



VANDERBILT UNIVERSITY
MEDICAL CENTER

Implementation of Pharmacogenomics in Clinical Medicine in the USA

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Vanderbilt University Medical Center, Nashville, TN

The vision



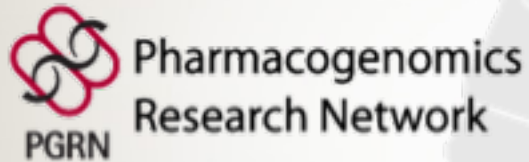
"Here's my sequence..."



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

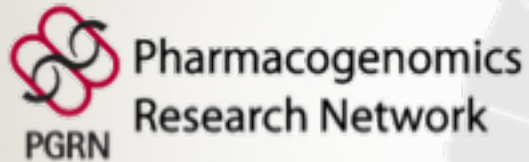
US pharmacogenomic implementation sites





-  Pre-emptive
-  Point of care



US pharmacogenomic implementation sites



-  Pre-emptive
-  Reactive



The vision



"Here's my sequence..."

New Yorker, 2000

PREDICT

Pharmacogenomic Resource for Enhanced
Decisions In Care and Treatment



The vision



"Here's my sequence..."

New Yorker, 2000

PREDICT

Pharmacogenomic Resource for Enhanced
Decisions In Care and Treatment

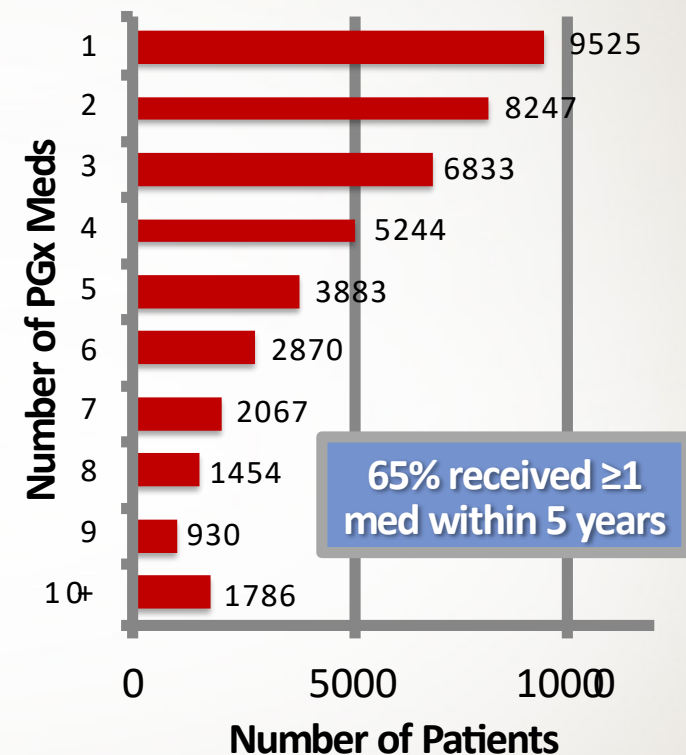
1. Select populations of patients who are “at high risk” for receiving a drug with a pharmacogenetic “story”.
2. Genotype them preemptively on a platform that assays many pharmacogenetic variants.
3. Store the genotypes, develop the informatics tools to provide point-of-care advice. Track outcomes.

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

Selection of PREDICT Drug-Gene Interactions



Selection of PREDICT Drug-Gene Interactions



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

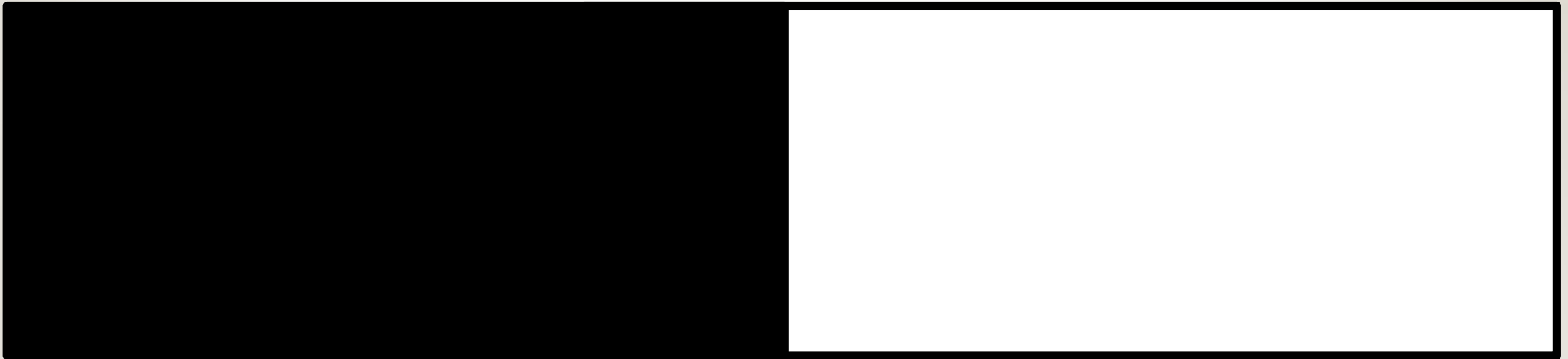
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

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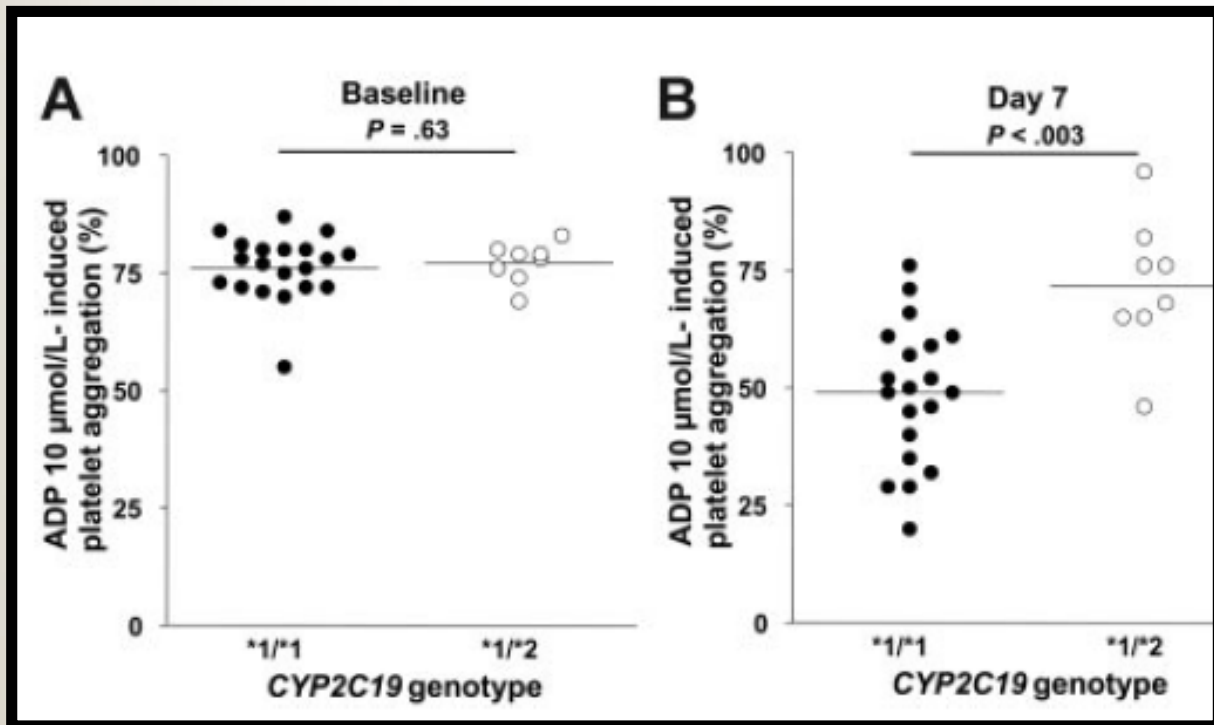
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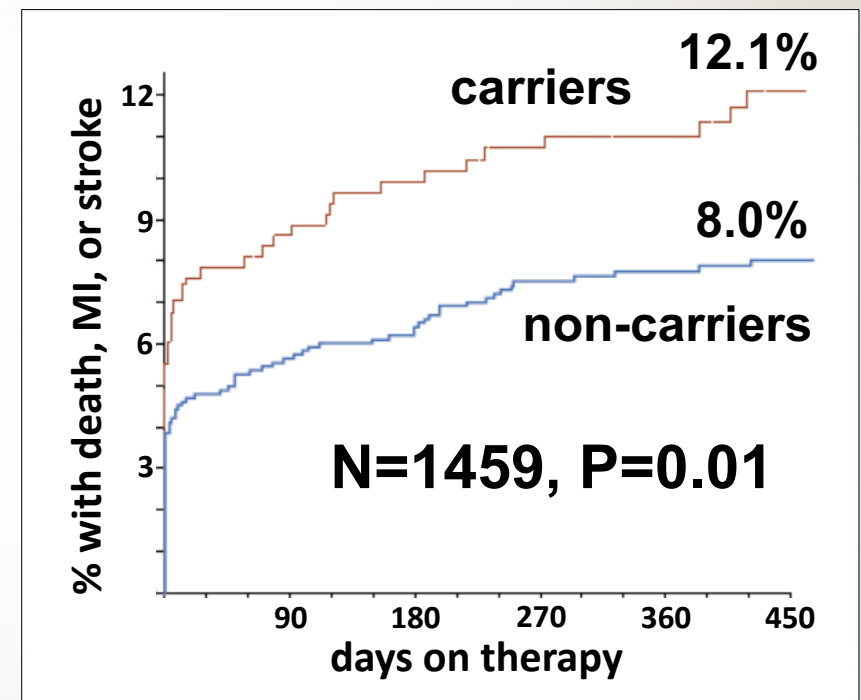
Genetic data, prediction, and “actionability”



CYP2C19 loss of function variants → decreased anti-platelet effect

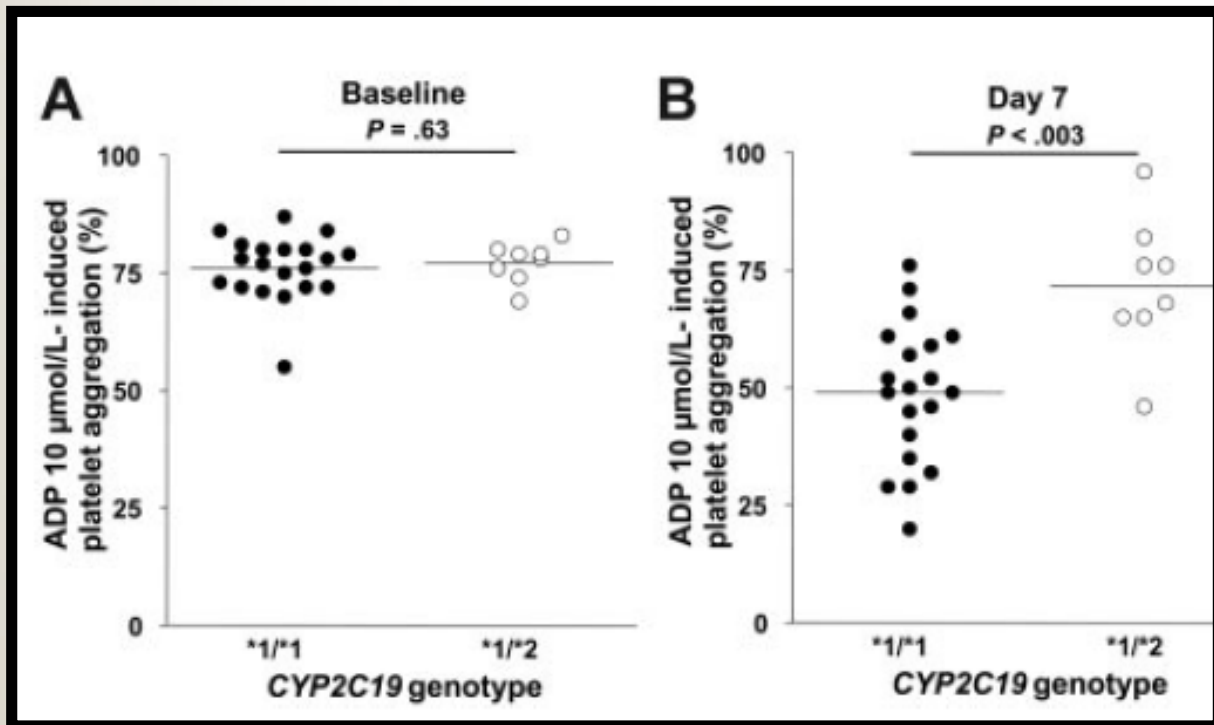


Hulot et al., 2006



Mega et al., 2009

CYP2C19 loss of function variants → decreased anti-platelet effect



Hulot et al., 2006

Number needed to genotype to potentially avert one adverse cardiac outcome: **25**

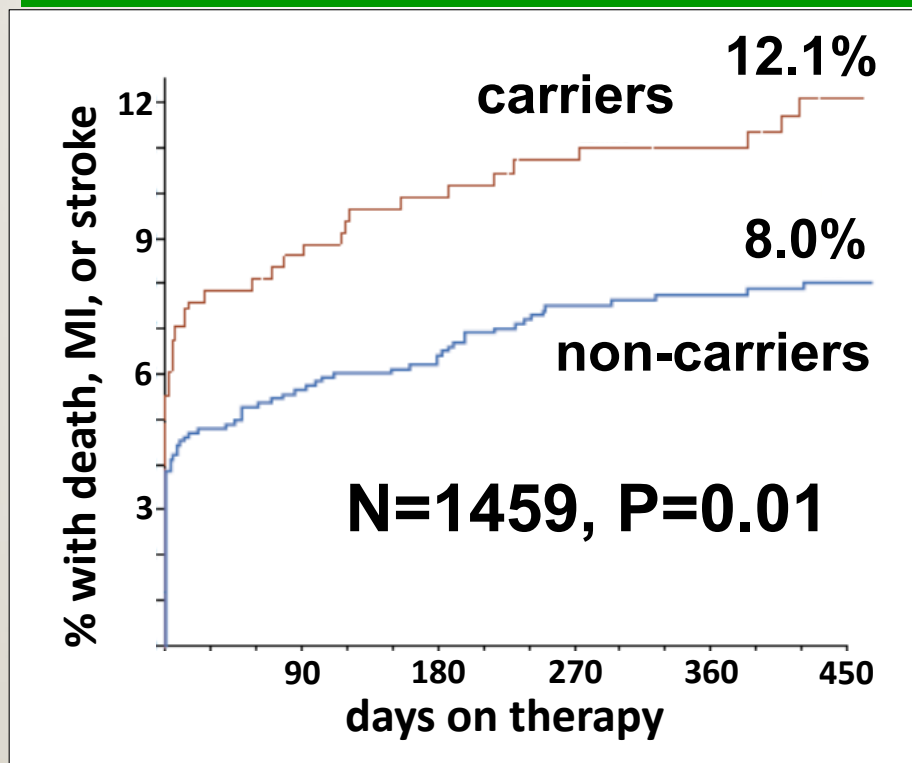
carriers 12.1%

days on therapy

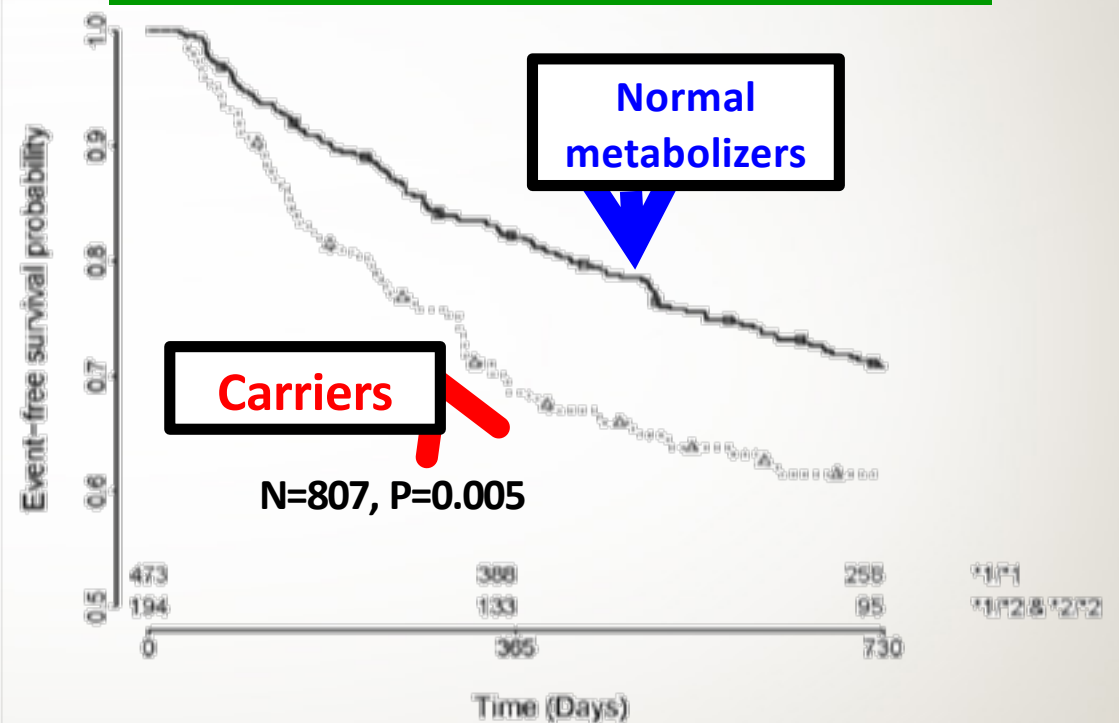
Mega et al., 2009

Clopidogrel adverse events associated with *CYP2C19* status in BioVU

From clinical trials



From the EHR



The future is here

The screenshot displays the Epic Hyperspace interface for a patient's report. The top navigation bar includes 'Patient Calls' and 'Cosign Orders'. The main window is titled 'Report Viewer' and shows a 'Pharmacogenetics PNL (Predict) Report' for a patient. The report includes the following data:

Gene/Enzyme	Metabolism/Status
CYP2C19-Clopidogrel-interpretation	4yr ago ultra rapid metabolizer
CYP2C19-Clopidogrel-result	*17 HET
SLCO1B1-Simvastatin-interpretation	intermediate risk
SLCO1B1-Simvastatin-result	*1B HET;*5 HET
TPMT-Thiopurines-interpretation	normal metabolizer
TPMT-Thiopurines-result	*1A/*1A
CYP3A5-Tacrolimus-interpretation	standard responder
CYP3A5-Tacrolimus-result	*3 VAR
VKORC1/CYP2C9-Warfarin-interpretation	vkorc1 a/g; cyp2c9 *1/*1
VKORC1-result	VKORC1 c.-1639 HET, CYP2C9 *9 No Call
SLCO1B1-Simvastatin-	intermediate risk

Drug-Gene Interaction

Clopidogrel Poor Metabolizer Rules

Genetic testing has been performed and indicates this patient may be AT RISK for inadequate anti-platelet response to clopidogrel (Plavix) therapy

This patient has been tested for CYP2C19 variants, which has identified the presence of two copies of a risk allele which is associated with reduced metabolism of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

Treatment modification is recommended if not otherwise contraindicated:

- Prescribe prasugrel (EFFIENT) 10 mg daily
- or
- Prescribe ticagrelor (BRILINTA) 90 mg twice daily

WARNING: Prasugrel should only be prescribed to patients weighing more than 60kg. This patient does not have a weight entered in the system - please ensure the patient meets the weight criteria before prescribing prasugrel.

Prasugrel should **not** be given to patients who:

- have a history of stroke or transient ischemic attack


Ticagrelor should **not** be given to patients who:

- have a history of severe hepatic impairment or intracranial blood


[Evidence Link](#)


The Vanderbilt P&T Committee has approved this recommendation based on the detailed review of the literature and consensus guidelines.

Remove the following orders?

 clopidogrel (PLAVIX) 75 mg tablet
Take 1 tablet (75 mg total) by mouth daily. Normal, Disp-30 tablet, R 6

Apply the following?

 prasugrel (EFFIENT) tablet 10 mg

 ticagrelor (BRILINTA) tablet 90 mg

Acknowledge Reason

Hyperspace - CARDIOLOGY EP MCE 5 -

Epic Patient Lookup

Report Viewer

Report History

History

07/17/2013 00:00
Show images for

05/12/2011 00:00
Show images for

06/26/2017 06:00

More

Order: 51716630

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



CDS KnowledgeBase is the engine that drives precision medicine.



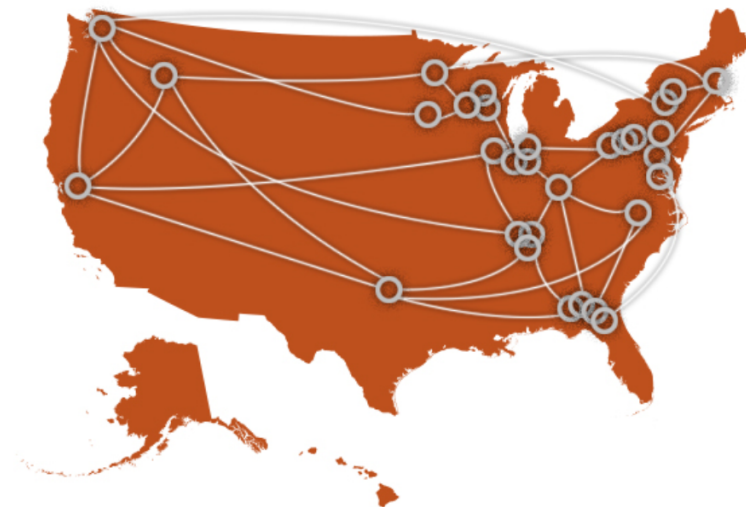
who are we?

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

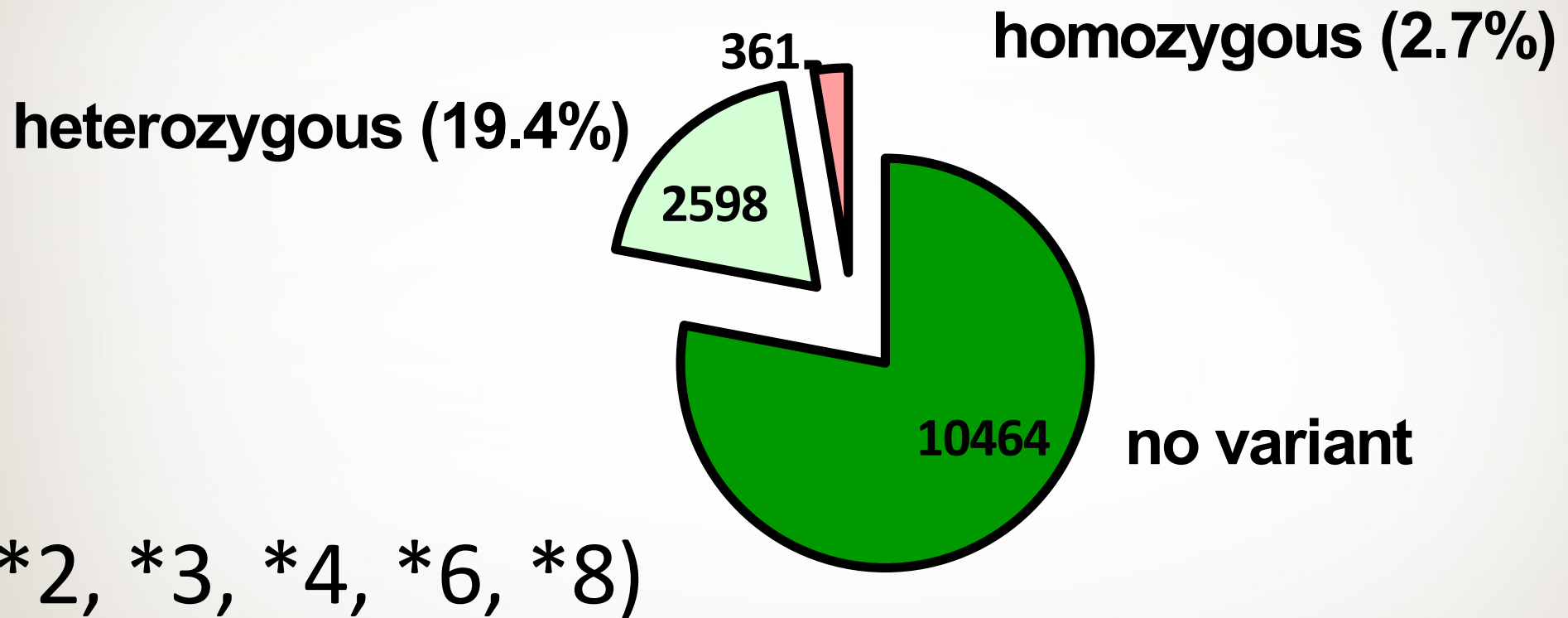


THE COMMUNITY: IDEAS FROM ONE OF MANY



○ CONNECTIONS, RESOURCES,
AND PEER REVIEWS

CYP2C19 genotypes in 13,423 patients at Vanderbilt University Hospital



CYP2C19 genotypes in 13,423 patients at Vanderbilt University Hospital

361 homozygous (2.7%)

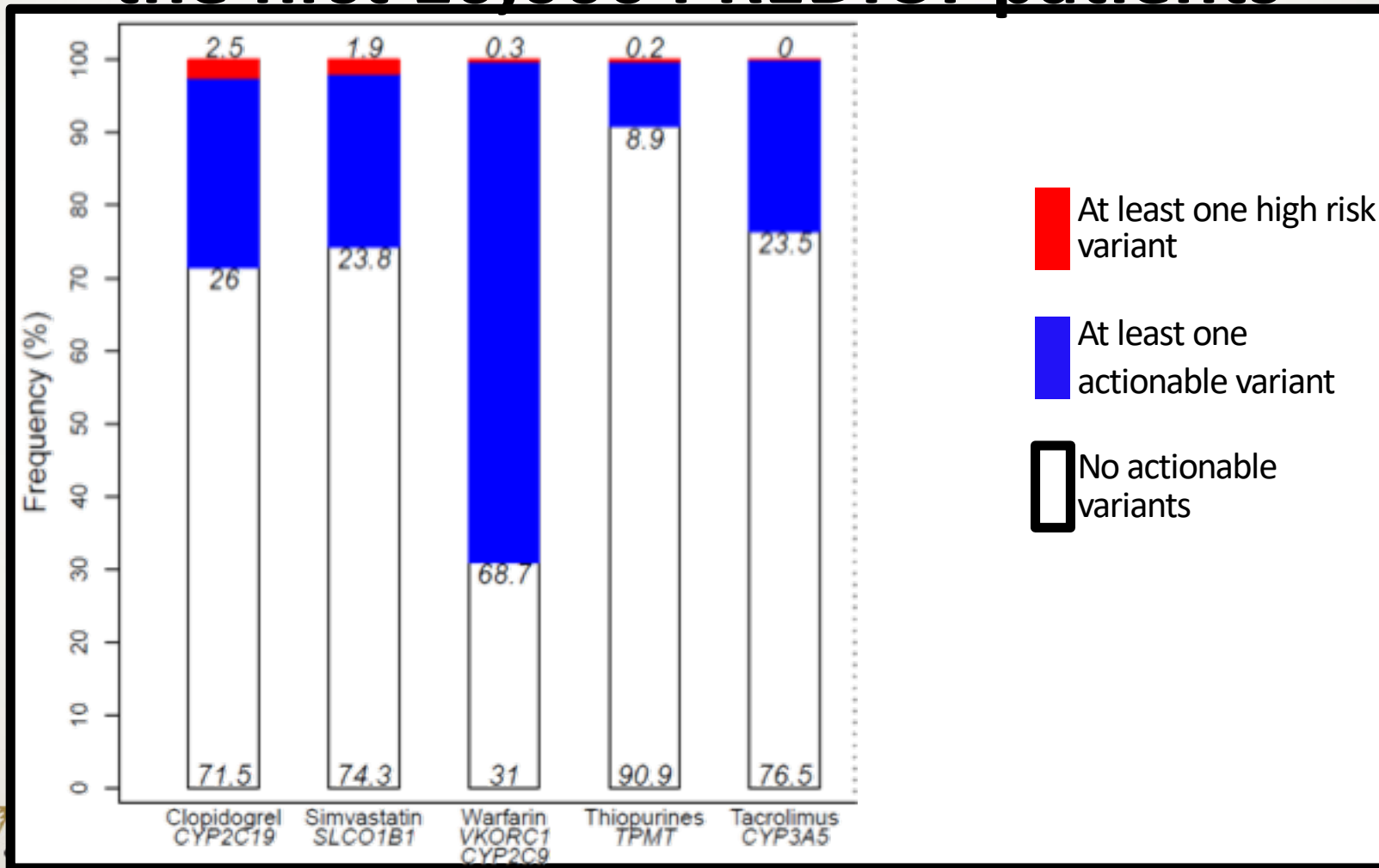
heterozygous (10.4%)

gnomAD

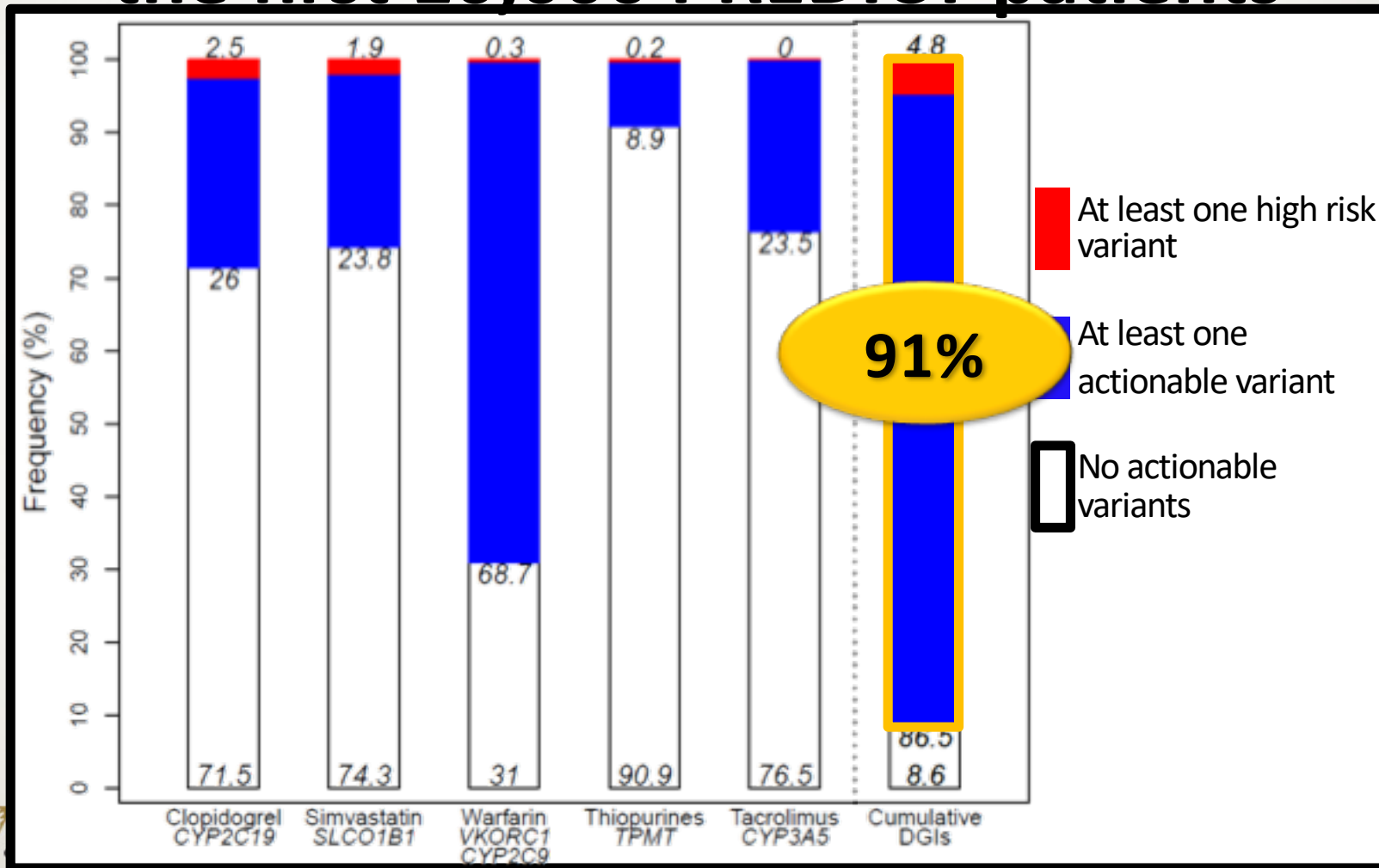
- 442 non-synonymous variants
- 9 with MAF>1% in at least one population
- splice variants (e.g. *2) clinically important

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

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









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



Patient Notification of Drug Sensitivities

VANDERBILT UNIVERSITY MEDICAL CENTER ▼ Pay HOLIDAY VOID#ZTESTSYC's Bill Hi, HOLIDAY VOID#ZTESTSYC ▼

 Appointments  Messages  My Record  My Forms  Health Management  My Accounts

Go to: ▼

Personalized Medicine

Each person responds differently to medicines. Your genes play a role in how you respond to medicines. Based on your history, your provider has ordered a test to learn more about which drugs are right for you. Having this information can help predict and prevent bad drug side effects.

Medication	Does your genetic test result affect your response to medicines?
Clopidogrel/Plavix®	Yes
Simvastatin/Zocor®	Yes
Tacrolimus®	Yes
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.

The results of your test show that you have two versions of the gene that may put you at increased risk for this negative outcome.

More About Clopidogrel

[Show more >](#)

More About Your Risk

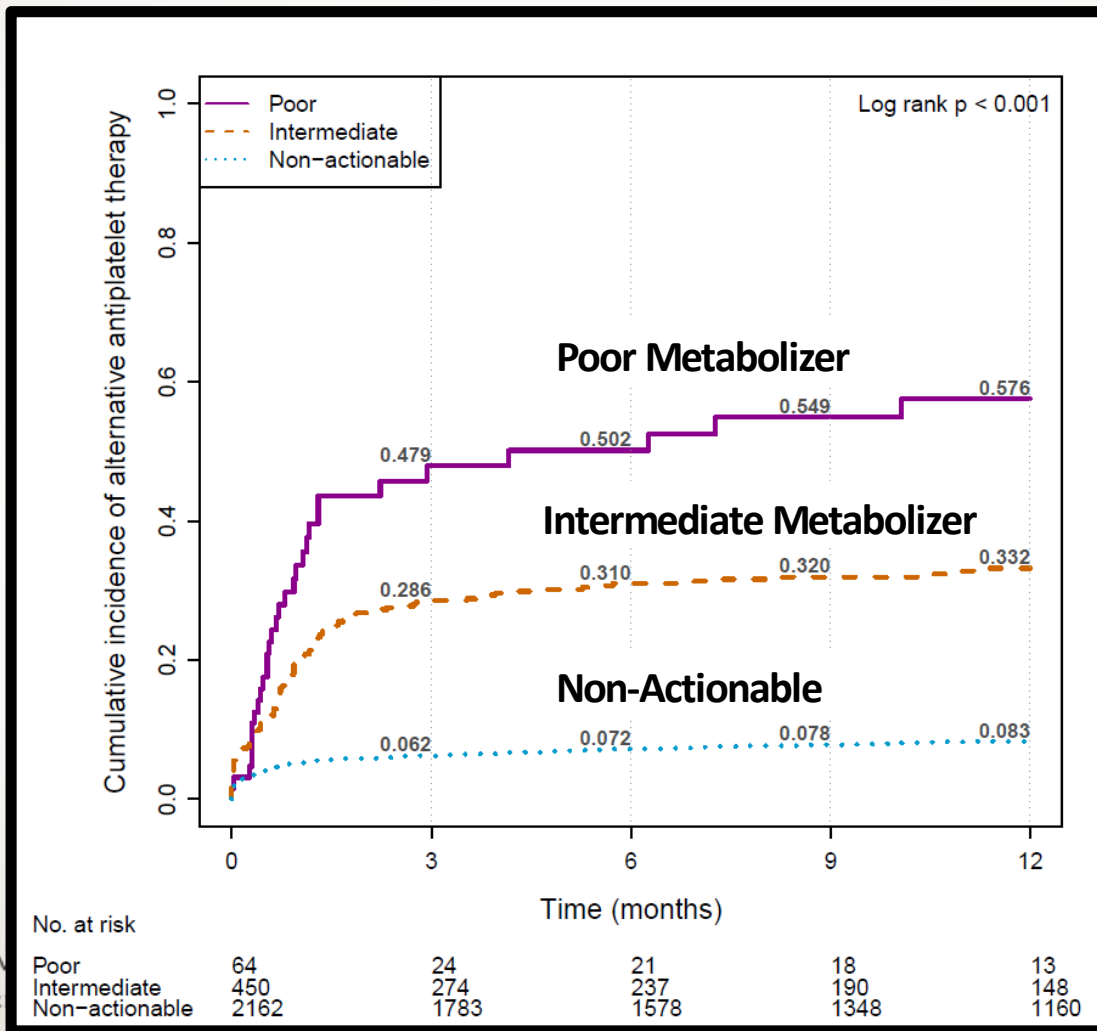
[Show more >](#)

MY HEALTH HOME
HELP

GUIDE
For Patients and Visitors

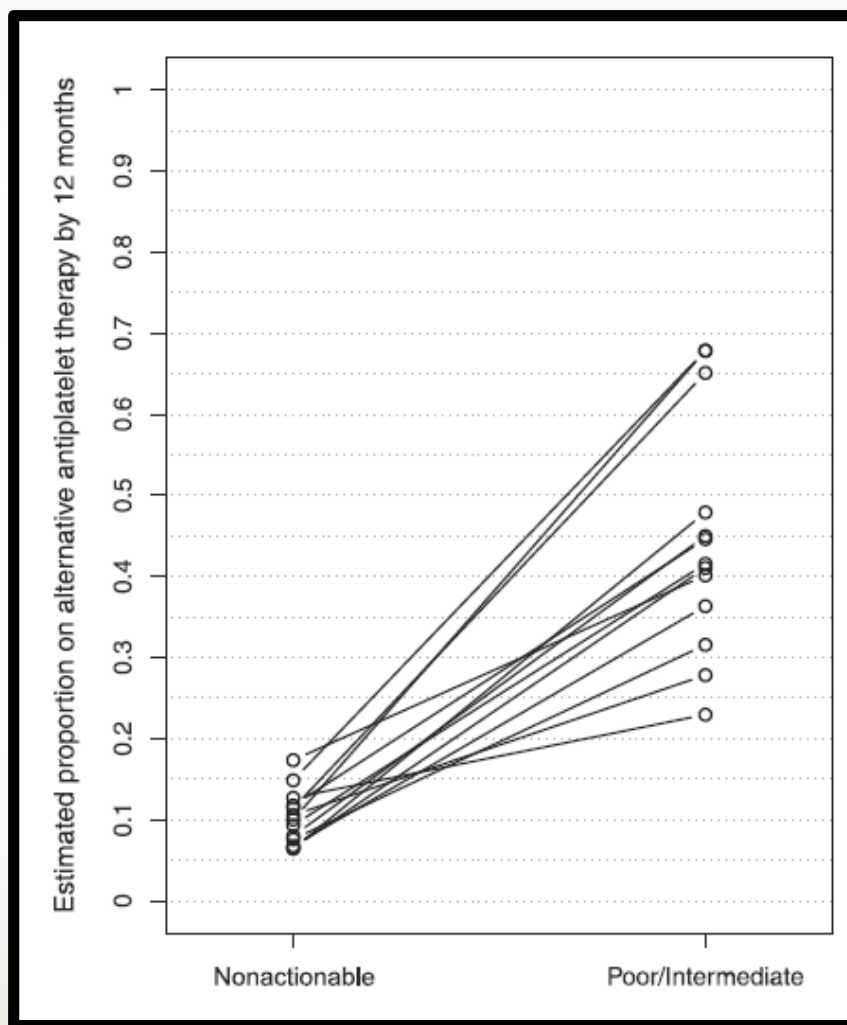
VANDERBILT
MEDICAL

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



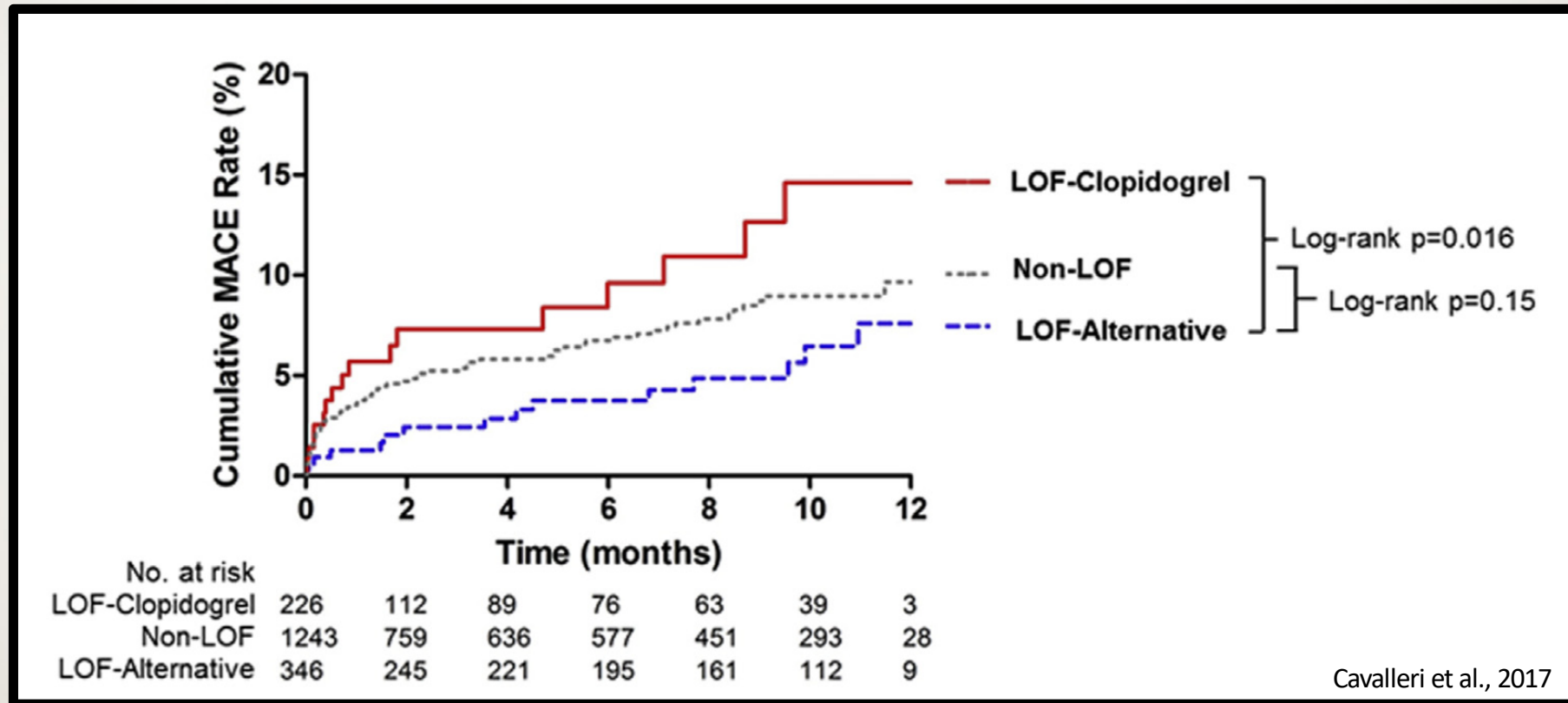
Rate	Adjusted HR
58%	8.1 (5.4,12.1)
33%	5.0 (4.0,6.3)
8%	Ref

One predictor of switching



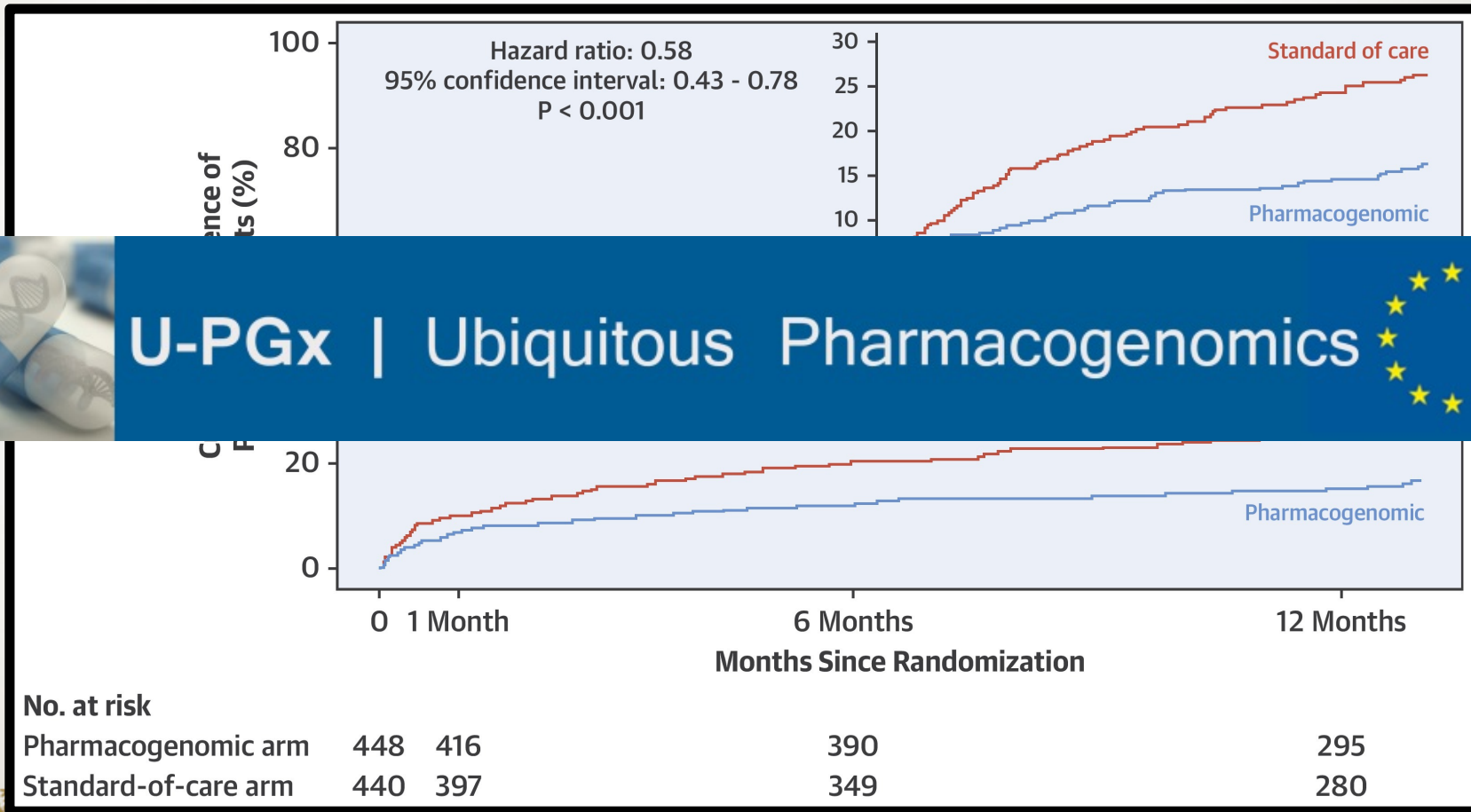
Cardiologists
with >40 subjects
genotyped

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



(European) evidence shows PGx improves outcomes

Randomized Controlled Trial of PGx vs. Standard of Care



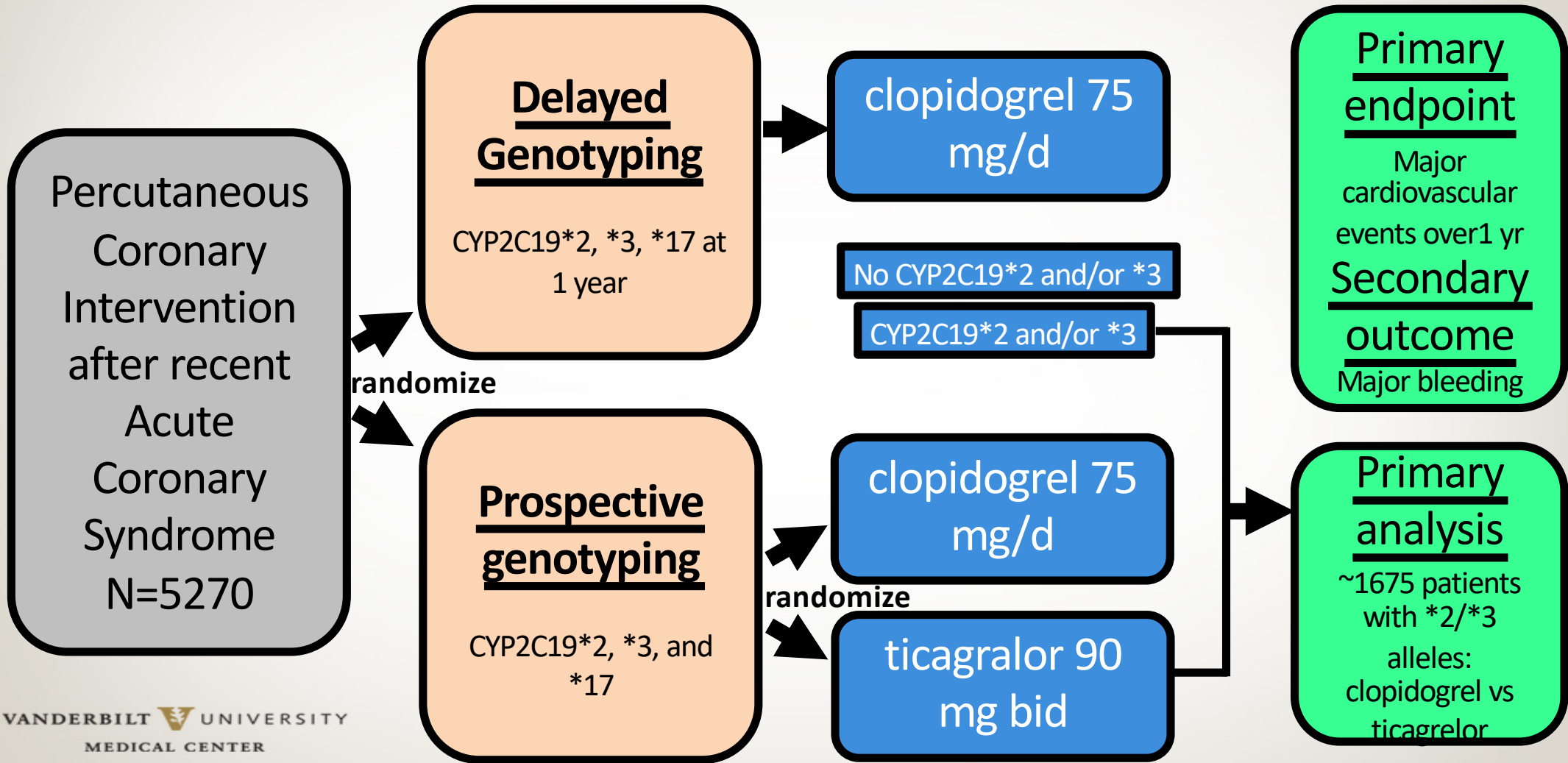
U-PGx | Ubiquitous Pharmacogenomics



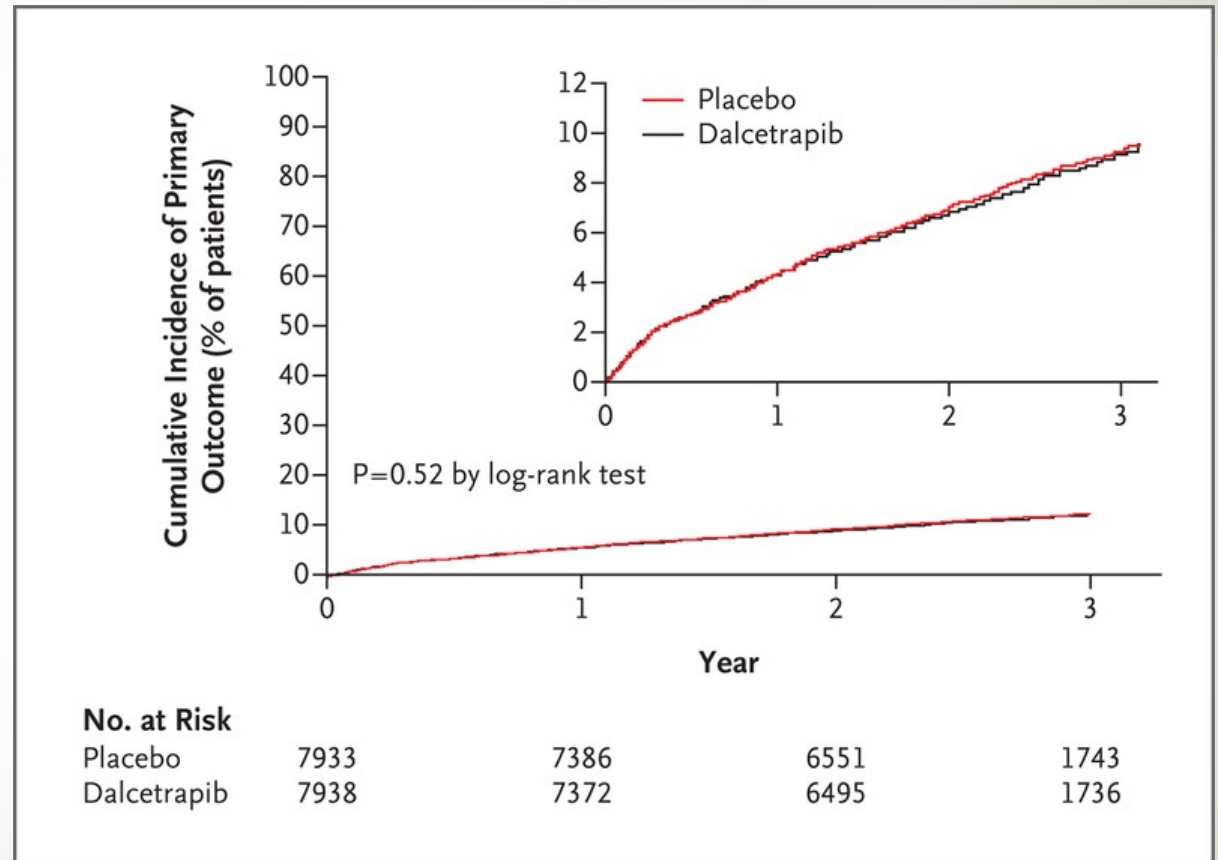
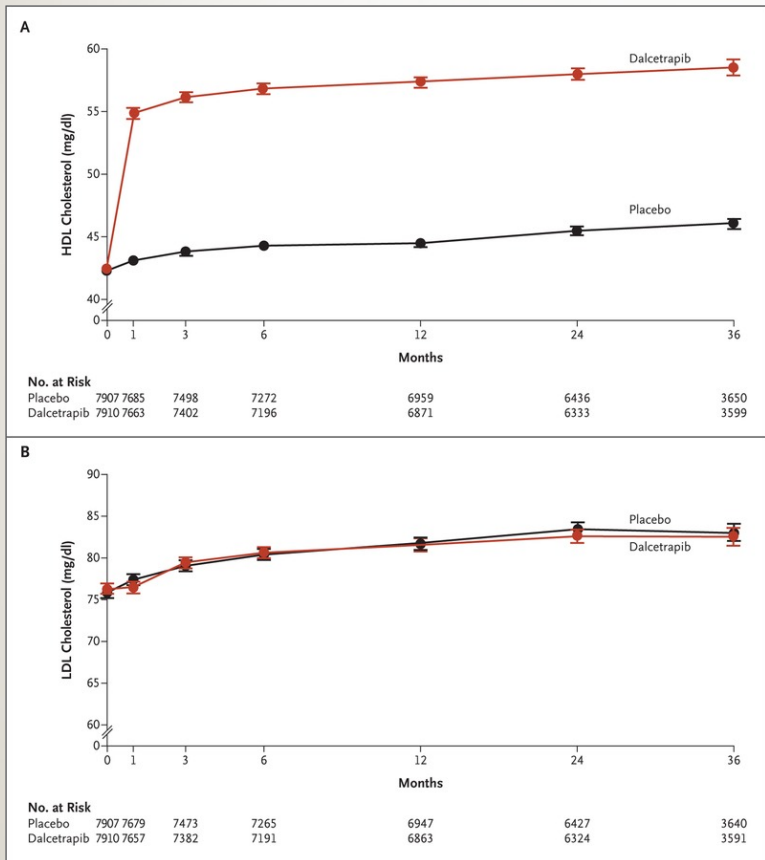
No. at risk

Pharmacogenomic arm	448	416	390	295
Standard-of-care arm	440	397	349	280

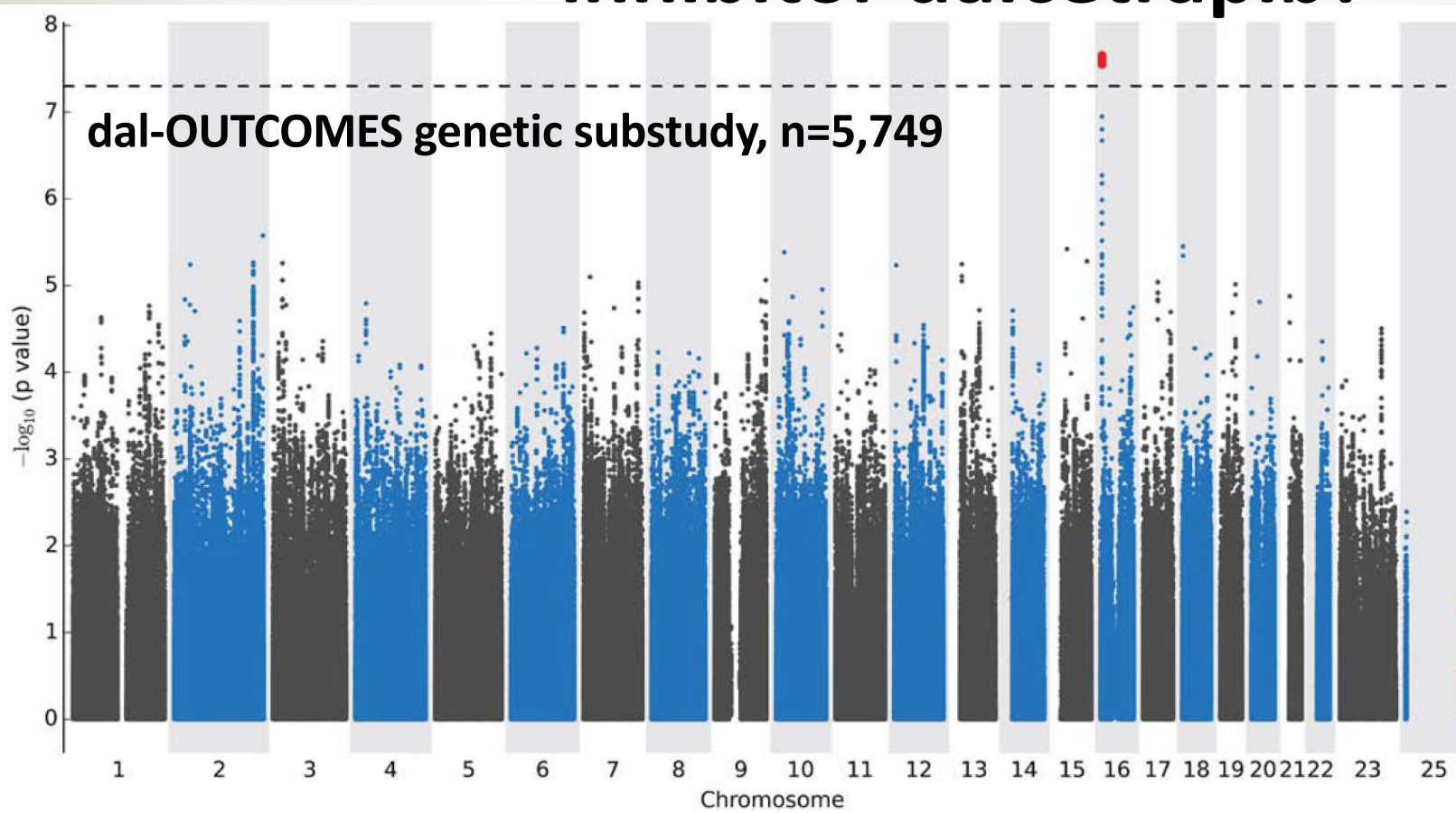
Tailor PCI



The case of the CETP inhibitor dalcetrapib

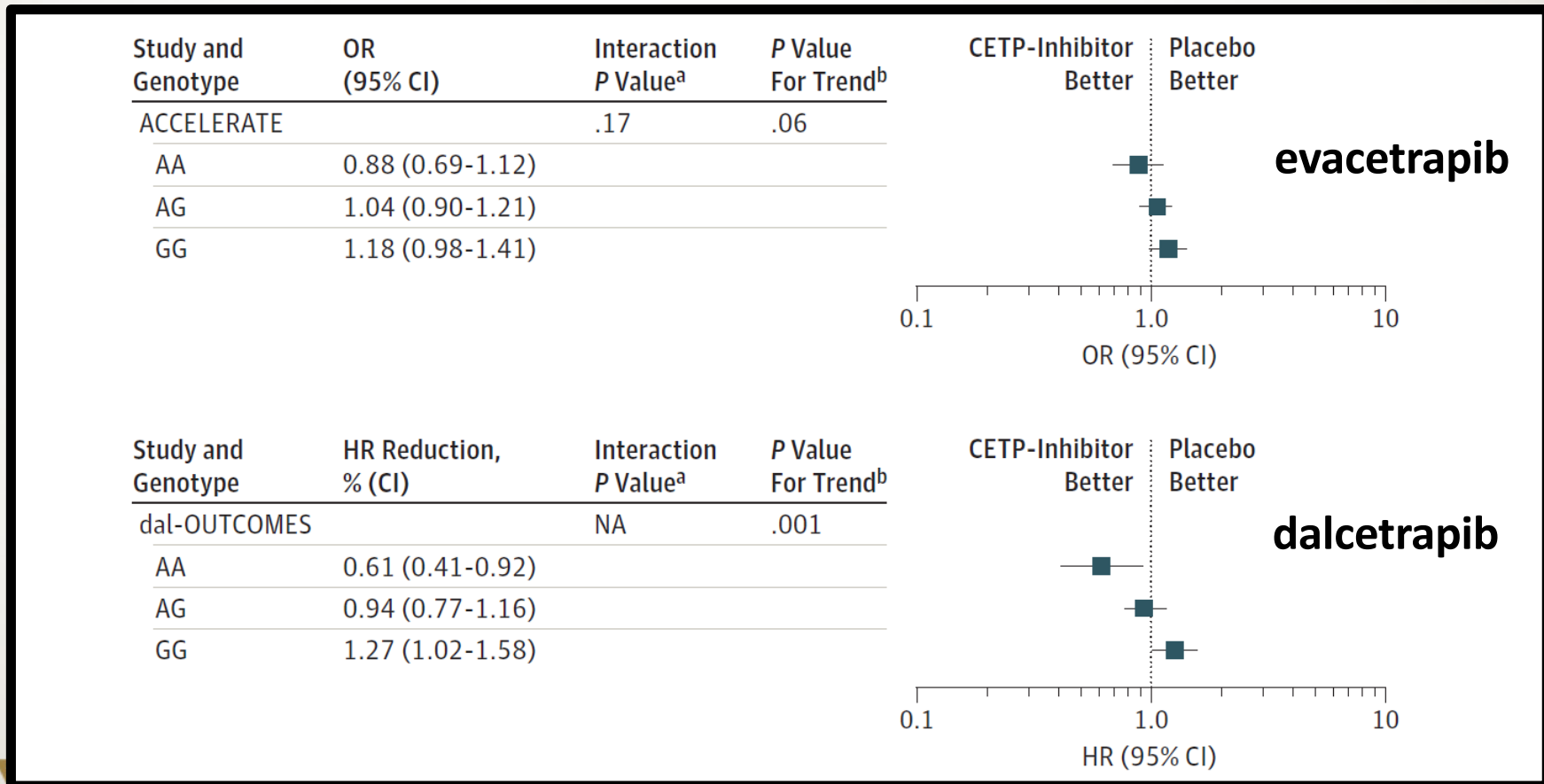


A genetic predictor of response to the CETP inhibitor dalcetrapib?

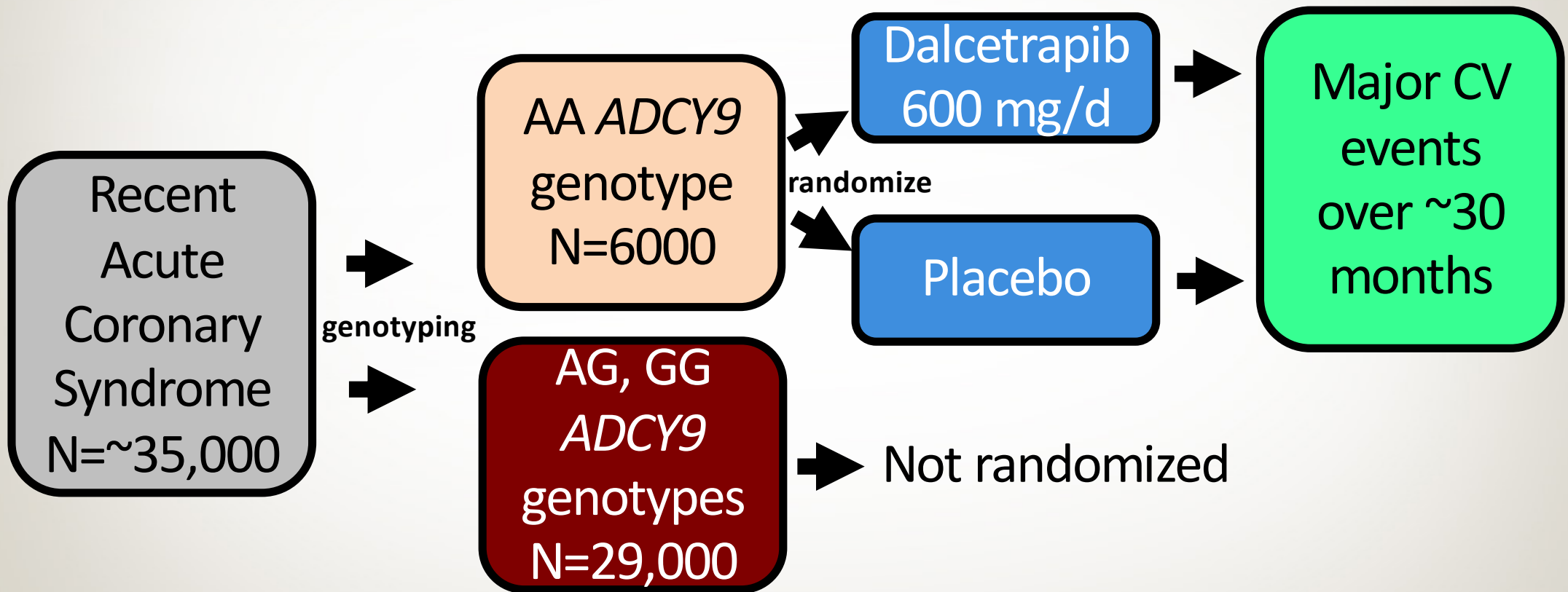


- Supporting evidence from
- dal-PLAQUE-2 (n=386)
 - changes in CRP and cholesterol efflux studies
 - CETP x ACYD9 mice fed atherogenic diets

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



The dal-GenE trial





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

All of UsSM | The
Precision
Medicine
Initiative[®]
THE FUTURE OF HEALTH BEGINS WITH YOU

*"I want the country that eliminated polio and mapped
the human genome to lead a new era of medicine..."*

- PRESIDENT BARACK OBAMA

State of the Union Address, Jan. 20, 2015

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

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.

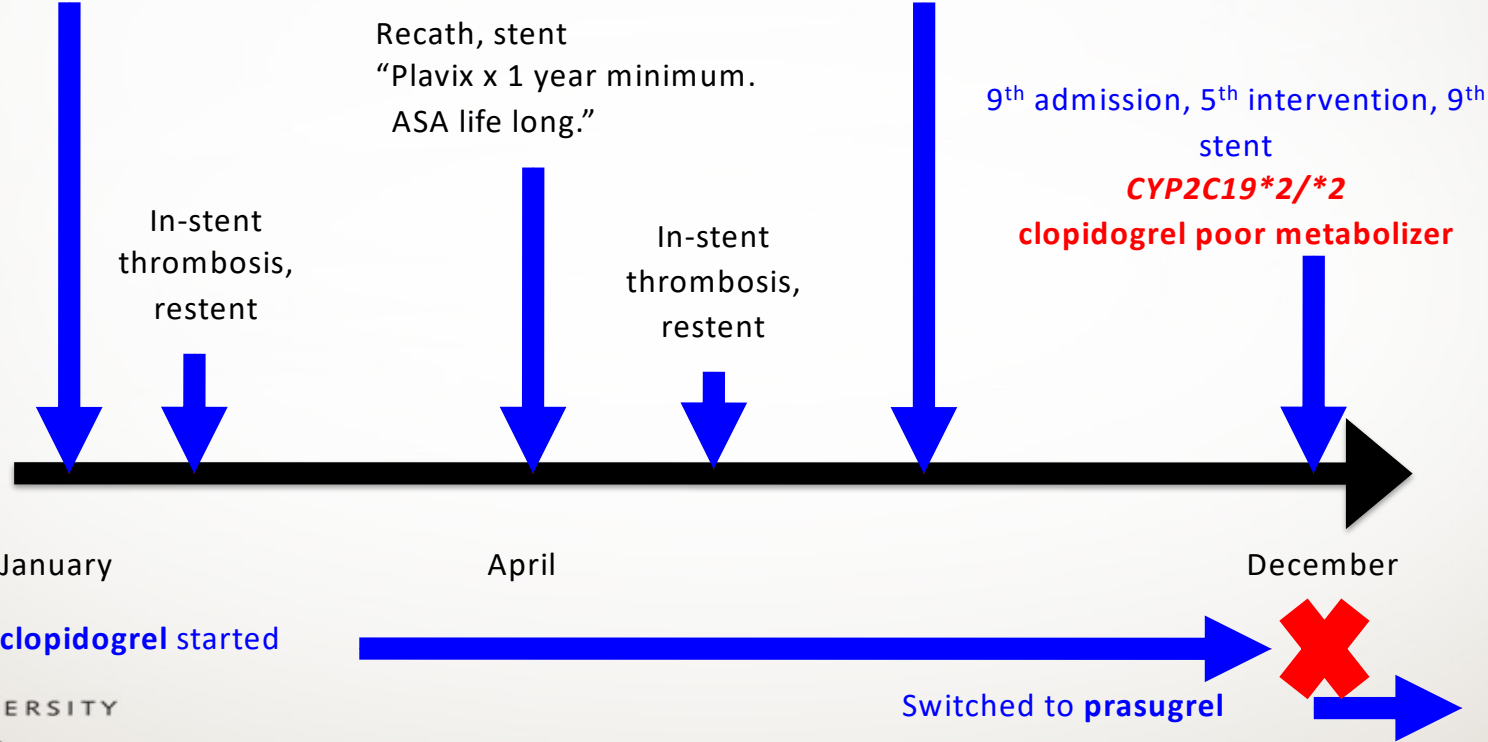
The three genome centers, which will ramp up operations over the next few months, will produce genomic data for the research effort and will analyze data that will be [returned to participants](#). All of Us participants interested in receiving results will initially obtain information from a list of 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



What happens when we implement? Process outcomes

