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MEDICAL CENTER

Implementation of Pharmacogenomics in Clinical Medicine in the USA

Dan M. Roden, MD
Senior Vice President for Personalized Medicine
Vanderbilt University Medical Center, Nashville, TN

The vision

"Here's my sequence..."

New Yorker, 2000

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

Francis Collins, NEJM 9/16/2009

US pharmacogenomic implementation sites

Pharmacogenomics Research Network
PGRN

eMERGE PGx
EMRs • Genomics • Pharmacogenomics

eMERGE Network
electronic medical records & genomics

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Pre-emptive

Point of care

IGNITE
Implementing GeNomics In pracTicE

US pharmacogenomic implementation sites

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Pre-emptive

Reactive

IGNITE

Implementing GeNomics In pracTicE

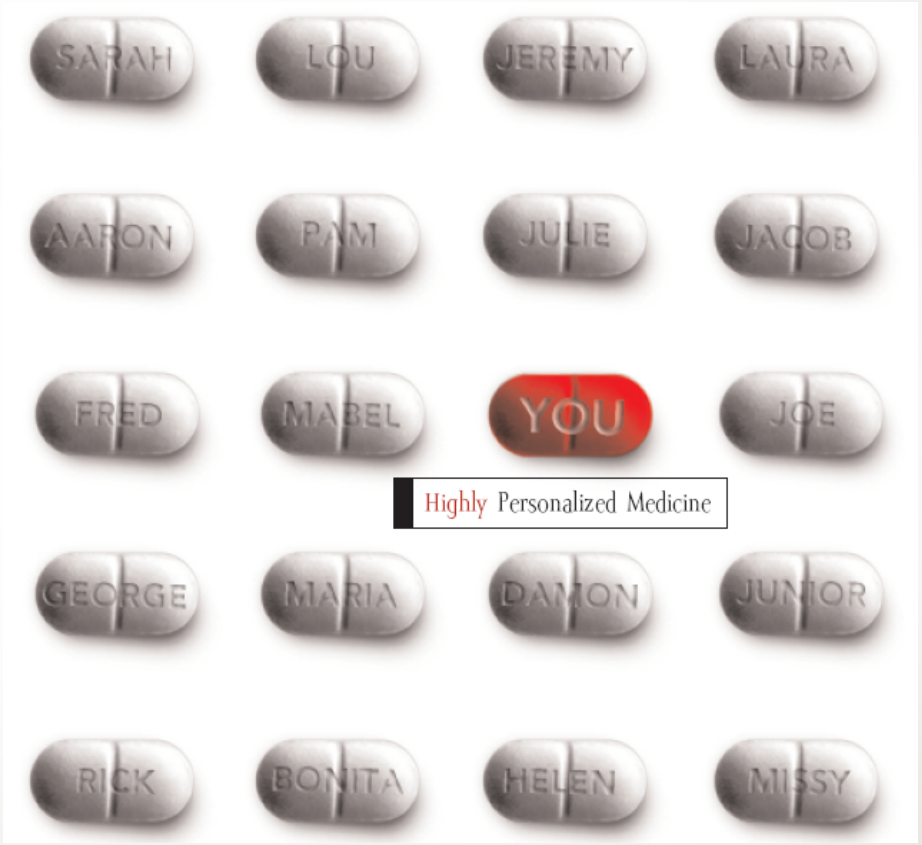
The vision

"Here's my sequence..."

New Yorker, 2000

PREDICT

Pharmacogenomic **R**esource for **E**nhanced **D**ecisions **I**n **C**are and **T**reatment



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The vision

"Here's my sequence..."

New Yorker, 2000

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PREDICT

Pharmacogenomic **R**esource for **E**nhanced **D**ecisions **I**n **C**are and **T**reatment

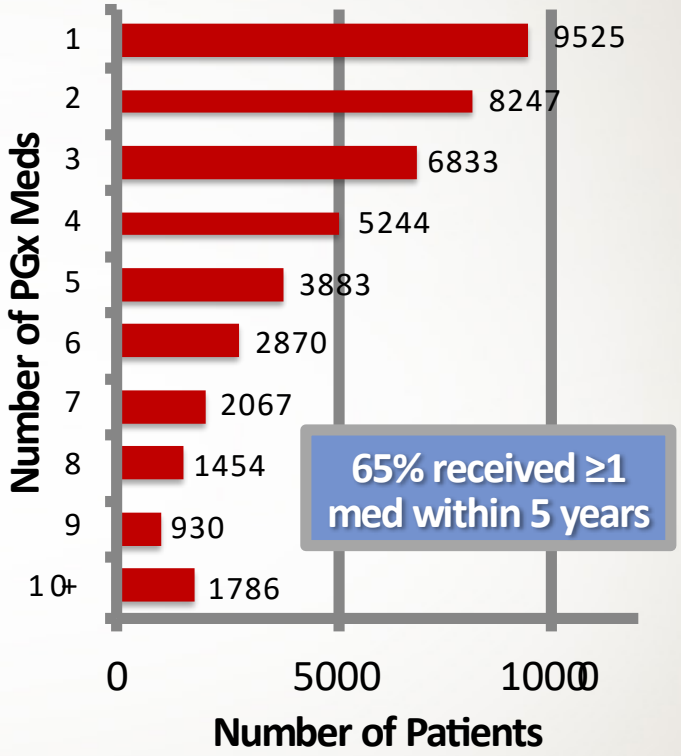
1. Select populations of patients who are "at high risk" for receiving a drug with a pharmacogenetic "story".
2. Genotype them preemptively on a platform that assays many pharmacogenetic variants.
3. Store the genotypes, develop the informatics tools to provide point-of-care advice. Track outcomes.

A Case for Prospective Genotyping

Identifying a 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

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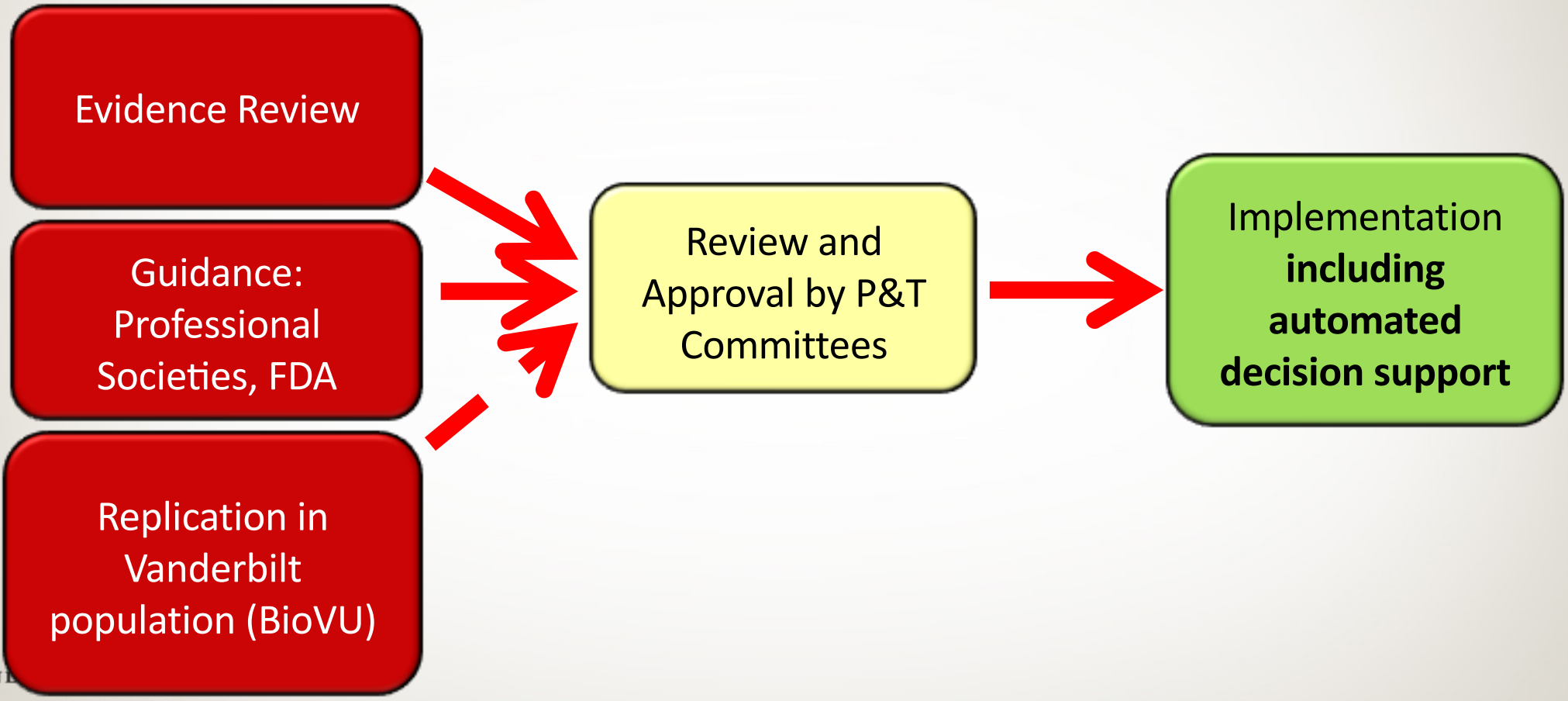
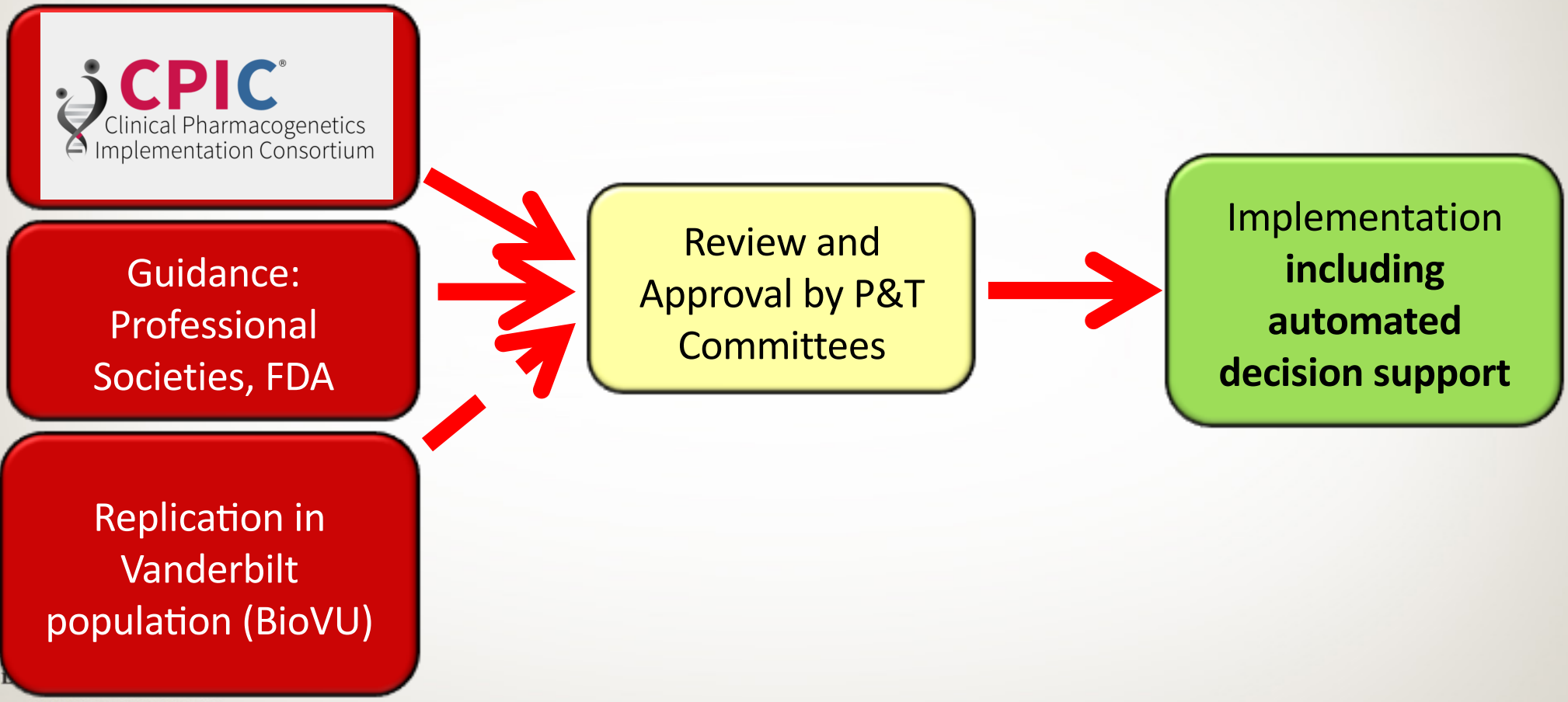
Schildcrout et al, CPT 2012

Selection of PREDICT Drug-Gene Interactions



Selection of PREDICT Drug-Gene Interactions



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Clopidogrel label revision March 2010 identifies a high risk group

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

Clopidogrel label revision March 2010 identifies a high risk group

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- Consider alternative treat[illegible] nt strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

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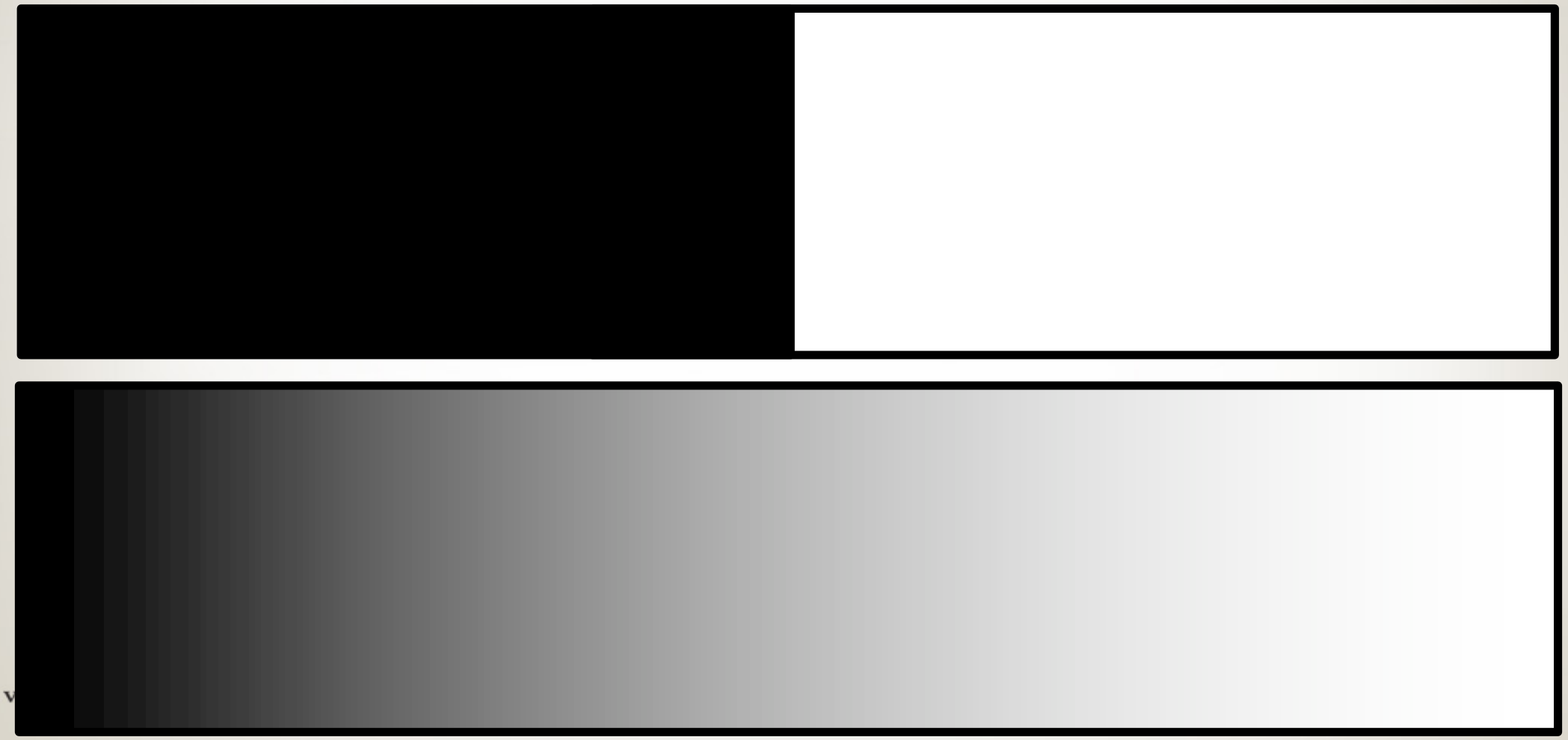
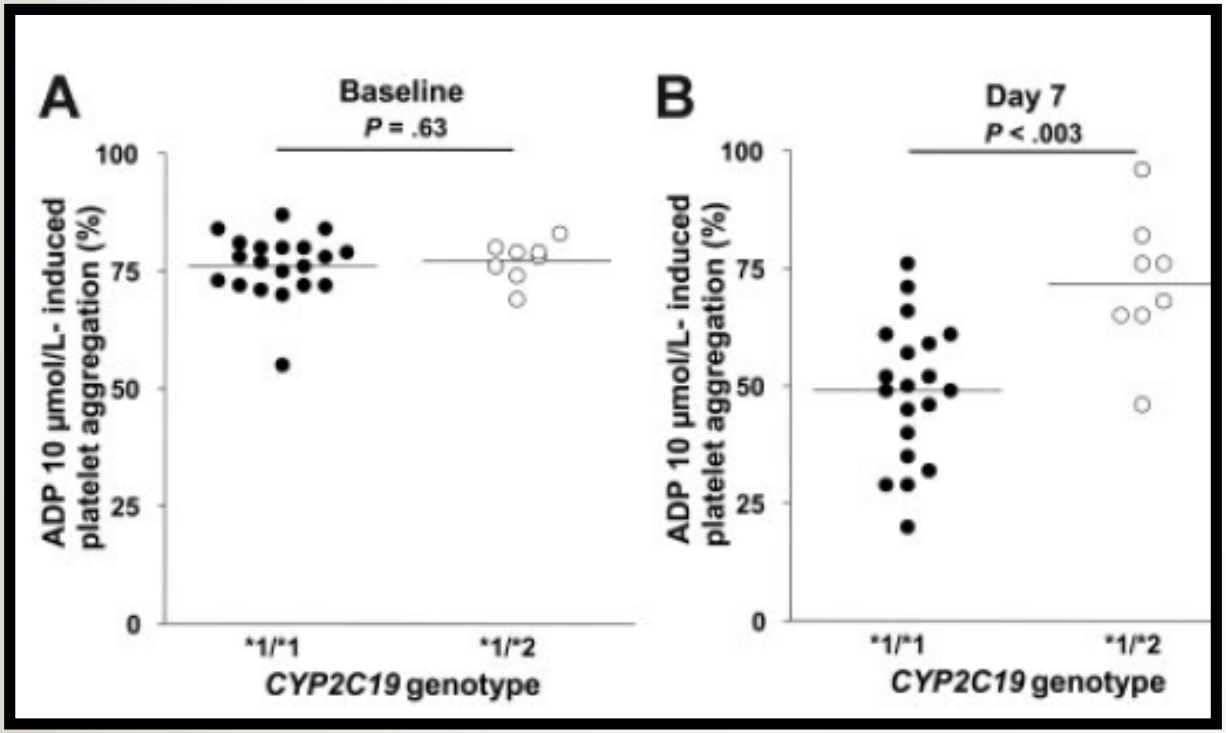
ME

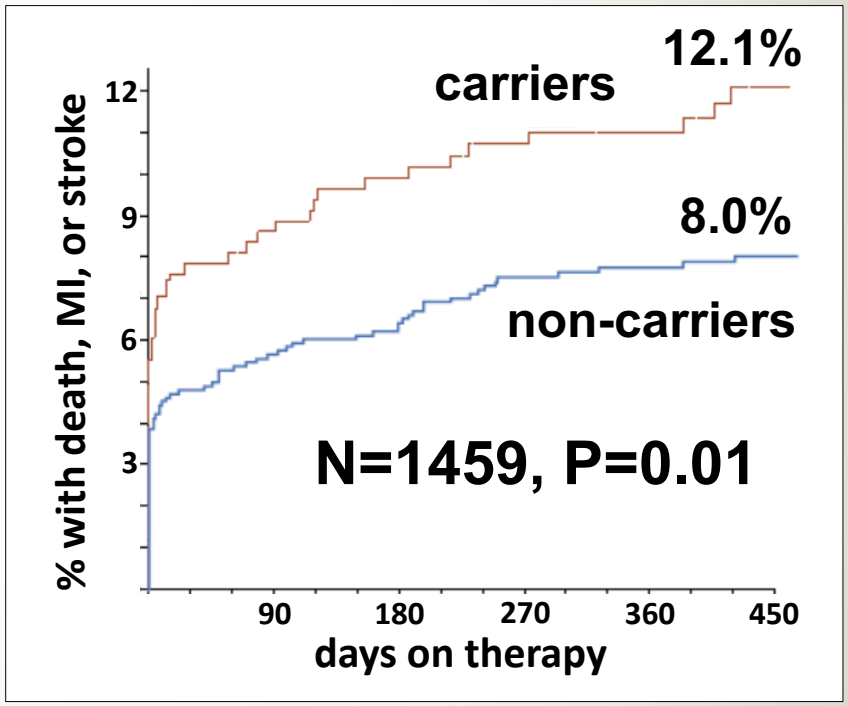
Genetic data, prediction, and “actionability”



CYP2C19 loss of function variants → decreased anti-platelet effect

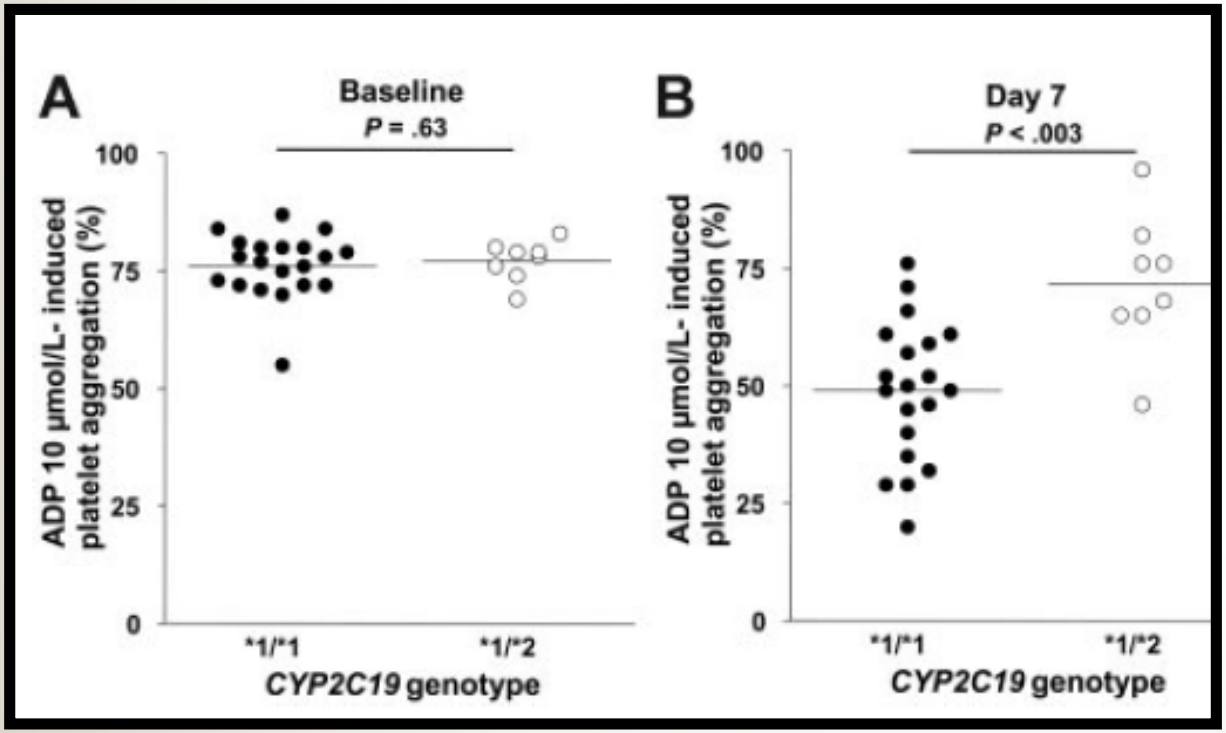


Hulot et al., 2006

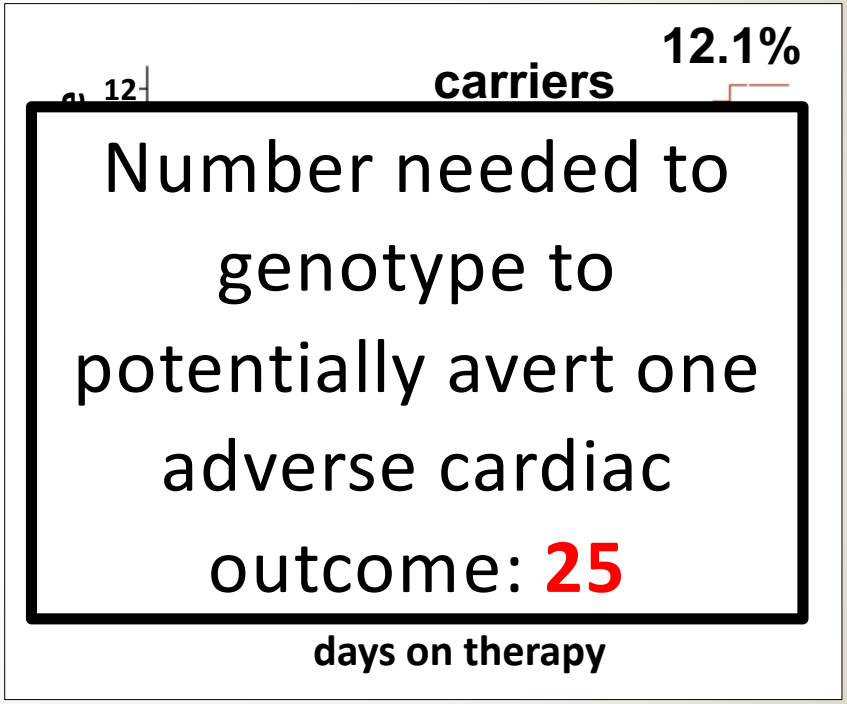


Mega et al., 2009

CYP2C19 loss of function variants → decreased anti-platelet effect



Hulot et al., 2006



Mega et al., 2009

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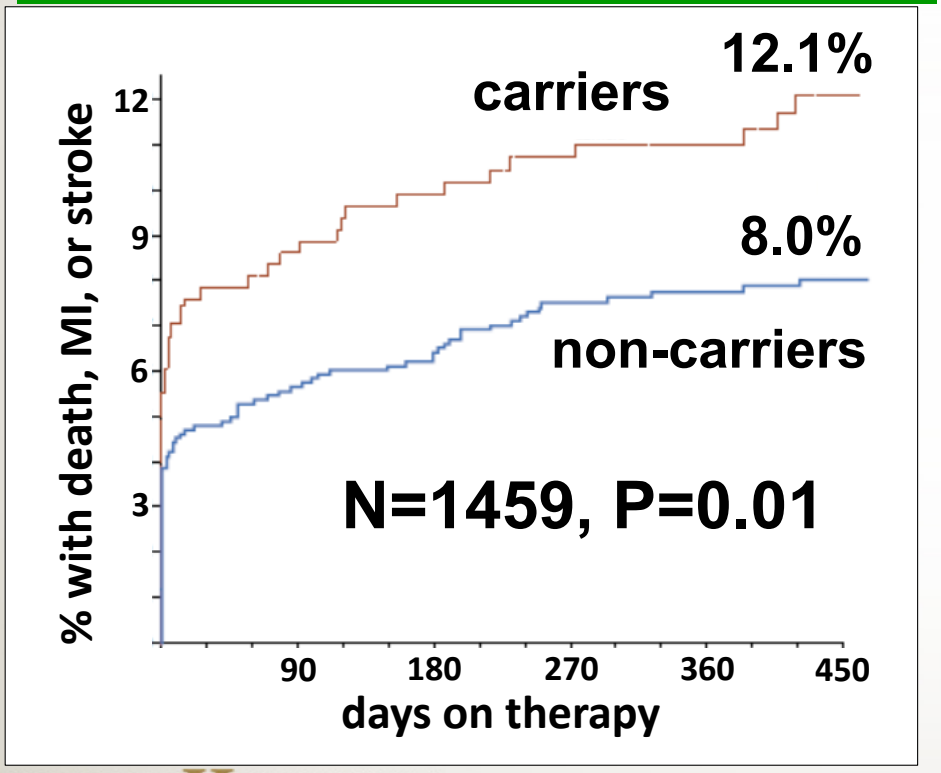
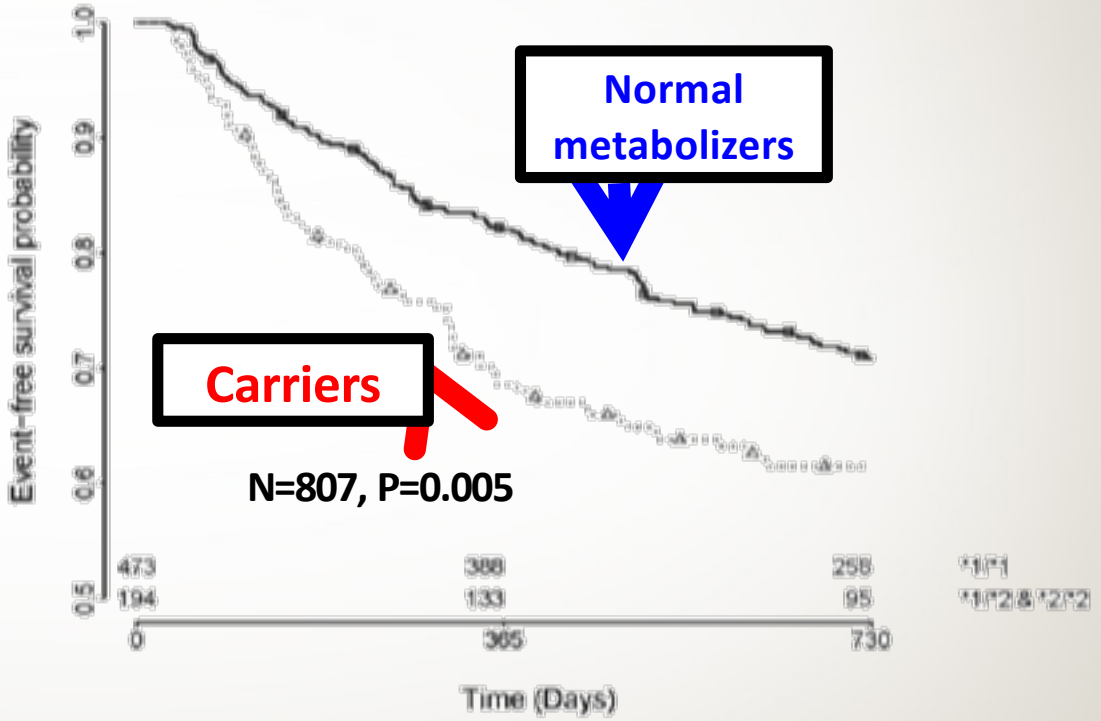
Clopidogrel adverse events associated with *CYP2C19* status in BioVU

From clinical trials



Mega et al., 2009

From the EHR



Delaney et al. *Clin Pharm Ther.* 2012

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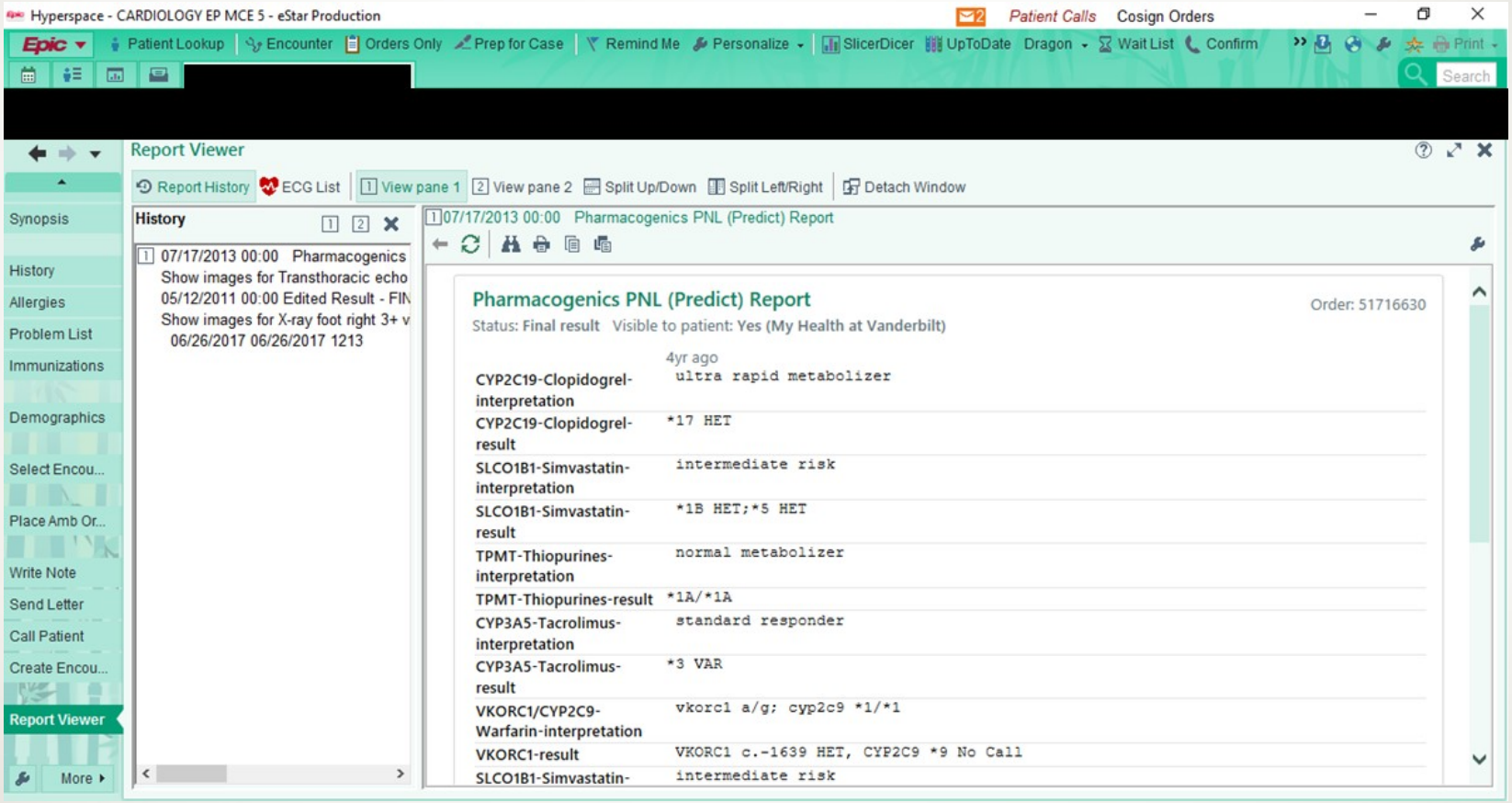
The future is here



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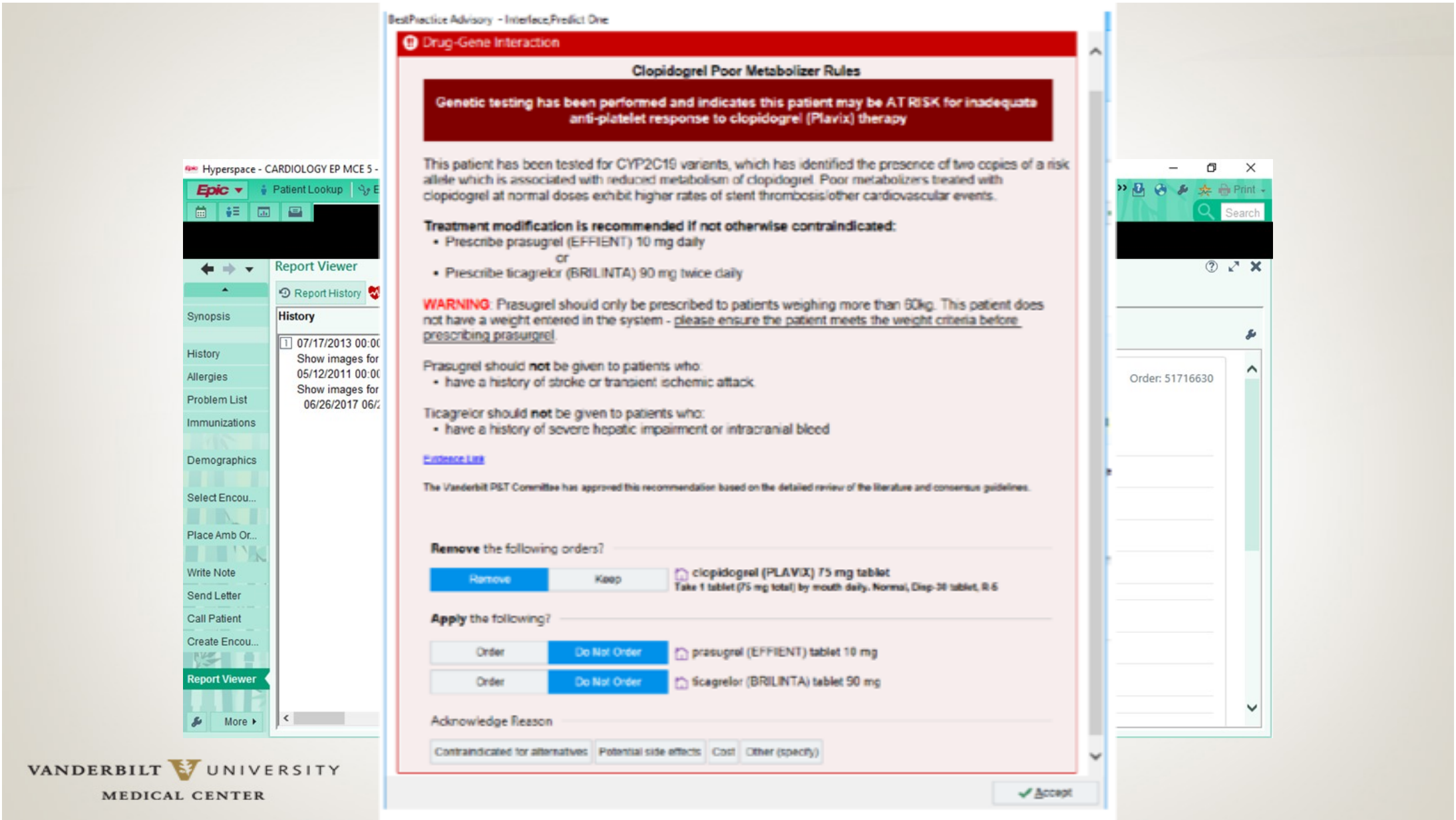

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cdskb.org – a joint project of eMERGE and IGNITE to share Clinical Decision Support elements

eCDS_KB
CLINICAL DECISION SUPPORT KNOWLEDGEBASE

CDS KnowledgeBase is the engine that drives precision medicine.

who are we?

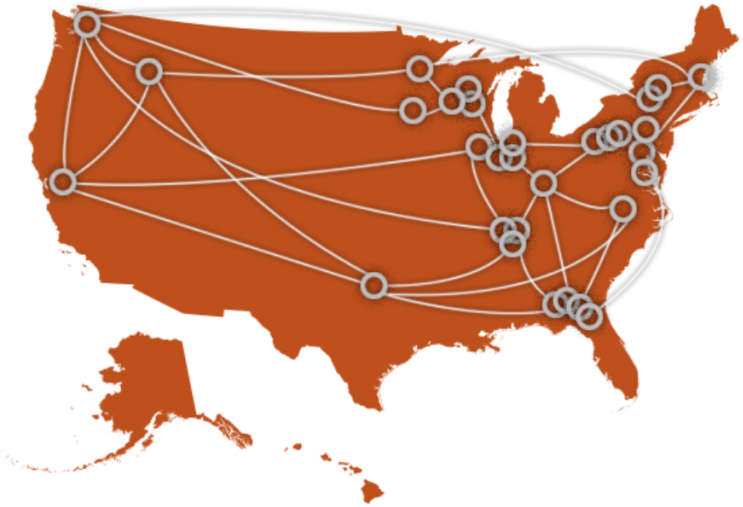
Clinical decision support (CDS) forms a significant part of the field of clinical knowledge management technologies through their capacity to support the clinical process and use of knowledge, from diagnosis and investigation through treatment and long-term care.

CDS KnowledgeBase Partners

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

IGNITE
Implementing GeNomics In pracTicE

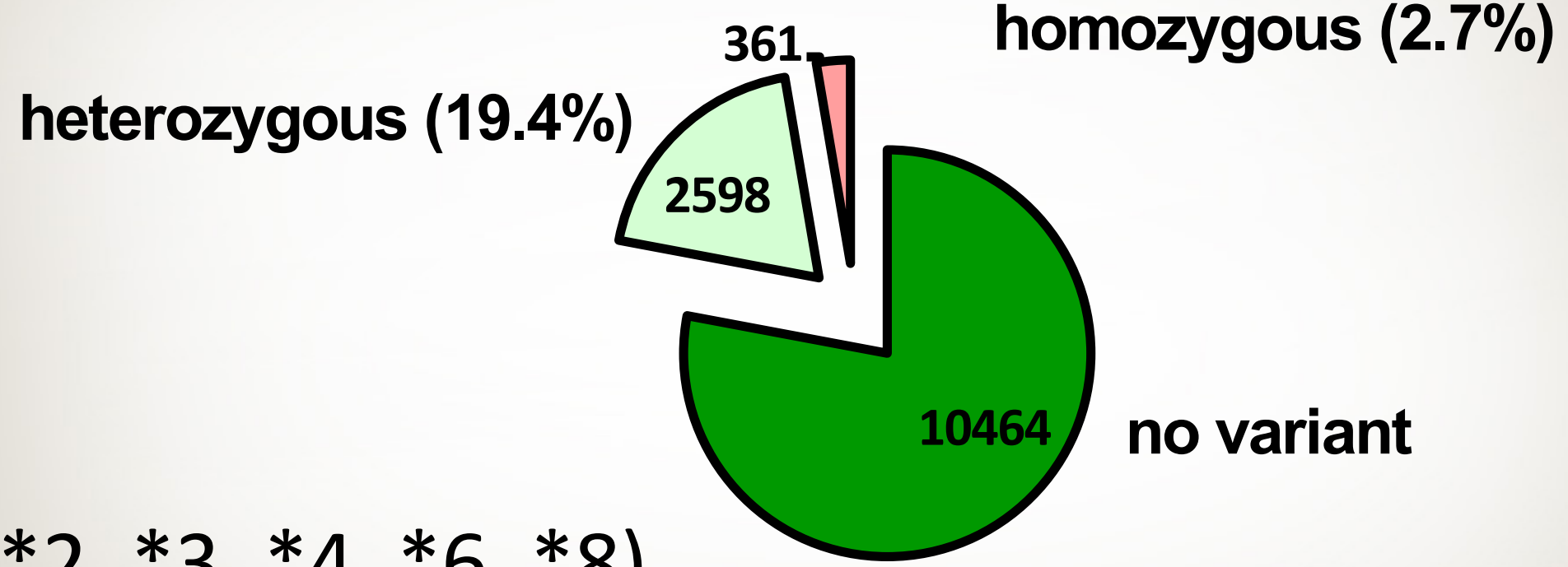
THE COMMUNITY:
IDEAS FROM ONE OF MANY



CONNECTIONS, RESOURCES, AND PEER REVIEWS

VANDERBILT MEDICAL

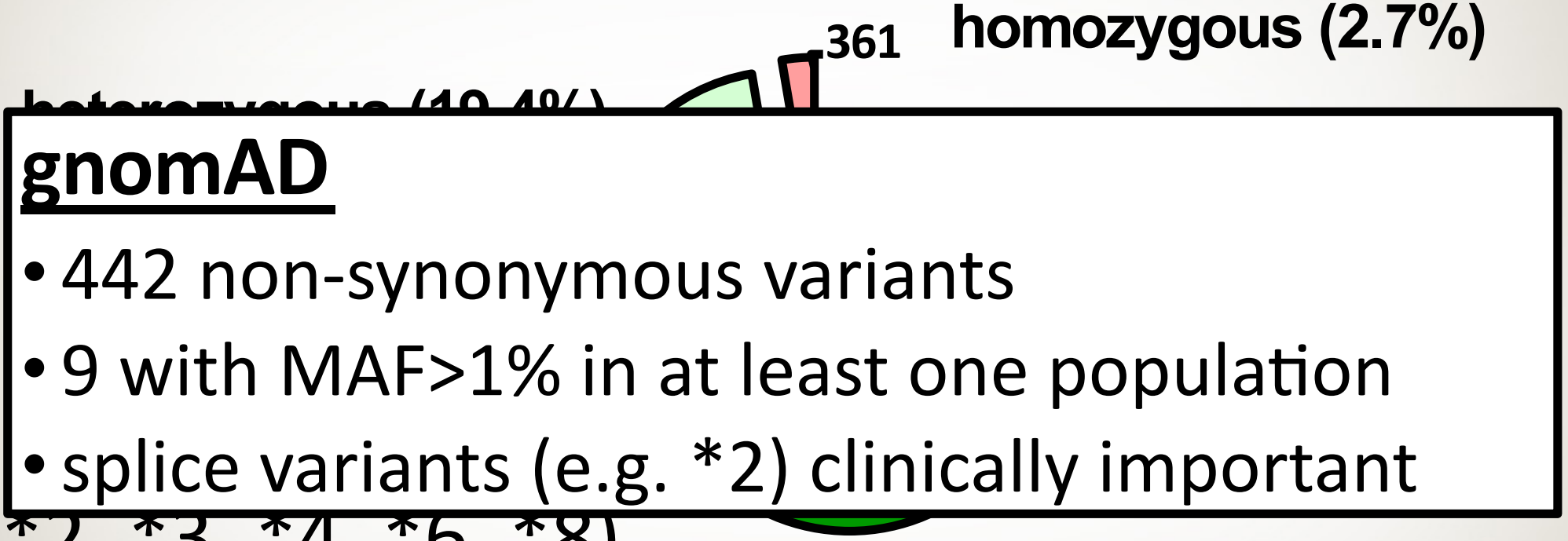
CYP2C19 genotypes in 13,423 patients at Vanderbilt University Hospital



(*2, *3, *4, *6, *8)

VANDERBILT UNIVERSITY
MEDICAL CENTER

CYP2C19 genotypes in 13,423 patients at Vanderbilt University Hospital

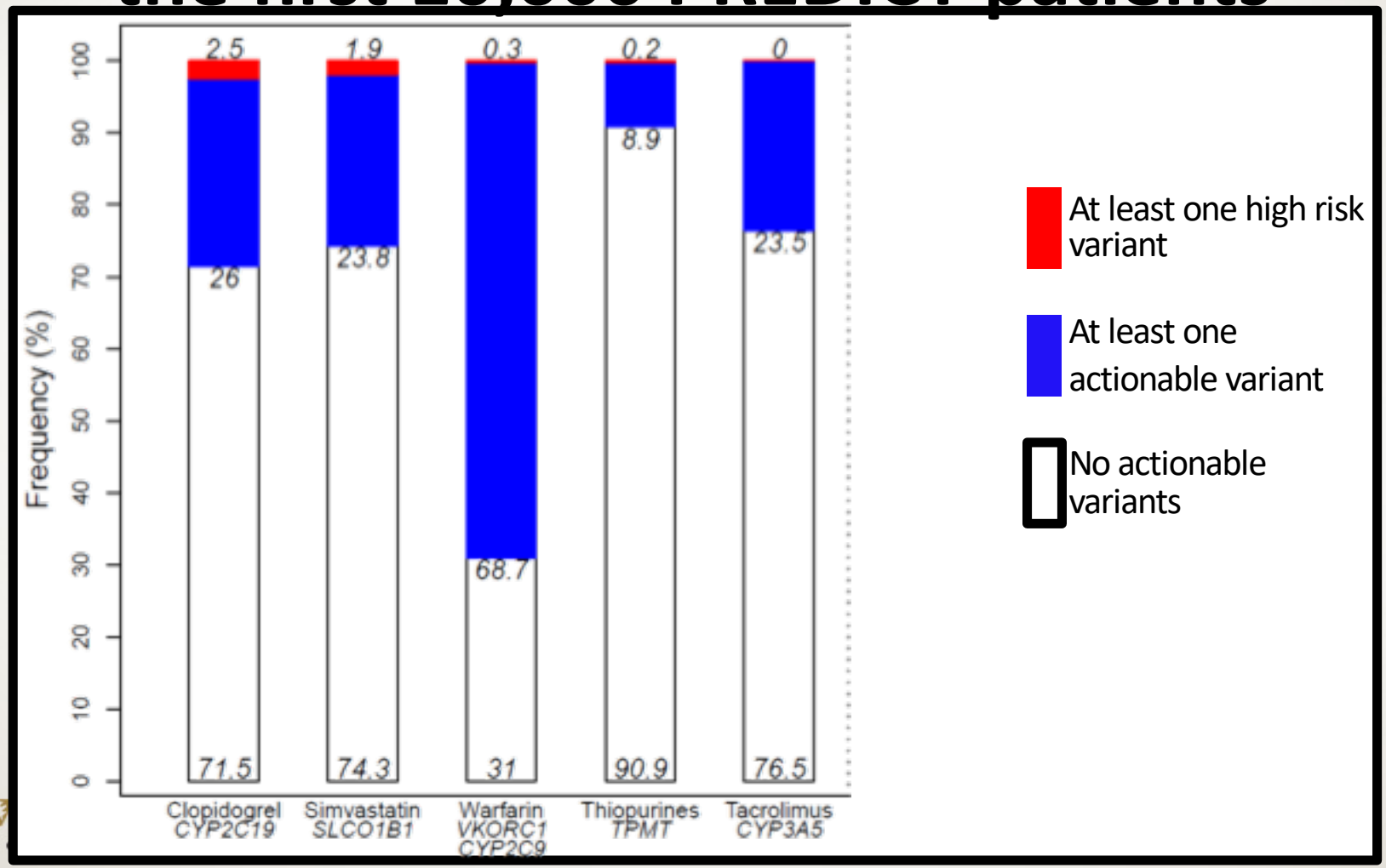


gnomAD

- 442 non-synonymous variants
- 9 with MAF>1% in at least one population
- splice variants (e.g. *2) clinically important

(*2, *3, *4, *6, *8)

Frequency of actionable genotypes in the first 10,000 PREDICT patients



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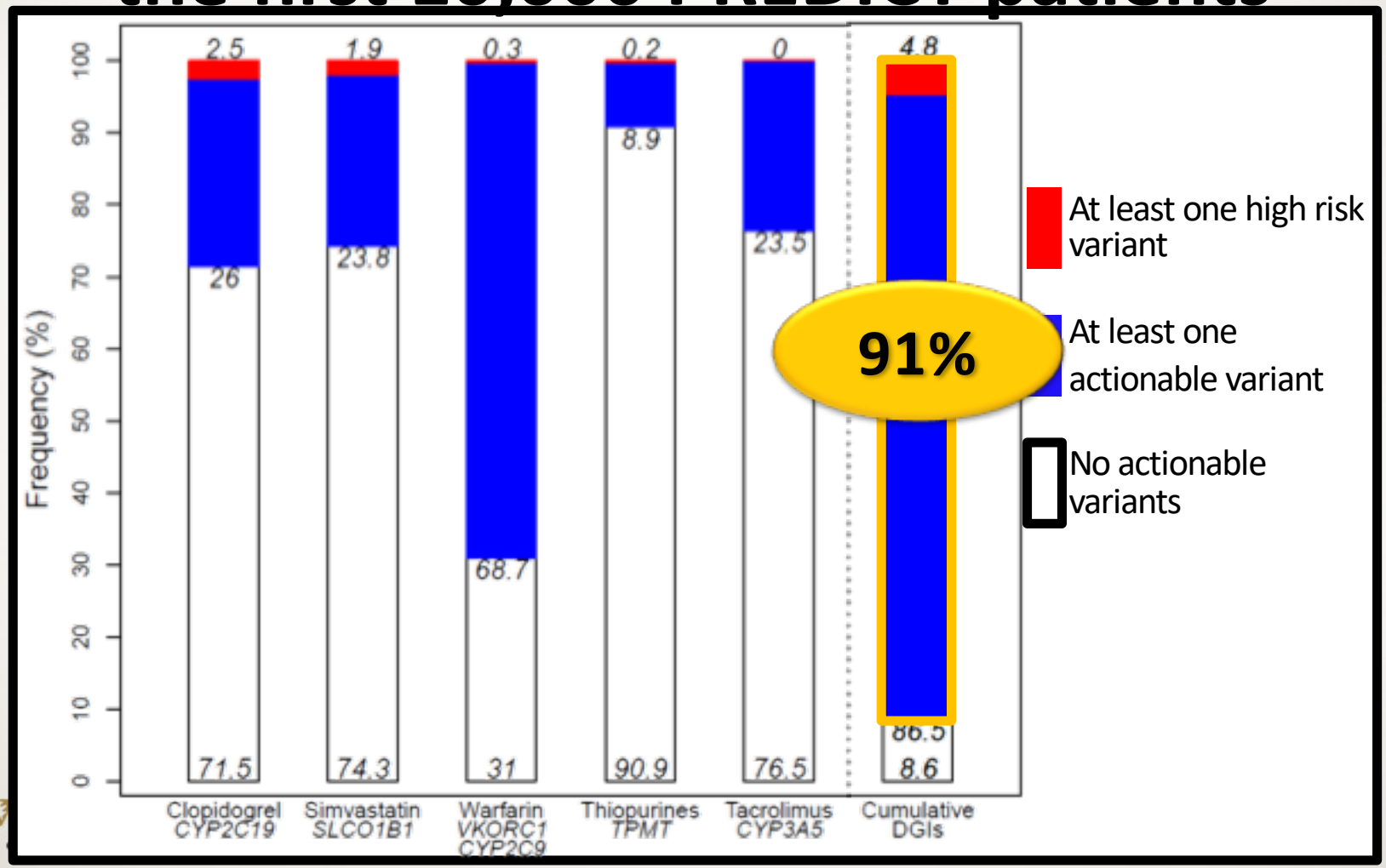

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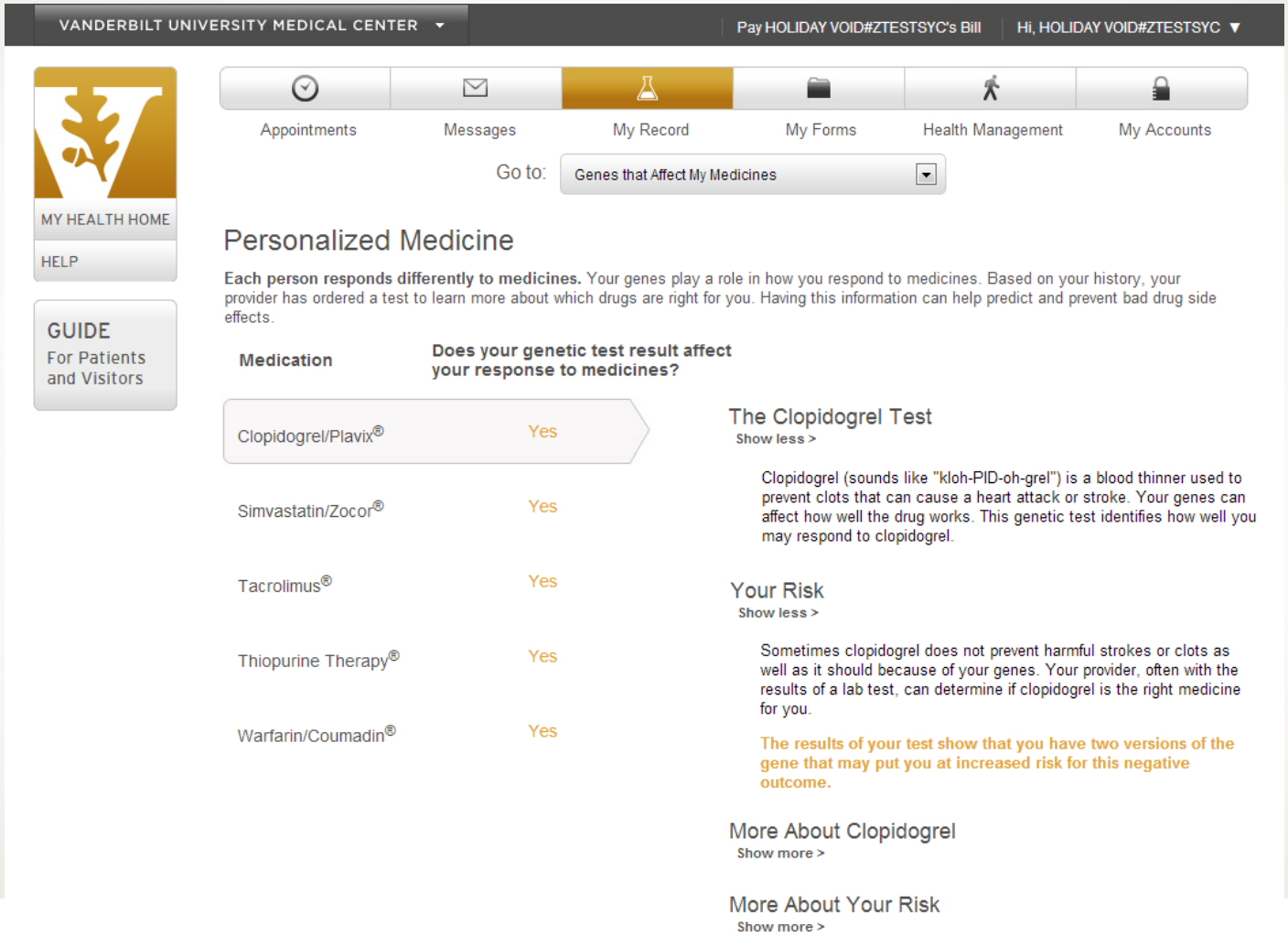
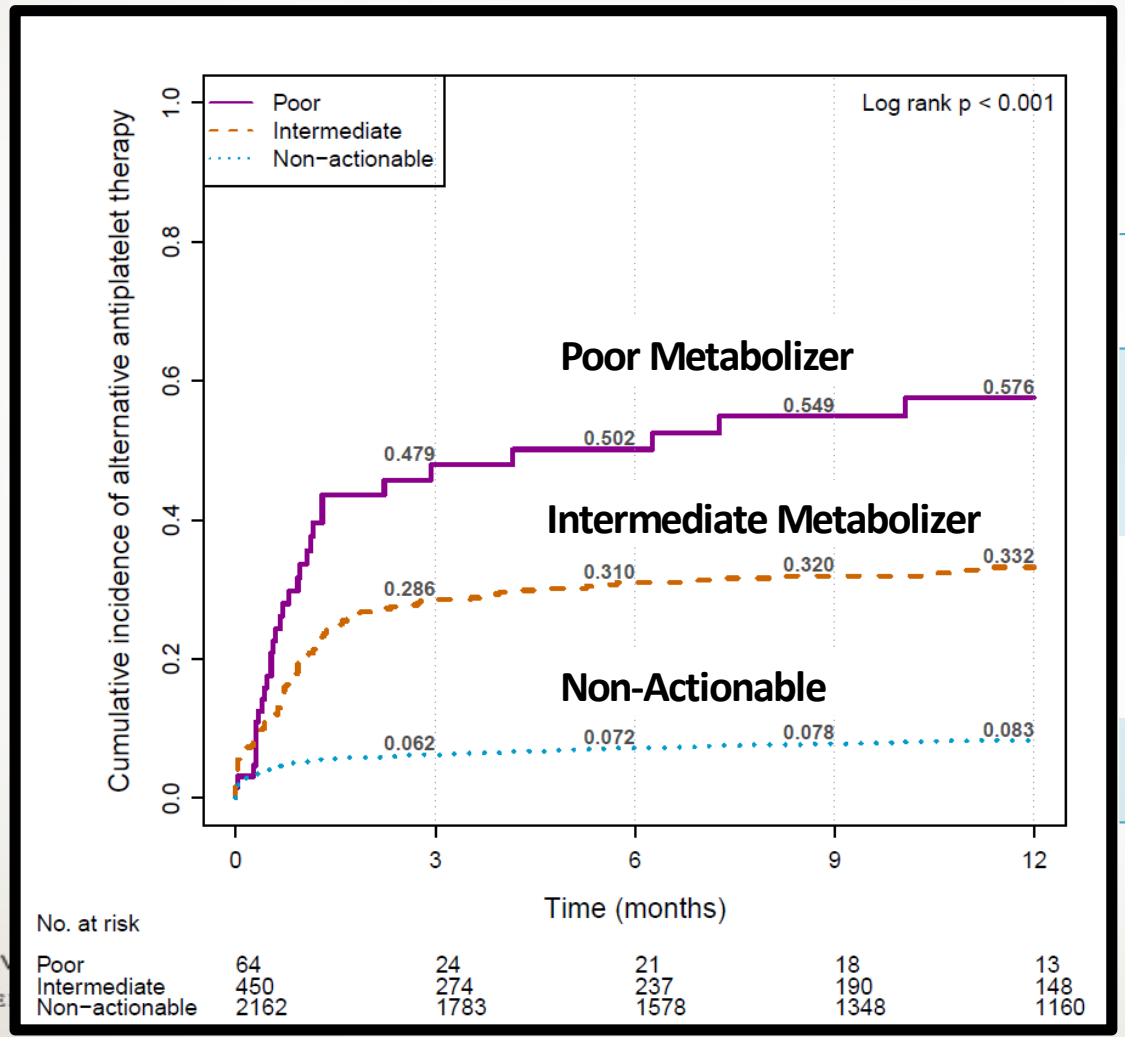
Patient Notification of Drug Sensitivities



Once clinicians get a genotype, do they act on it?



Rate	Adjusted HR
58%	**8.1** (5.4,12.1)
33%	**5.0** (4.0,6.3)
8%	**Ref**

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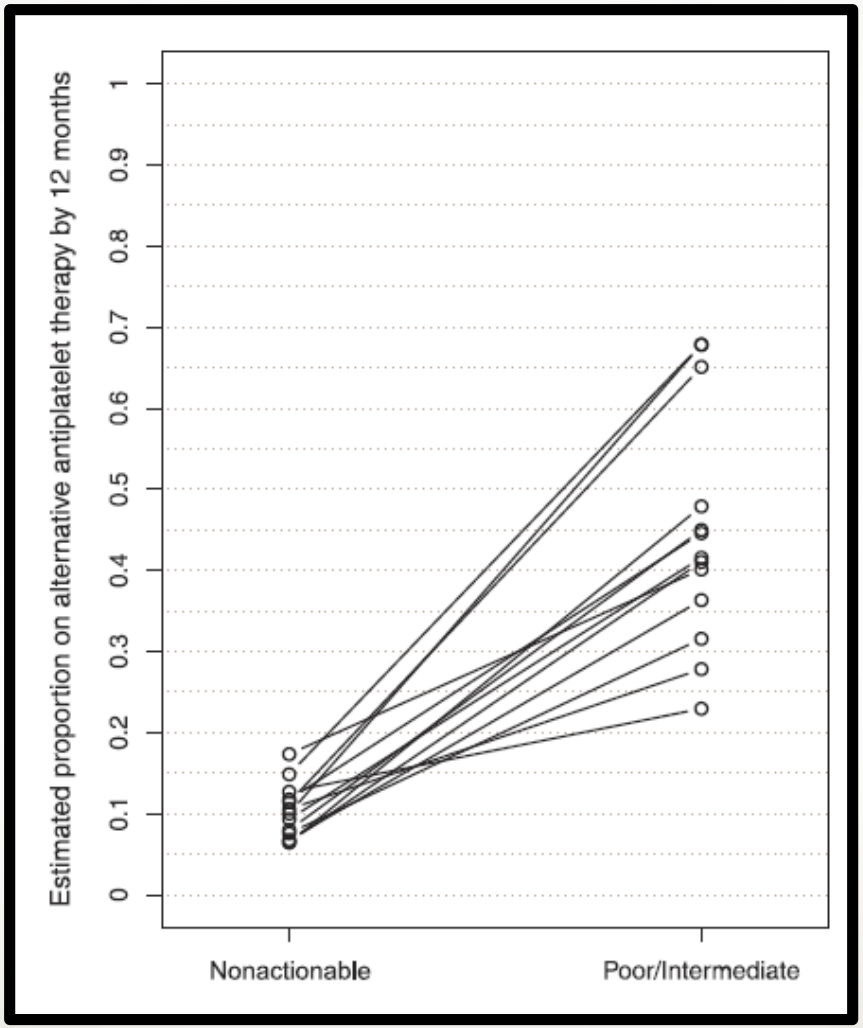
MEDICAL CENTE

Peterson, CPT 2016

One predictor of switching



Cardiologists
with >40 subjects
genotyped

Peterson et al., 2016

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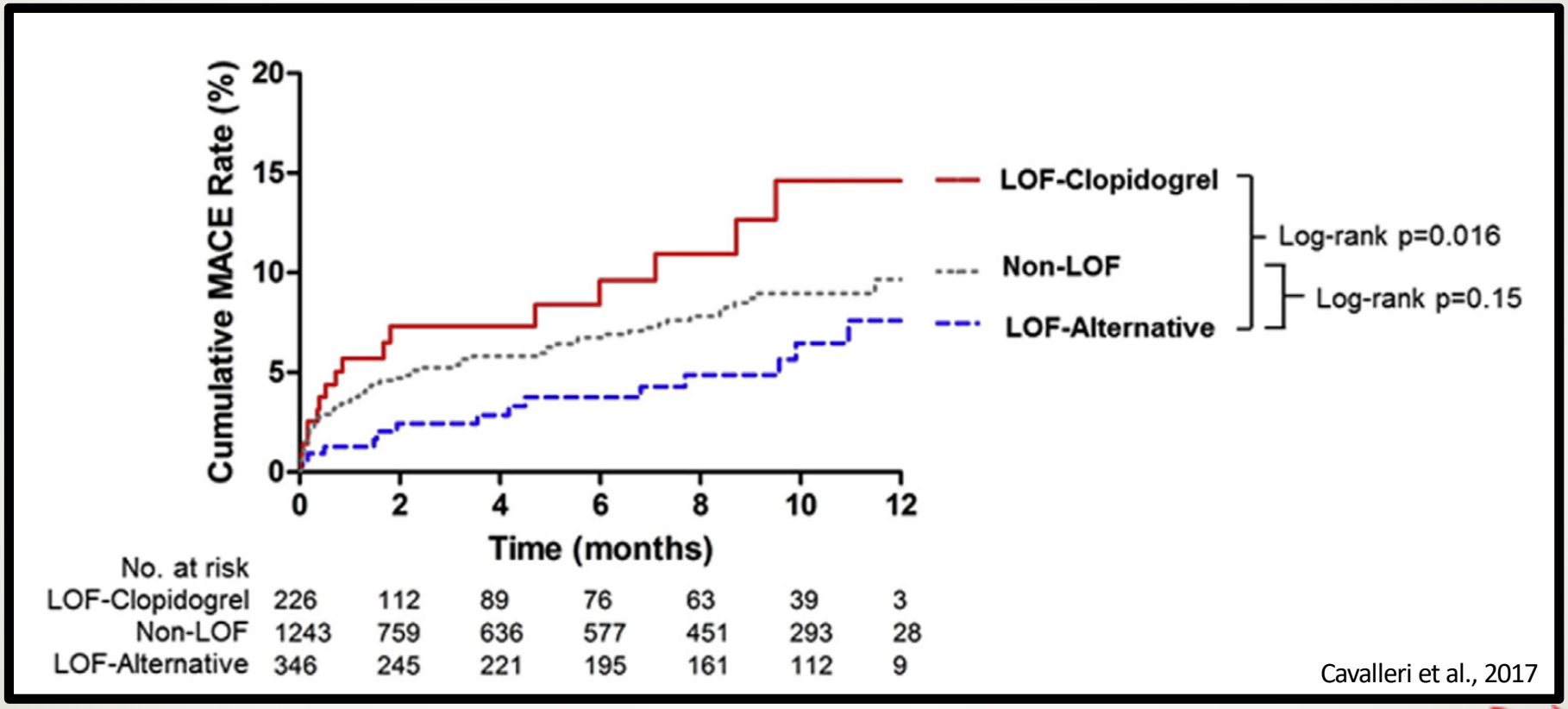
Major adverse cardiovascular events (MACE) by genotype in the IGNITE network



Cavalleri et al., 2017

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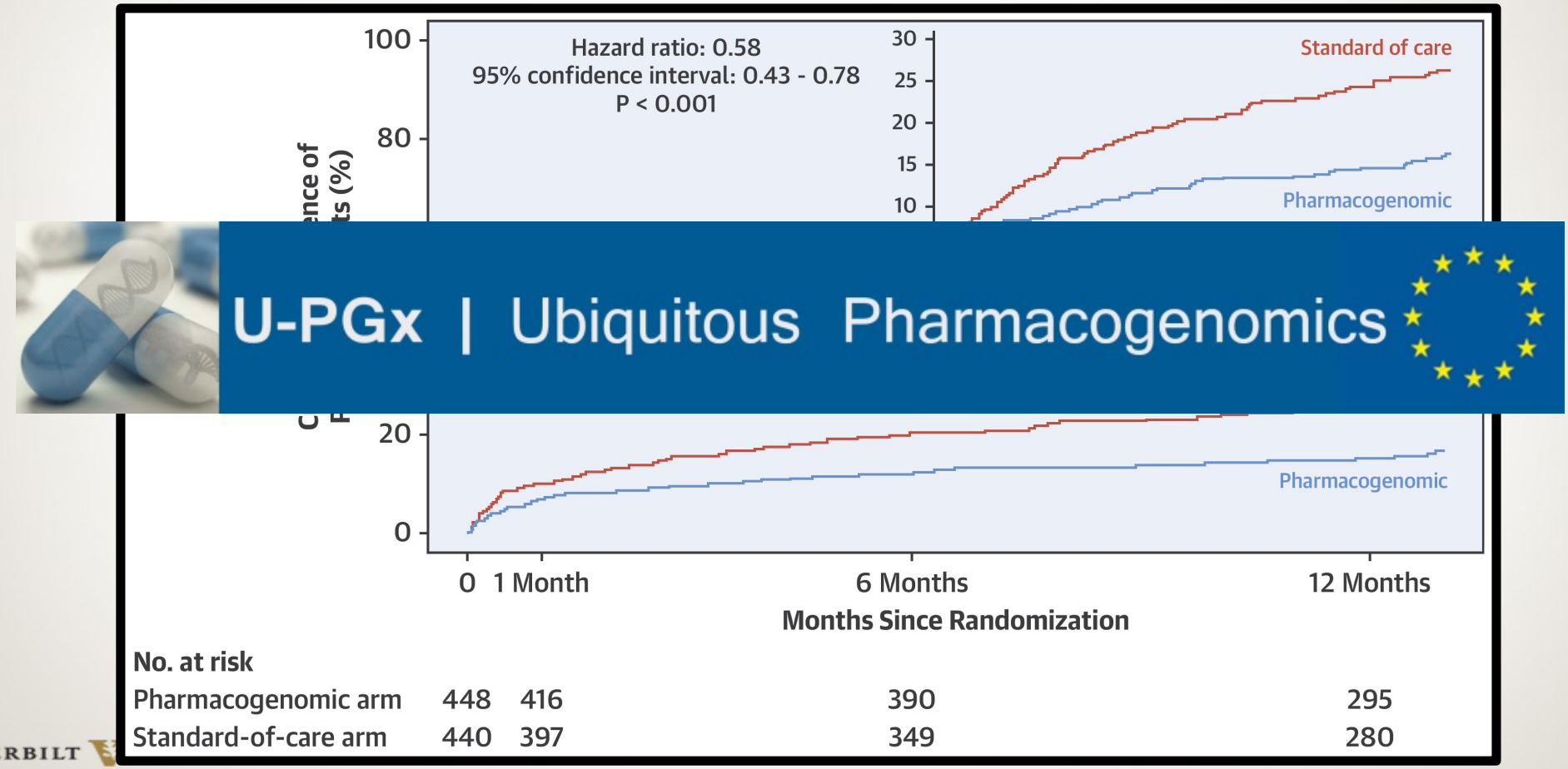
IGNITE Implementing GeNomics In pracTicE

(European) evidence shows PGx improves outcomes

Randomized Controlled Trial of PGx vs. Standard of Care



U-PGx | Ubiquitous Pharmacogenomics

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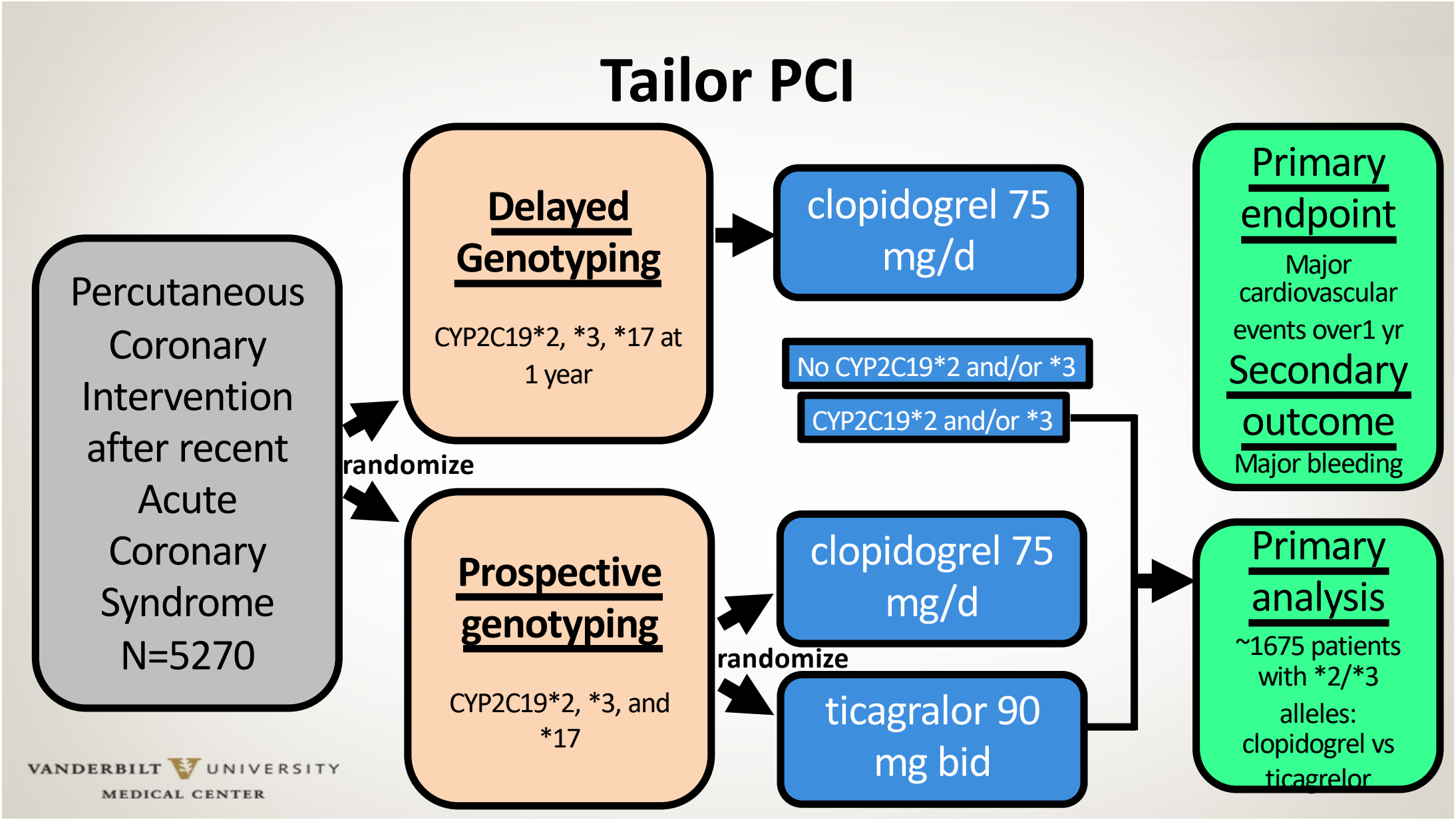
Notarangelo et al. *JACC* 2018


Tailor PCI
Percutaneous Coronary Intervention after recent Acute Coronary Syndrome N=5270
randomize
Delayed Genotyping
CYP2C19*2, *3, *17 at 1 year
clopidogrel 75 mg/d
No CYP2C19*2 and/or *3
CYP2C19*2 and/or *3
Prospective genotyping
CYP2C19*2, *3, and *17
randomize
clopidogrel 75 mg/d
ticagralor 90 mg bid
Primary endpoint
Major cardiovascular events over1 yr
Secondary outcome
Major bleeding
Primary analysis
~1675 patients with *2/*3 alleles: clopidogrel vs ticagrelor
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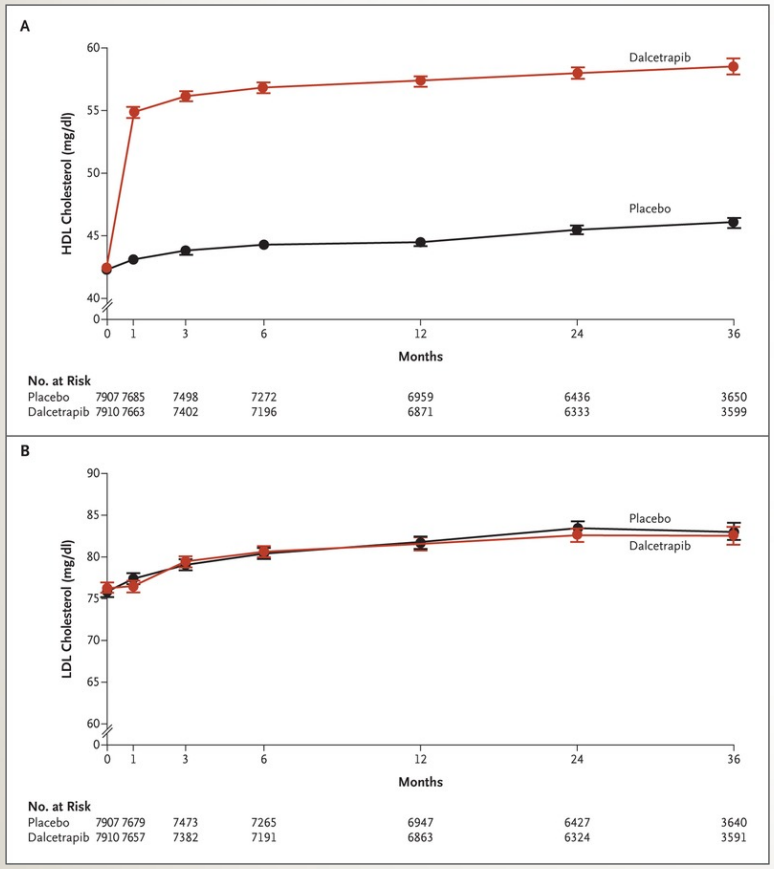
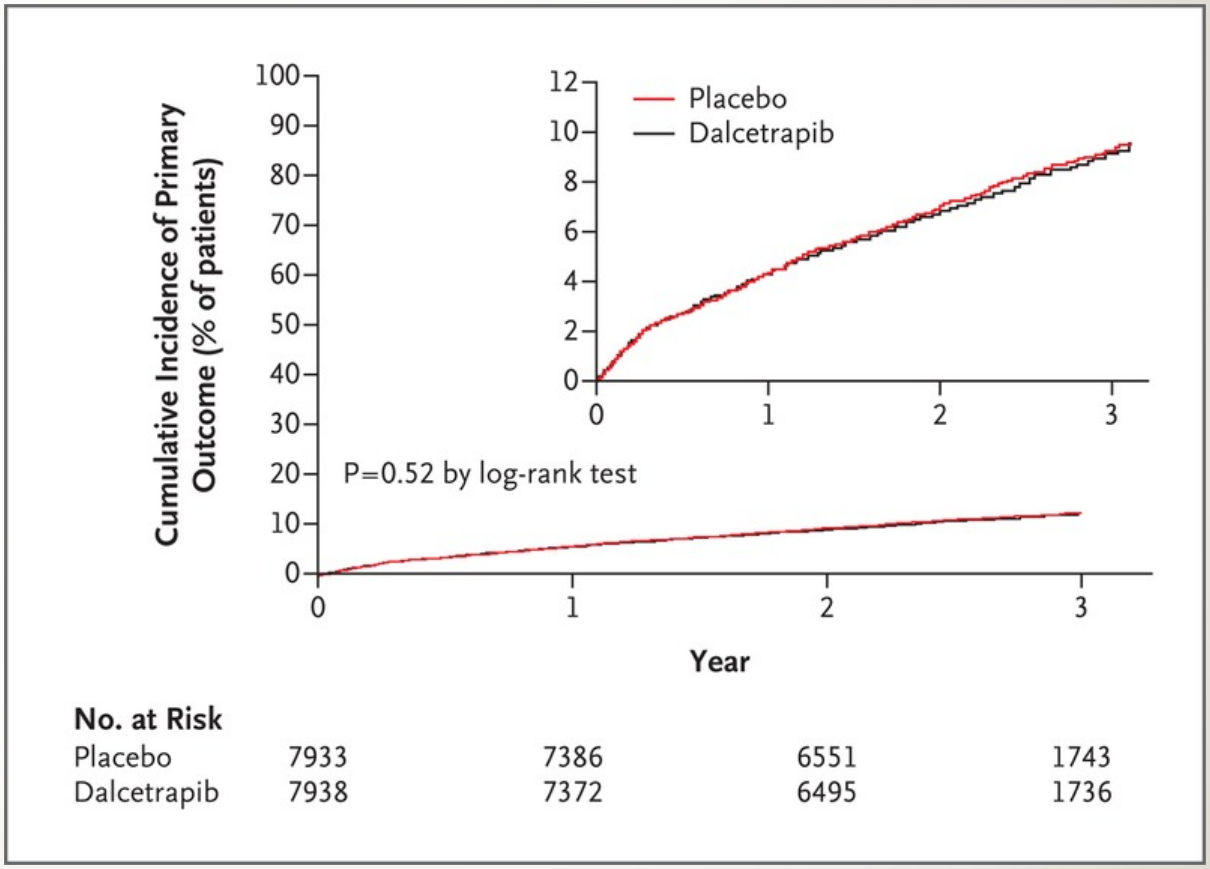
The case of the CETP inhibitor dalcetrapib





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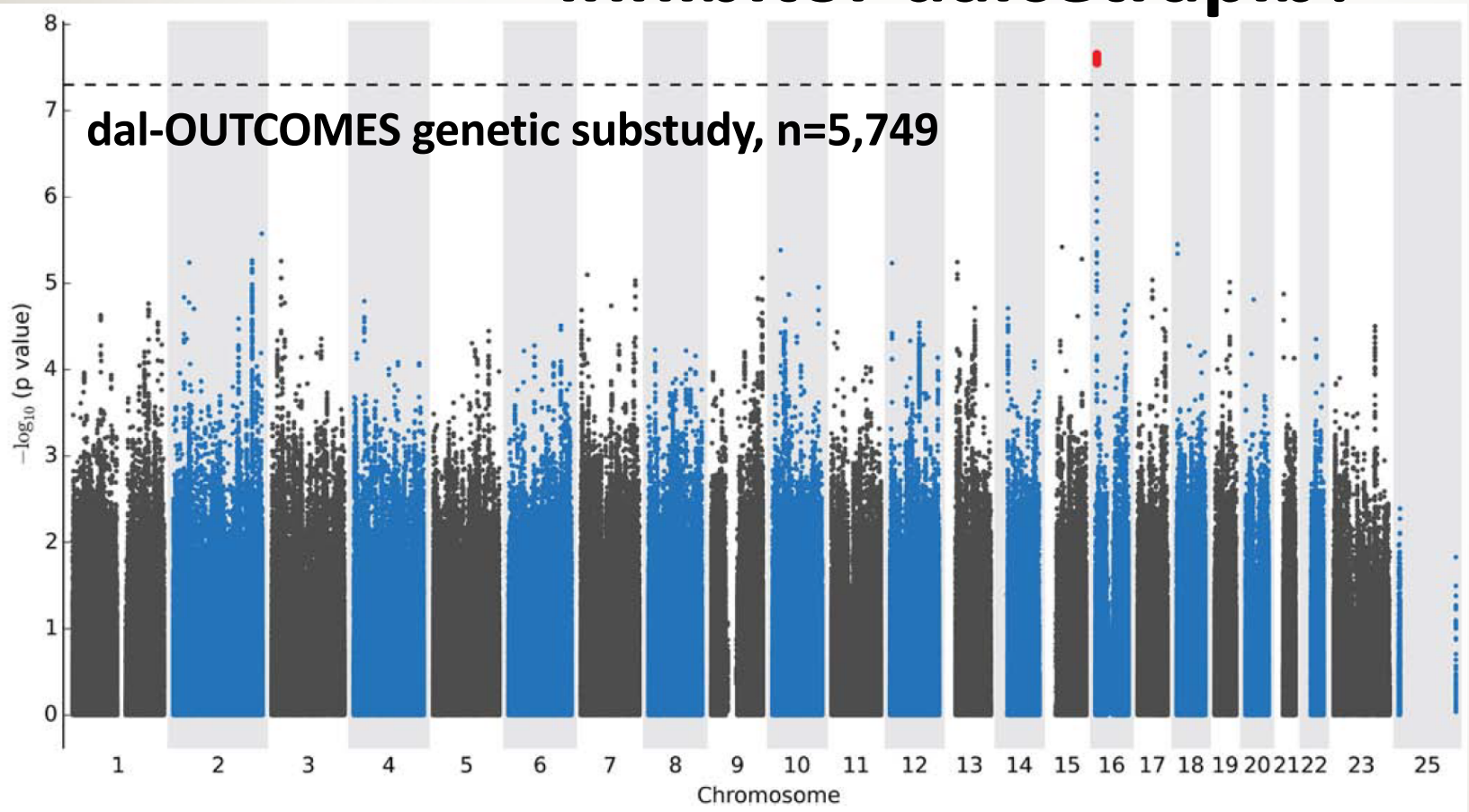
Schwartz et al, dal-OUTCOMES group, NEJM, 2012

A genetic predictor of response to the CETP inhibitor dalcetrapib?



Supporting evidence from

- dal-PLAQUE-2 (n=386)
- changes in CRP and cholesterol efflux studies
- CETP x ACDY9 mice fed atherogenic dets

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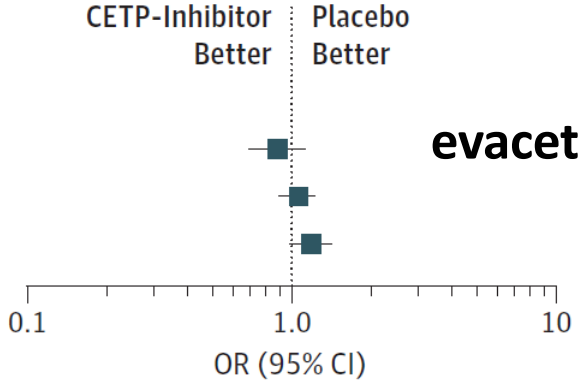
Tardif et al., 2015

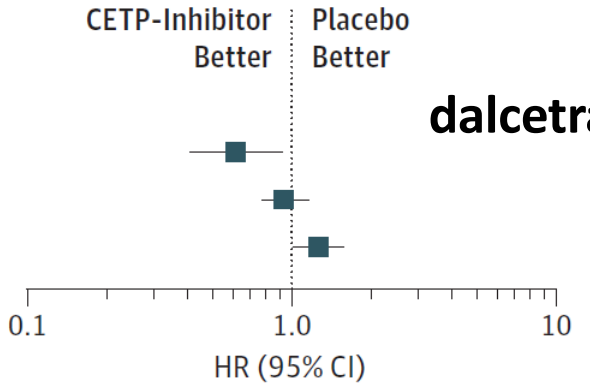
Effect of ADCY9 rs1967309 genotype on Major Adverse Cardiovascular Events during CETP inhibitor therapy

Study and Genotype	OR (95% CI)	Interaction *P* Value[a]	*P* Value For Trend[b]
ACCELERATE		.17	.06
AA	0.88 (0.69-1.12)		
AG	1.04 (0.90-1.21)		
GG	1.18 (0.98-1.41)		



evacetrapib

Study and Genotype	HR Reduction, % (CI)	Interaction *P* Value[a]	*P* Value For Trend[b]
dal-OUTCOMES		NA	.001
AA	0.61 (0.41-0.92)		
AG	0.94 (0.77-1.16)		
GG	1.27 (1.02-1.58)		



dalcetrapib

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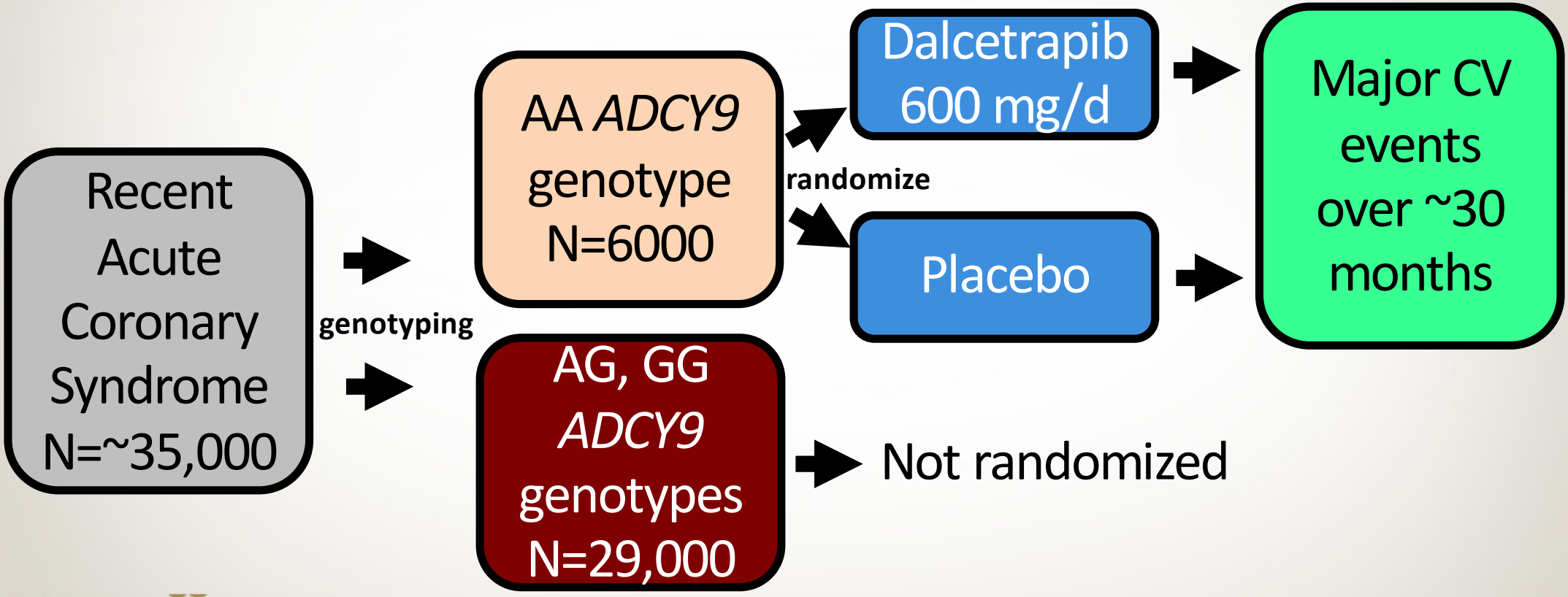
Nissen et al., 2018

The dal-GenE trial



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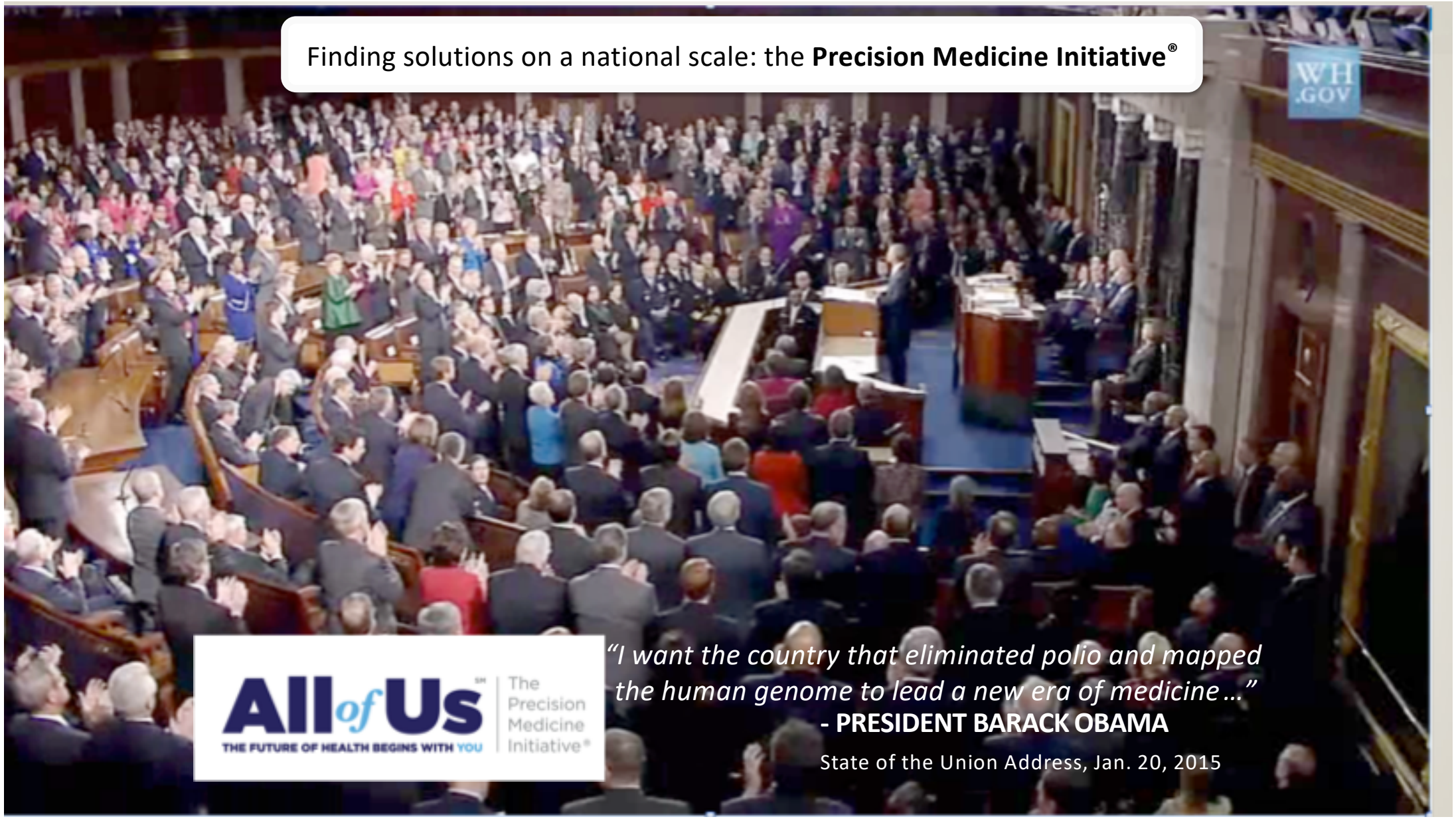
Finding solutions on a national scale: the **Precision Medicine Initiative®**



Major building blocks of the program

DATA AND RESEARCH CENTER (DRC)

Big data capture, cleaning, curation, & sharing in secure environment

Vanderbilt, Verily, Broad Institute

BIOBANK

Repository for processing, storing, & sharing biosamples (35+M vials)

Mayo Clinic

PARTICIPANT CENTER

Direct volunteer participant enrollment, digital engagement innovation, & consumer health technologies

Scripps Research Institute (with multiple partners)

PARTICIPANT TECHNOLOGY SYSTEMS CENTER

Web & phone-based platforms for participants

Vibrent Health

HEALTH CARE PROVIDER ORGS (HPOs)

Clinical & scientific expertise network, enrollment & retention of participants

30+ regional med centers, FQHCs, VA, future awards to grow network

COMMUNICATIONS & ENGAGEMENT

Comms, marketing, & design expertise; Engagement coordination & community partners network

Wondros, HCM, 4 community partner orgs, future awards to grow network

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NIH All of Us Program Awards $28.6M to Three Genome Centers Led by Baylor, Broad, UW

Sep 25, 2018 | staff reporter

Save for later

NEW YORK (GenomeWeb) – The National Institutes of Health's All of Us Research Program today awarded $28.6 million to establish three genome centers led by Baylor College of Medicine, the Broad Institute, and the University of Washington, which will generate and analyze genomic data from biosamples contributed by participants in the program.

The NIH said in a statement that the genome centers were selected "based on their proven track record at generating genomic data at scale, providing clinical validation services to verify medically-relevant variants, and participating in large-scale research collaborations." The awards may last up to five years, pending progress and the availability of funds.

The three genome centers, which will ramp up operations over the next few months, will produce genomic data for the research effort and will analyze data that will be returned to participants. All of Us participants interested in receiving results will initially obtain information from a list of 59 actionable disease risk genes, as defined by the American College of Medical Genetics and Genomics, as well as pharmacogenomic results. In the future, they will also obtain information about their ancestry and traits.

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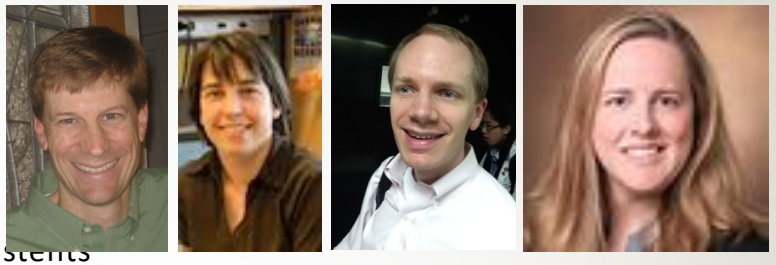
- Enrollment began May 7, 2018
- 114,305 consented
- 61,650 fully enrolled

One view of truly personalizing medicine



57yo with DM2, FHx heart disease, ↑chol admitted for chest pain, receives stent

In-stent thrombosis, restent

Recath, stent
"Plavix x 1 year minimum. ASA life long."

In-stent thrombosis, restent

Cath, more stents

9th admission, 5th intervention, 9th stent
CYP2C19*2/*2
clopidogrel poor metabolizer

January

clopidogrel started

April

December

Switched to **prasugrel**

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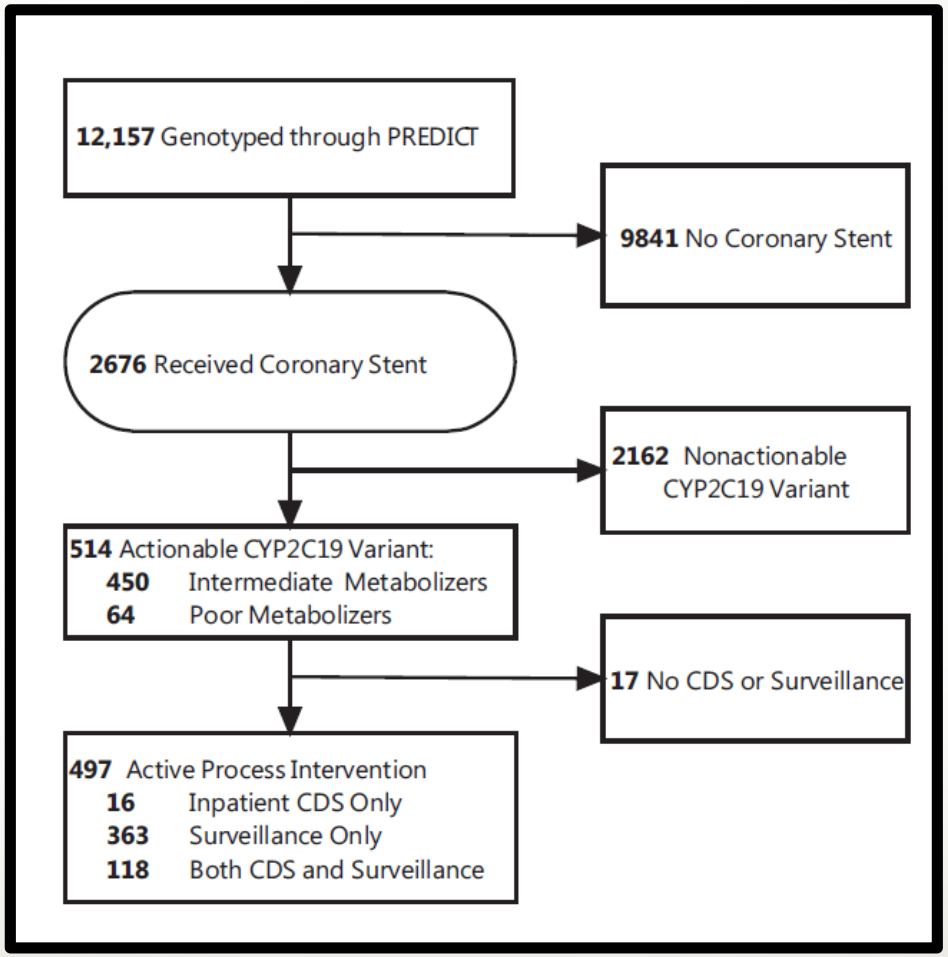
What happens when we implement? Process outcomes



Peterson et al., 2016