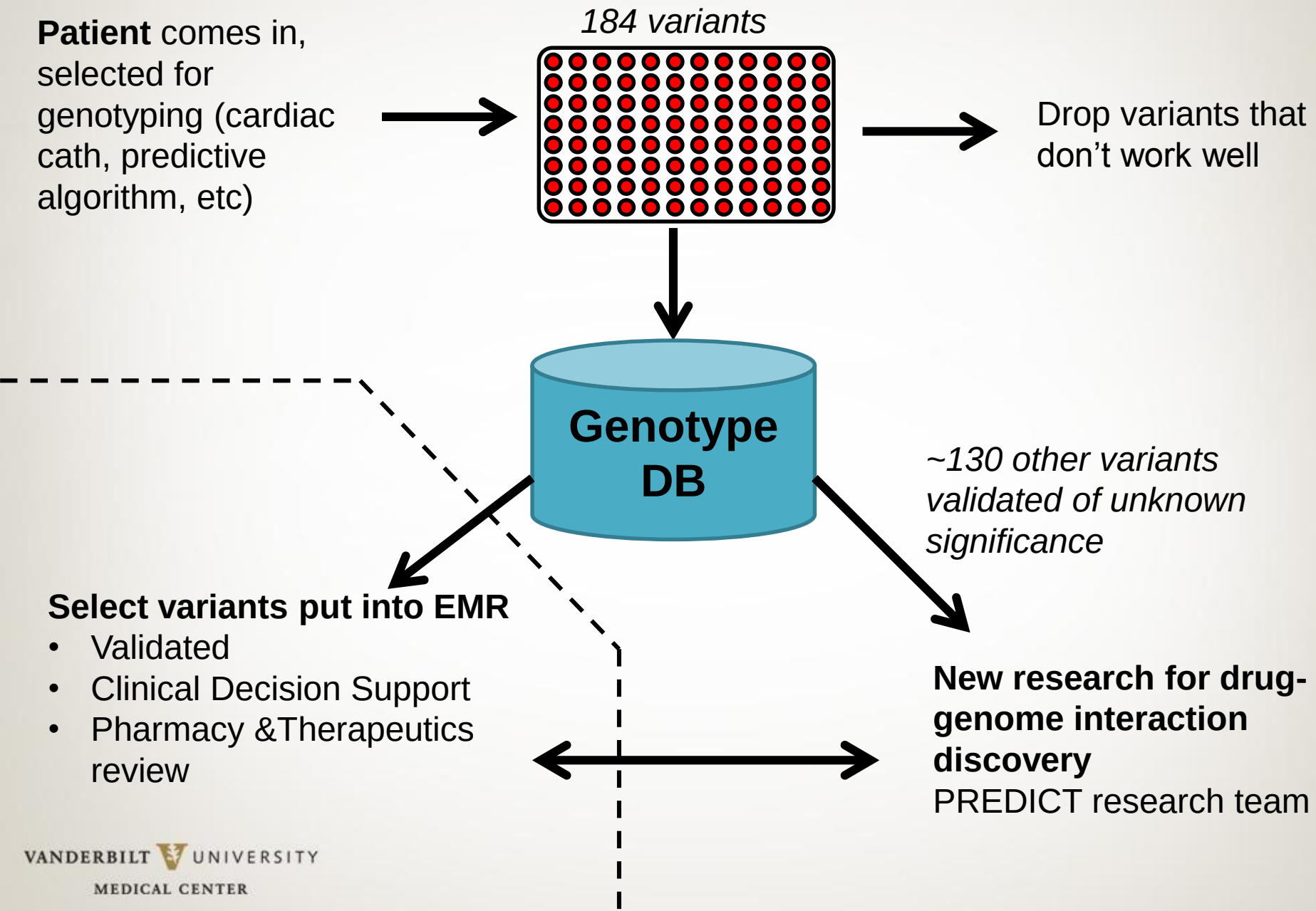
1. Select populations of patients who are at "high risk" for receiving a drug with an actionable "pharmacogenetic" story.
2. Genotype subjects on a platform that assays genotypes important for variable actions of many drugs preemptively.
3. Store the genotypes. Embed "actionable" drug-gene pairs in the EMR coupled to informatics tools to provide point-of-care advice. Track outcomes.


Vanderbilt Population
410,000
Target Clinics
90,000
Prognostic Flag for Testing
24,000
Prognostic Testing
~6,000
Reactive/Indication Testing
~8,000
Genotyped for PREDICT
~14,000
CLOPIDOGREL
SIMVASTATIN
WARFARIN
THIOPURINES
22%
25%
100%
3%
Clopidogrel Advisor
Simvastatin Advisor
Warfarin Advisor
Thiopurine Advisor

PREDICT: Multiplexing genotyping



PREDICT platform tests 184 variants in 34 drug-related genes



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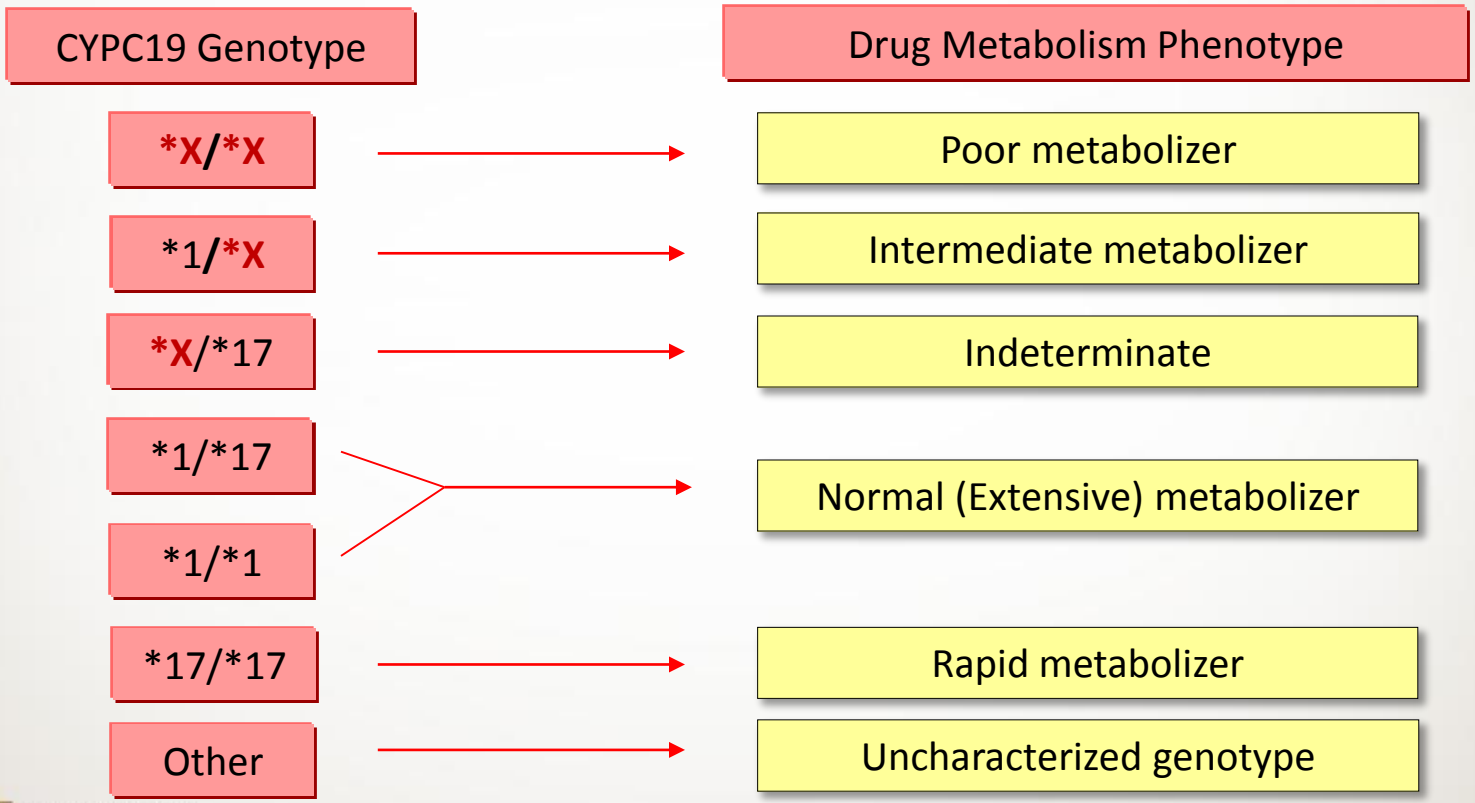
Genotype → Enzyme Phenotype

CYP2C19 - Clopidogrel

***X = CYP2C19 Loss of Function Variant in set {*2, *3, *4, *5, *6, *7, *8}**
***17 = CYP219 Gain of Function Variant**



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:

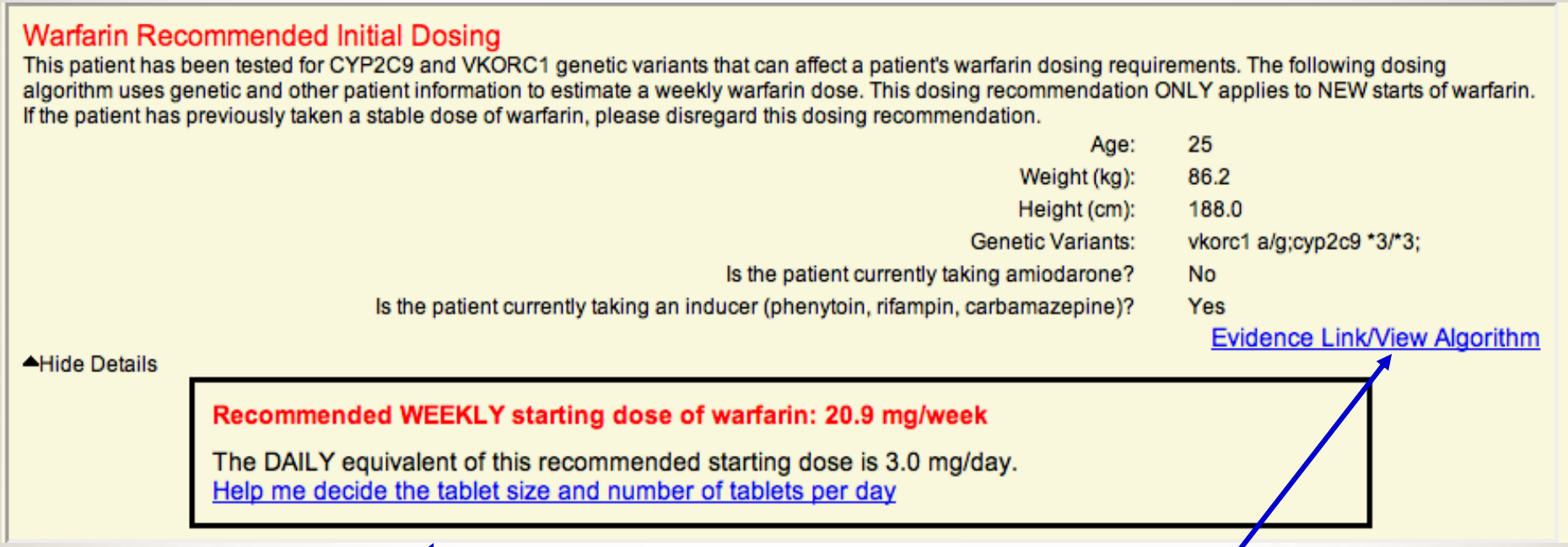
☐ Contraindicated for prasugrel or ticagrelor
☐ Potential side effects
☐ Provider/Patient opts for clopidogrel
☐ Cost

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

Decision Support for Warfarin Initial Dose



The advisor appears in the black box and shows the Recommended initial WEEKLY & DAILY dose

Links to clinical evidence and dosing table.

Medication	Does your genetic test result affect your response to medicines?
Clopidogrel/Plavix®	No
Simvastatin/Zocor®	No
Tacrolimus/Prograf®	No
Thiopurine Therapy	Yes
Warfarin/Coumadin®	Yes

The Clopidogrel Test

Show less >

Clopidogrel (sounds like "kloh-PID-oh-grel") is a blood thinner used to prevent clots that can cause a heart attack or stroke. Your genes can affect how well the drug works. This genetic test identifies how well you may respond to clopidogrel.

Your Risk

Show less >

Sometimes clopidogrel does not prevent harmful strokes or clots as well as it should because of your genes. Your provider, often with the results of a lab test, can determine if clopidogrel is the right medicine for you.

Based on the results of your test, your genes do not put you at increased risk for this negative outcome

More About Clopidogrel

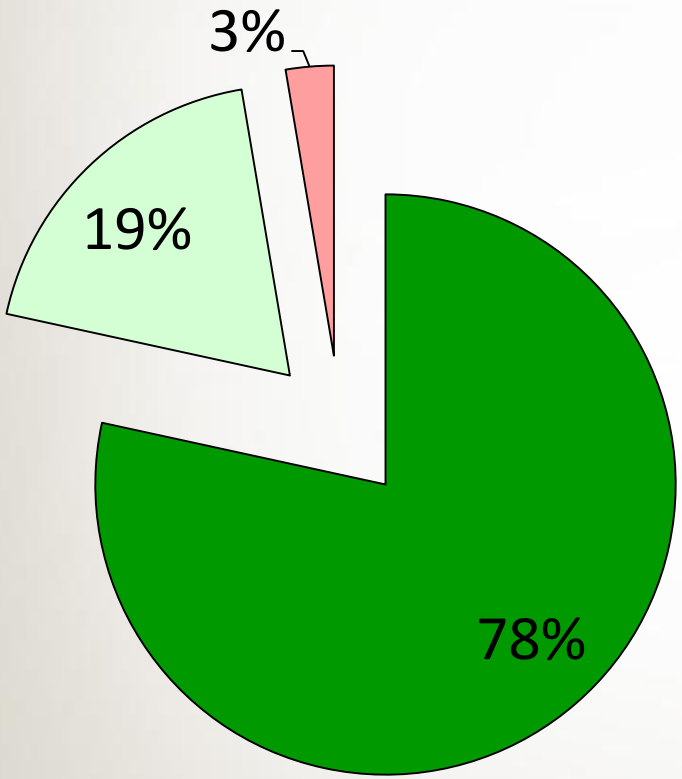
Show more >

More About Your Risk

Show more >

Testing for clopidogrel efficacy

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

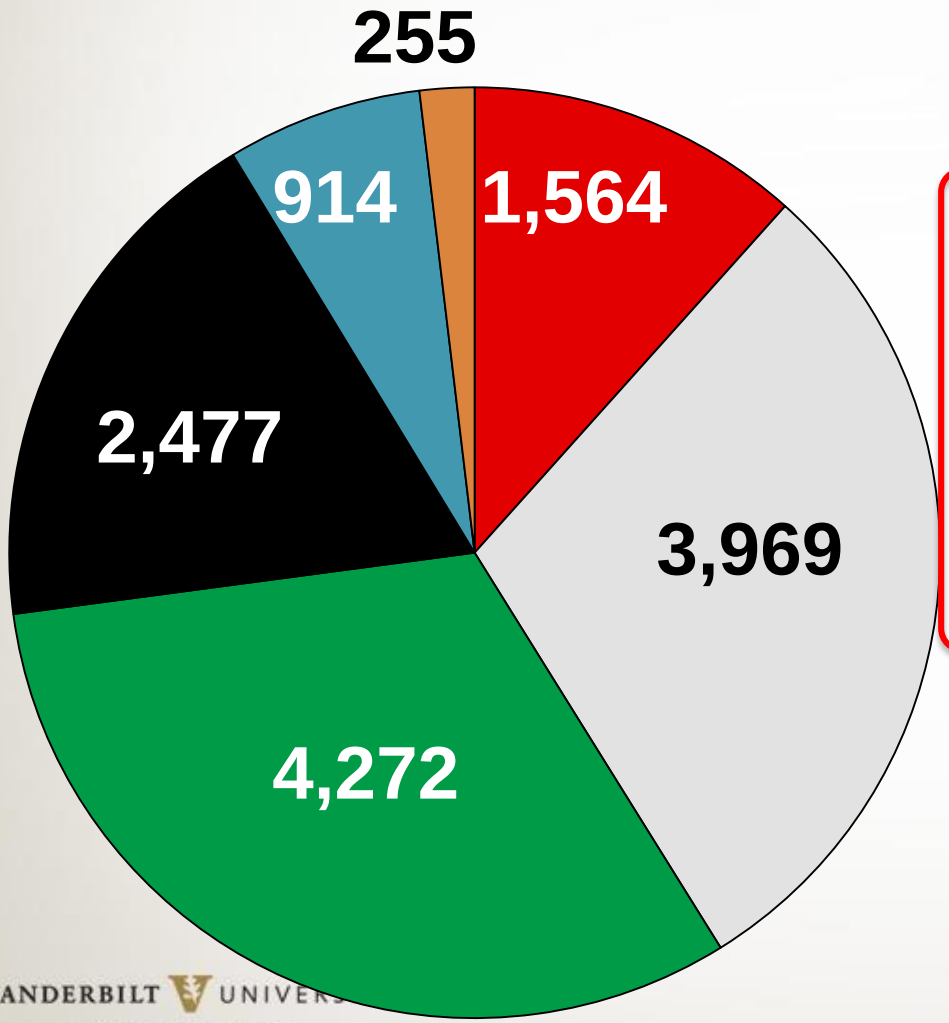


2.7% homozygous
18.9% heterozygous
} ↑ risk of MI

78.4% no common variant

Multiplexed testing for pharmacogenetic variants

(after 5 drug-gene pairs, n=13,451)



- 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 ≥1 risk variant

…but 99.8% of African Americans

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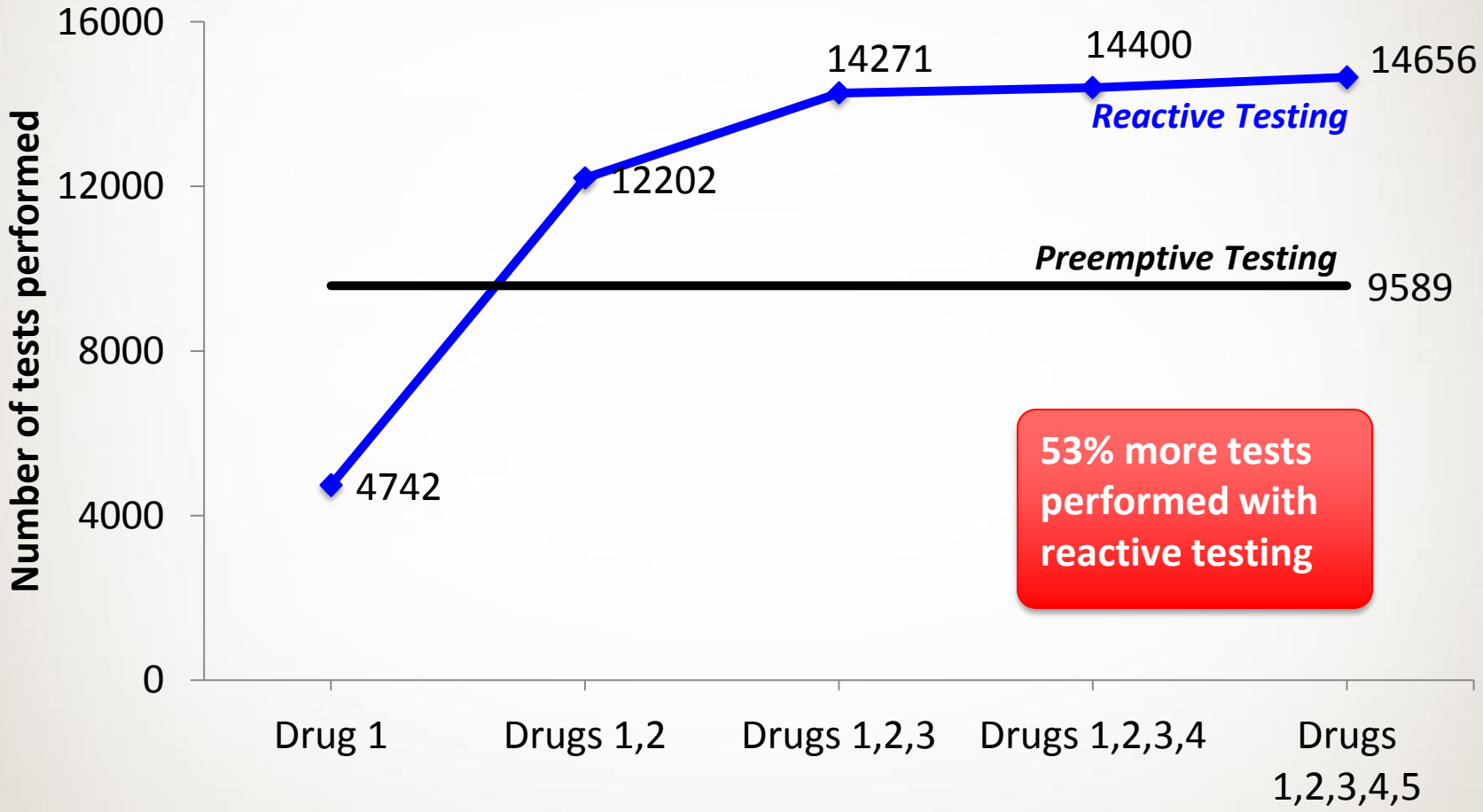
Van Driest et al, Clin Pharmacol Therap. 2013

Multiplexed Genetics Testing can save money too



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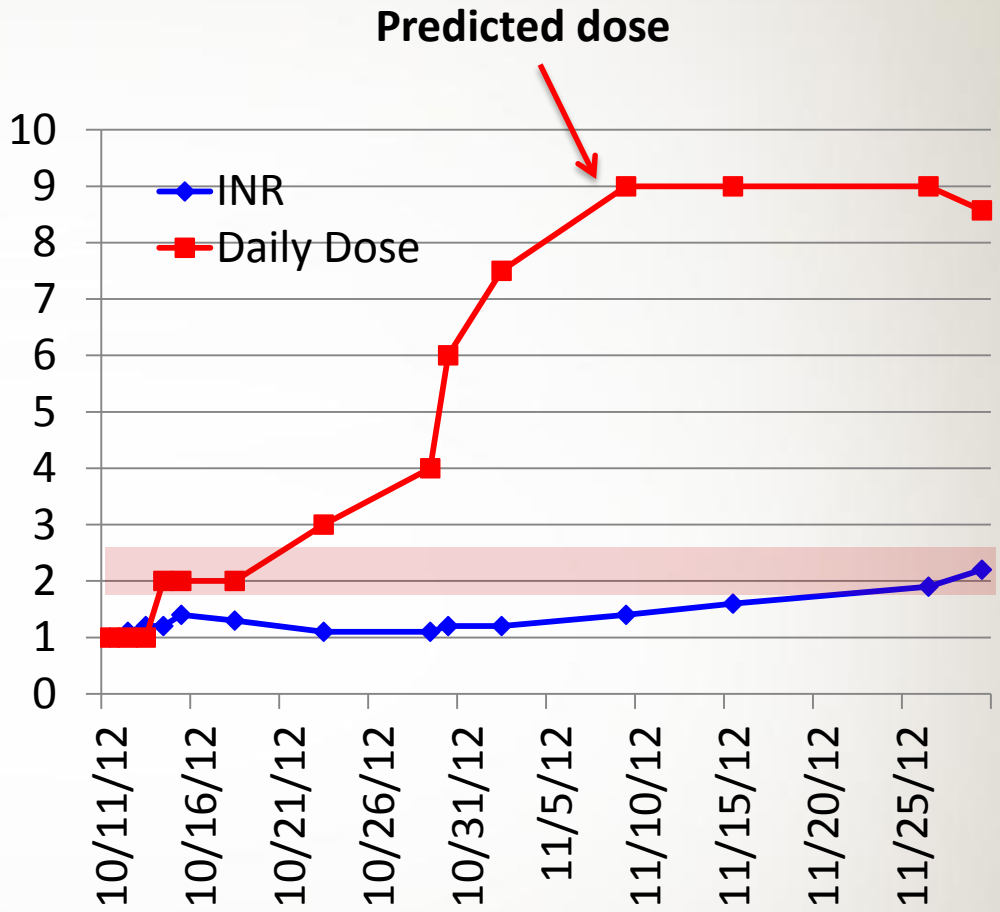
Van Driest et al, Clin Pharmacol Therap. 2013

Warfarin CDS Surveillance Example

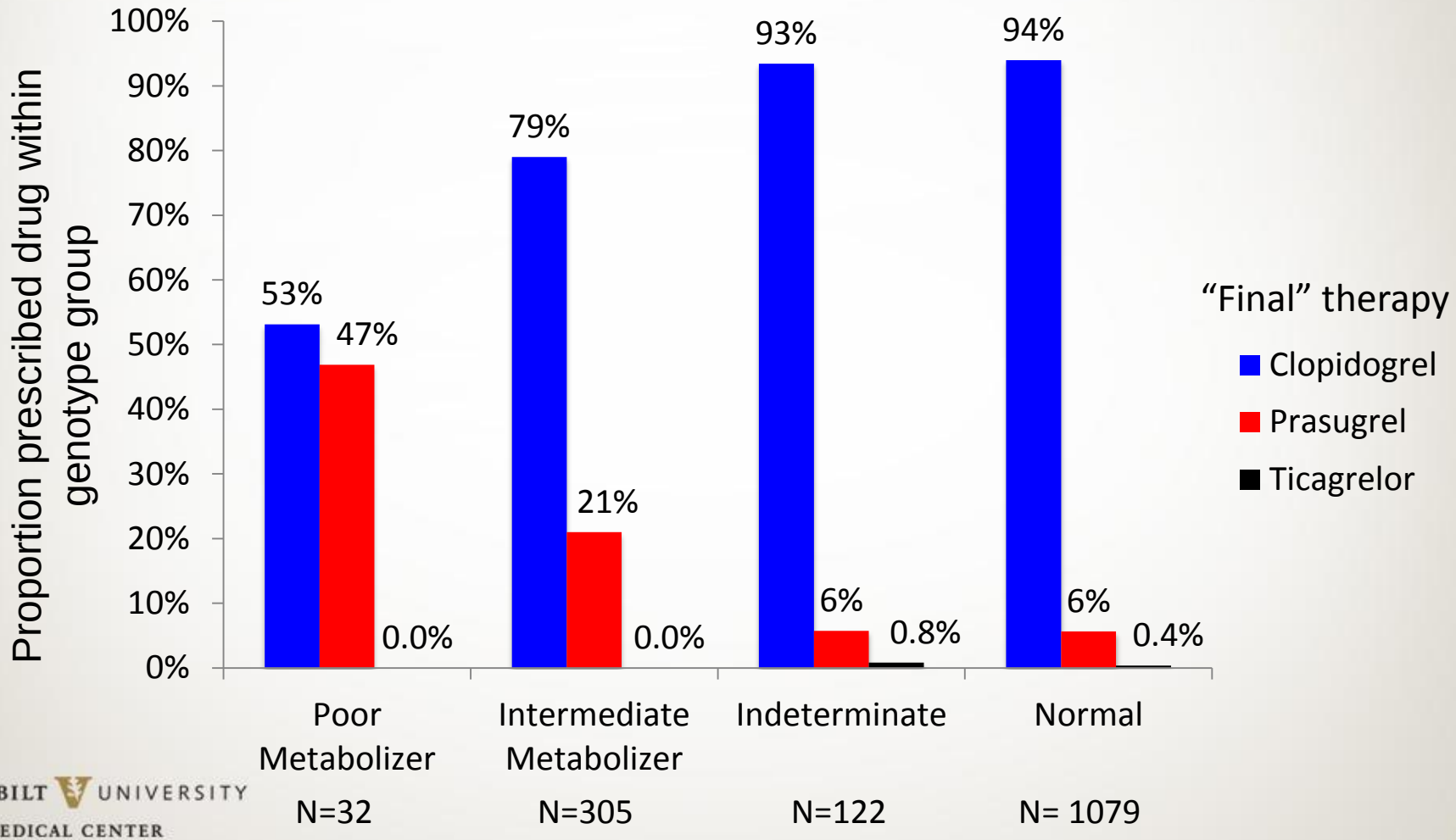
Recommended Daily Dose = 9 mg/d
Initial Dose Prescribed = 1mg/d

Gene Results = warfarin normal responder
Recommended Weekly Dose = 63.0
Amiodarone = 0
Inducer = 0
Age = 39
Height = 180
Weight = 78.5



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



VANDERBILT UNIVERSITY MEDICAL CENTER

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

PREDICT helps match patient with proper drug

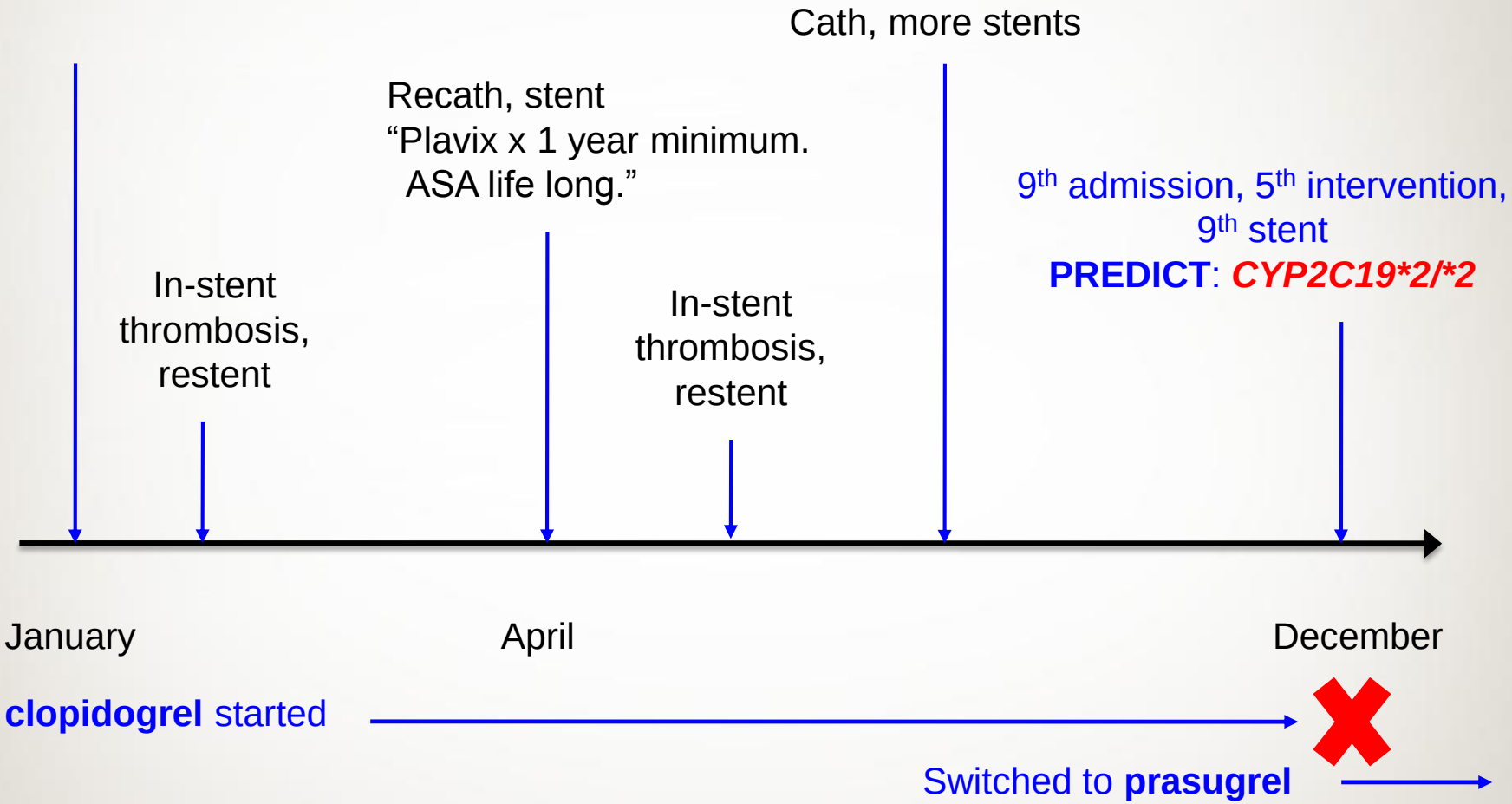
BY: KATHY WHITNEY

10/28/2010 - Had Scyble Van Cleve, a spry 83-year-old from Brentwood, had her heart procedure done a month ago instead of one week ago, she would have been prescribed the standard dose of clopidogrel, a blood thinner used to prevent blood clots from forming around her coronary stents.

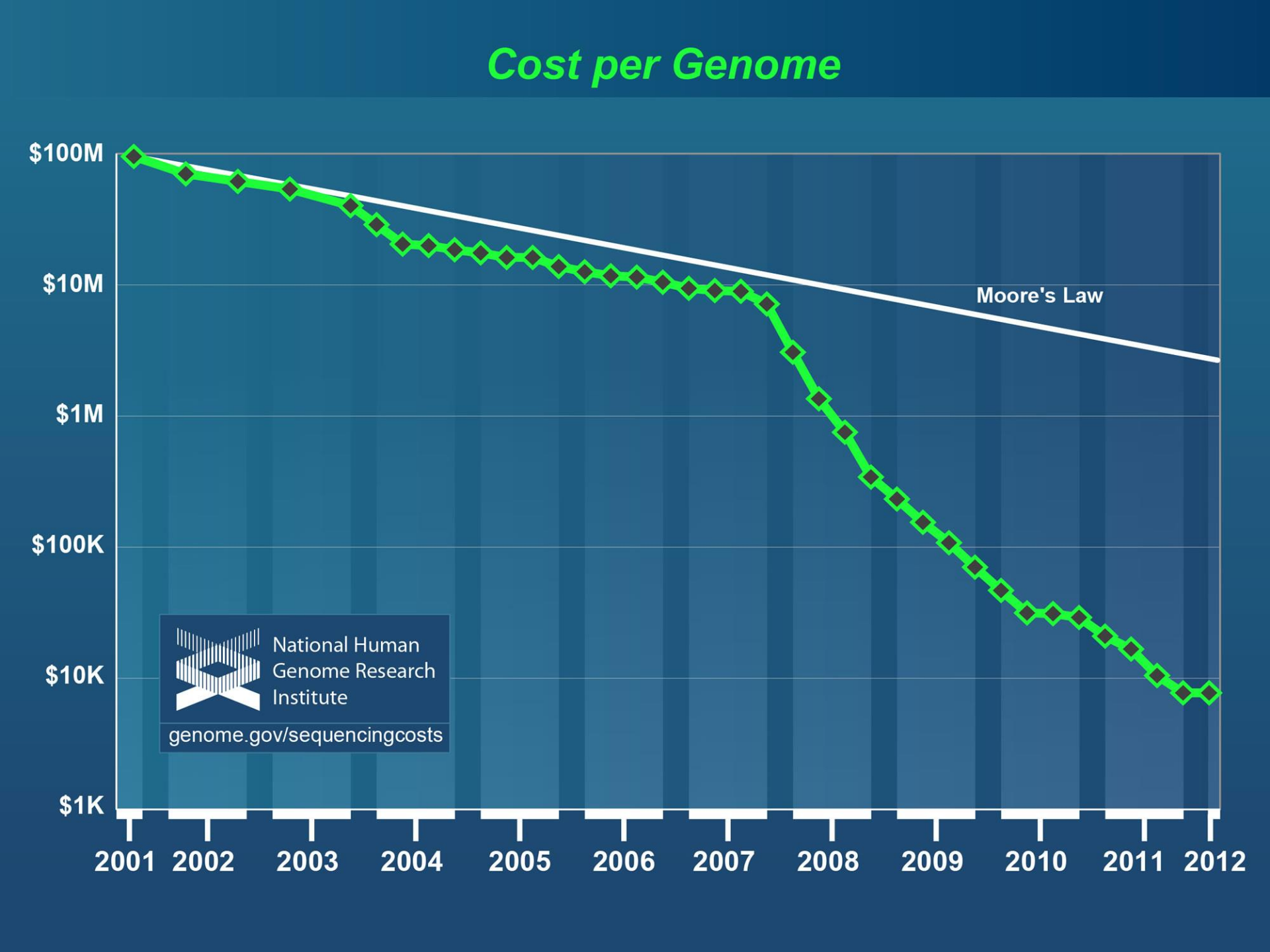
Scyble Van Cleve, right, is the first patient at Vanderbilt to benefit from a new program that puts genetic information in the patient's medical records to help physicians like John McPherson, M.D., choose the drug and dose that will benefit them the most. (photo by Susan Urmy)

57yo with admitted for angina, receives stent

Our case: What personalizing medicine really means



Cost per Genome

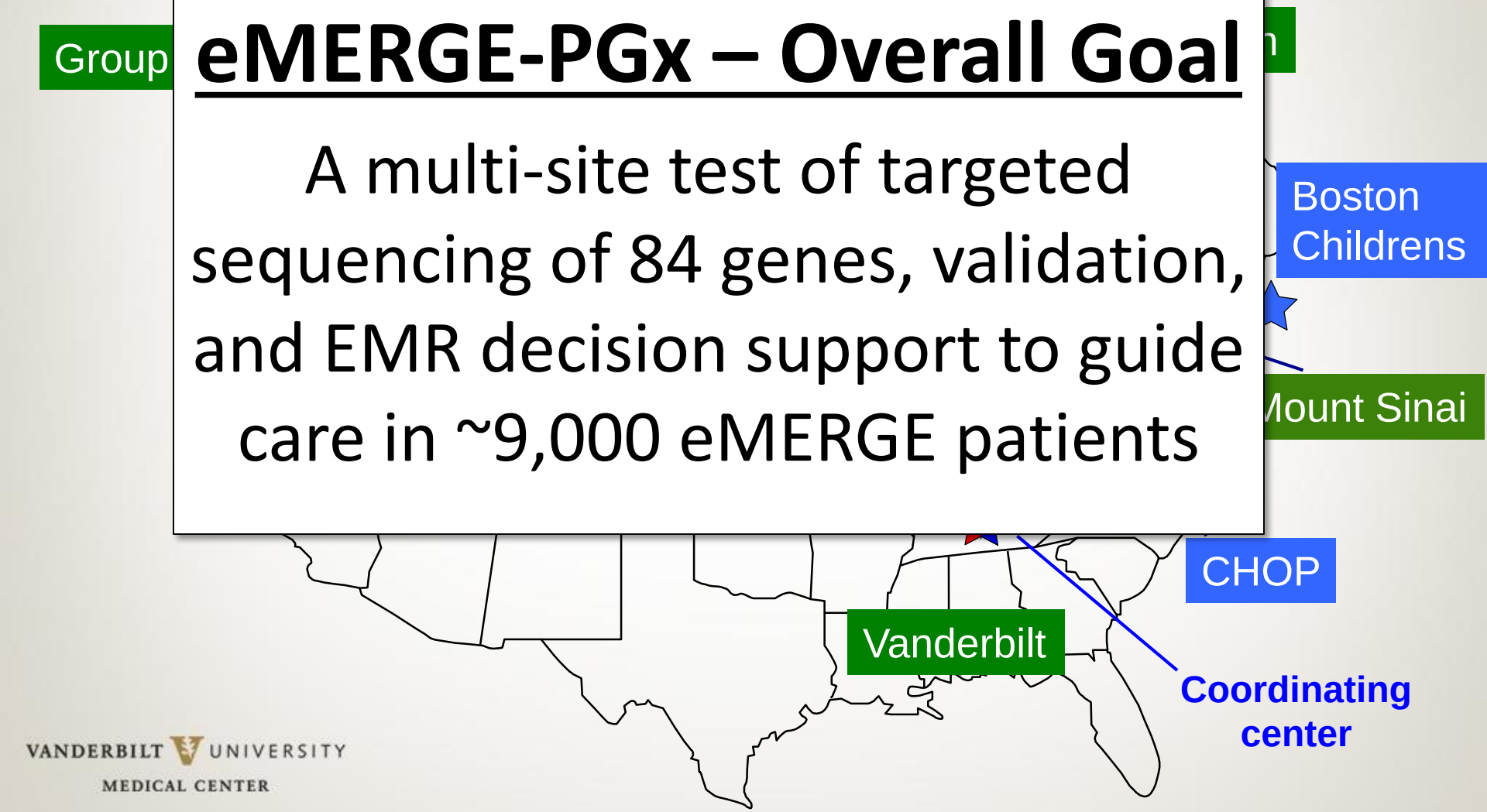


The *eMERGE* Network
electronic Medical Records & Genomics
A consortium of biorepositories linked to electronic medical records data for conducting genomic studies

PGRN Pharmacogenomics Research Network

eMERGE-PGx – Overall Goal

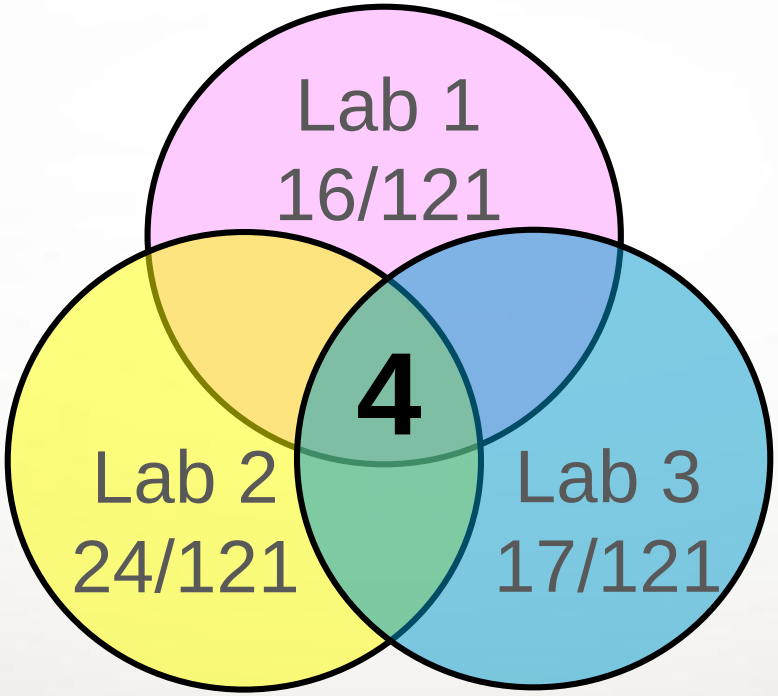
A multi-site test of targeted sequencing of 84 genes, validation, and EMR decision support to guide care in ~9,000 eMERGE patients



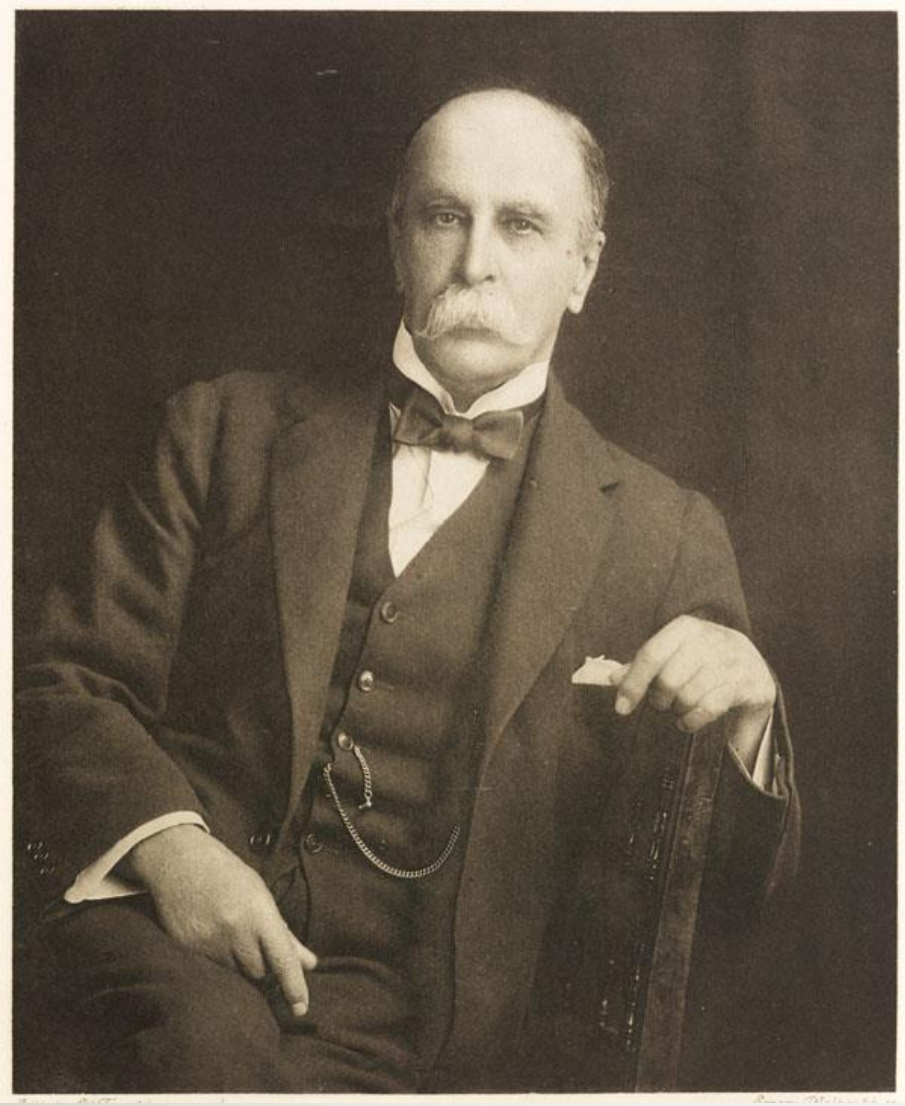
VANDERBILT UNIVERSITY MEDICAL CENTER

Preliminary PGRN-Seq Results *SCN5A* and *KCNH2* in 2,200 Patients

- 83 rare (MAF < 1%) in *SCN5A*, 45 in *KCNH2*
- 121/128 MAF < 0.5%, 92 singletons
- Three labs assessed known/likely pathogenicity



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

Summary

- EMRs and EMR-linked DNA biobanks play an important role in both discovery and implementation of genomic medicine. EMRs biobanks can accelerate discovery and save money.
- Prospective testing has an opportunity to change prescribing patterns, but requires decision support to help the physicians navigate the complex prescribing process
- Multiplexed testing of genetic variants prospectively reduces total numbers of tests and may reduce cost

The Teams

Informatics

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- Robert Carroll
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- Marylyn Ritchie
- Jonathan Haines

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- 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

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- NCI