Pharmacogenomics for Cardiovascular Care

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January 17, 2019

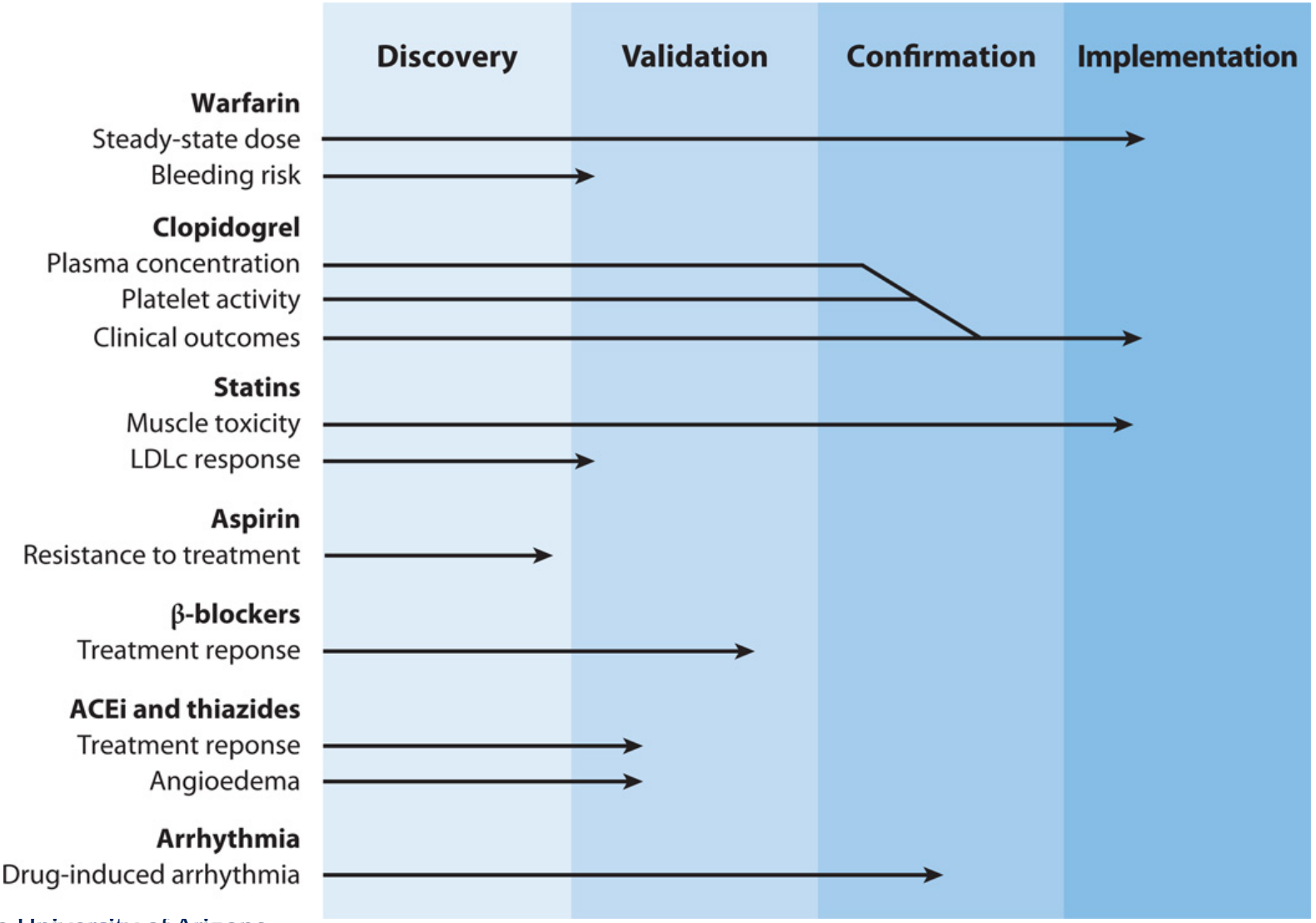
PGxP4 Symposium

@jasonhkarnes

The University of Arizona Health Sciences

THE UNIVERSITY OF ARIZONA

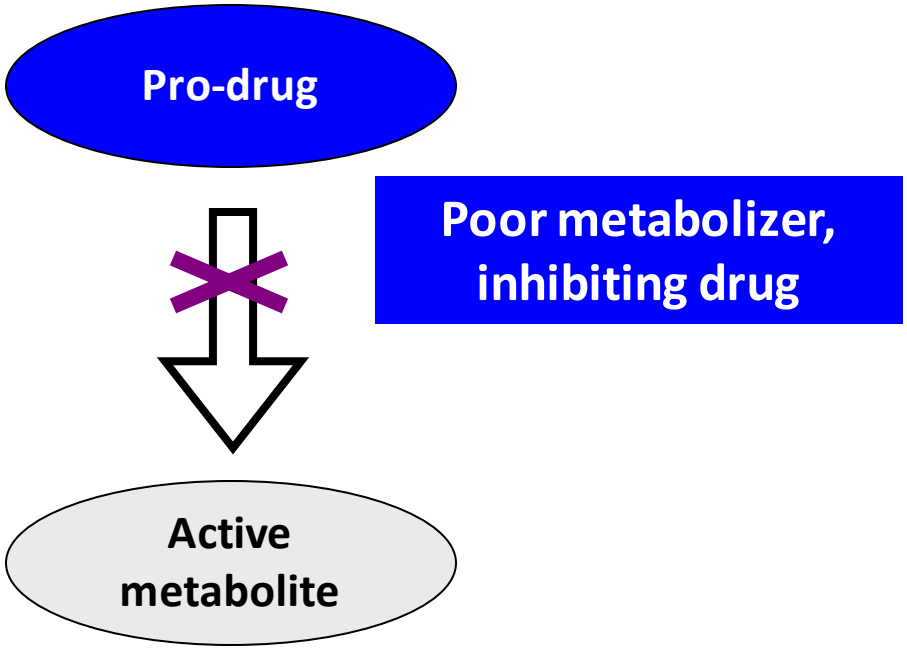
State of the evidence in cardiovascular pharmcogenomics



Annu Rev Med. 2014; 65: 81–94.

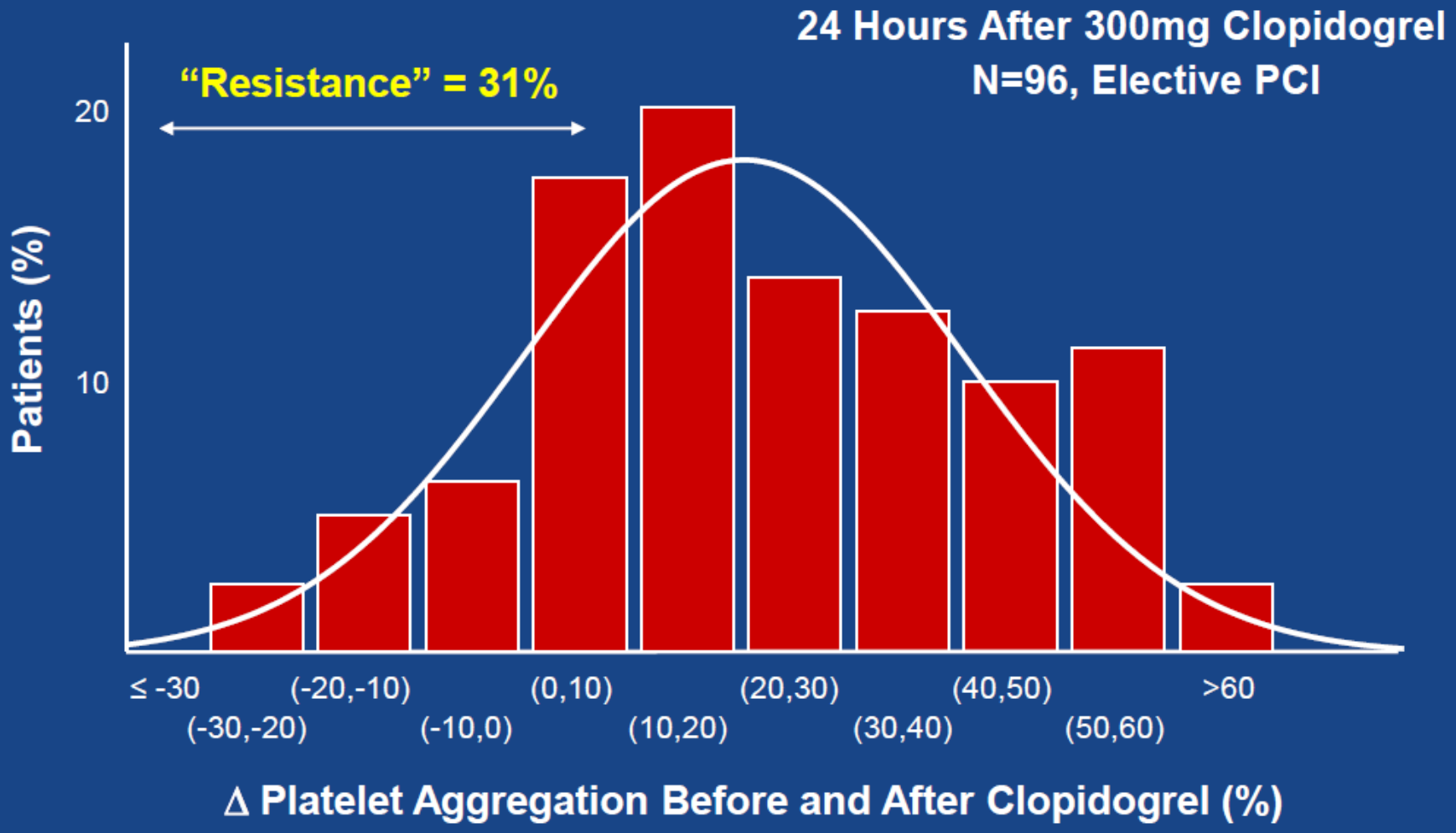
Where pharmacogenomics matters

Single pathway to bioactivation: High-risk pharmacokinetics



- encainide
- clopidogrel
- tamoxifen
- codeine

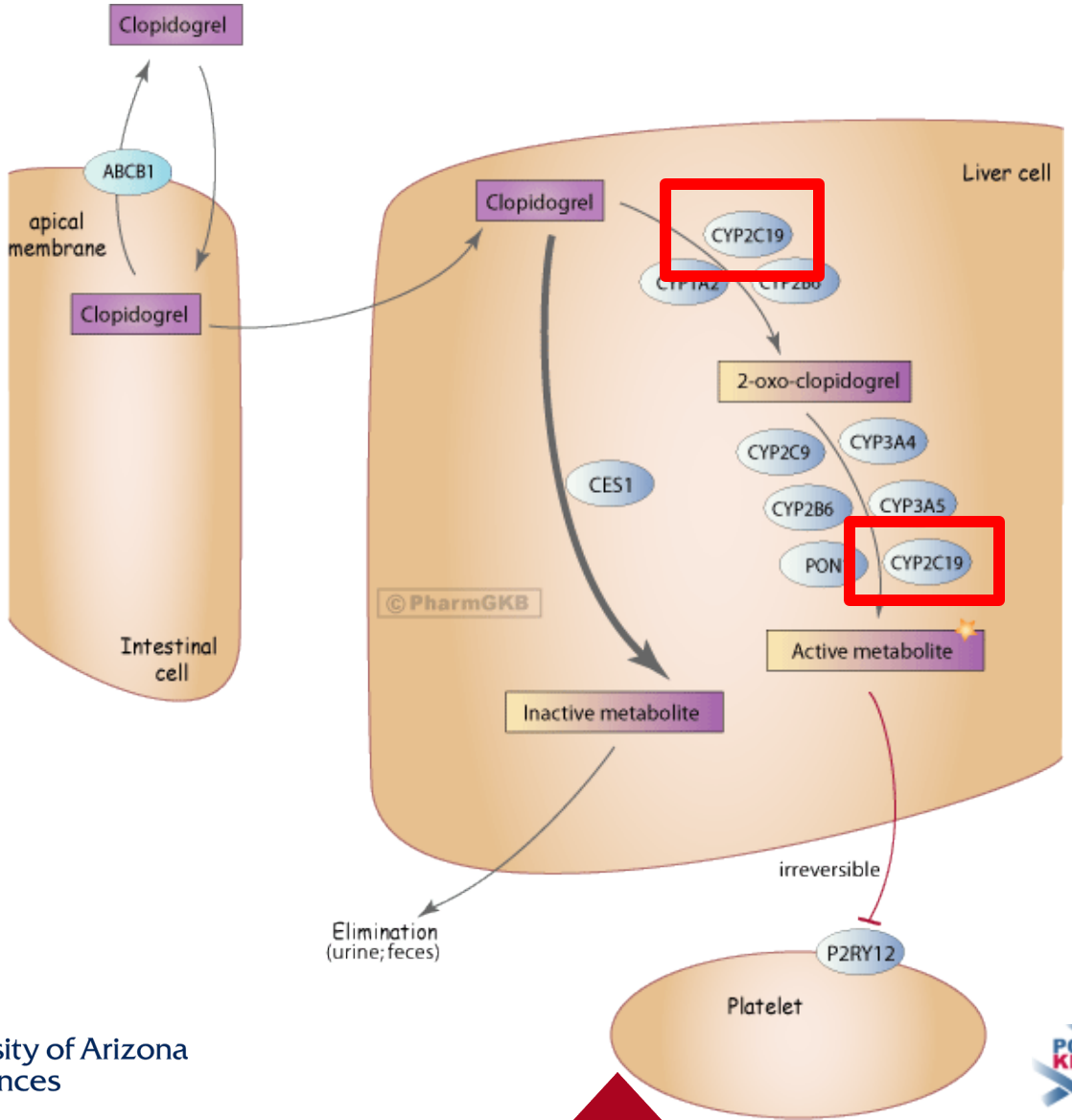
Variable Response to Clopidogrel



"Resistance" = ≤10% Δ platelet aggregation

Gurbel PA et al., *Circulation* 2003;107:2908-2913

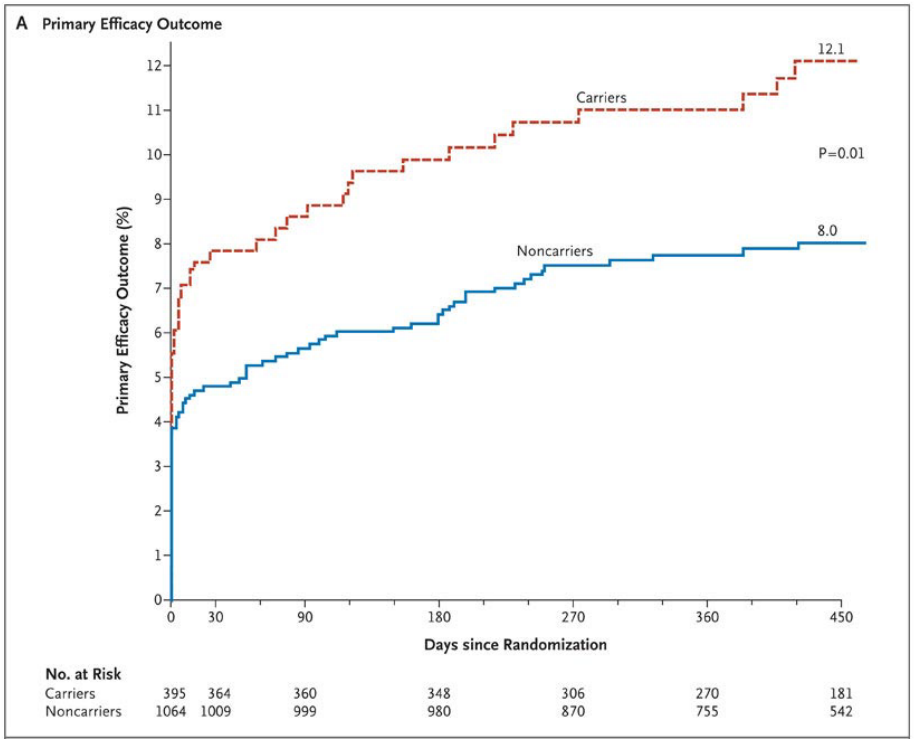
Clopidogrel pharmacokinetic and pharmacodynamic pathways



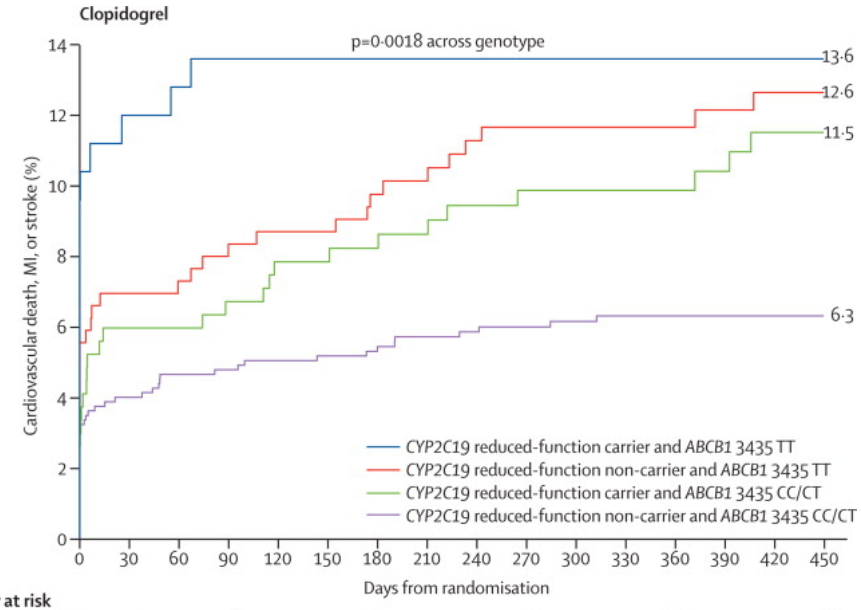
CYP2C19 metabolizer phenotypes based on genotypes

Phenotype (% patients)	**Genotypes**	**Diplotype examples**
Ultrarapid metabolizer (~5-30%)	One or more gain of function alleles	*17/*17, *1/*17
Extensive metabolizer (~35-50%)	two copies of functional alleles	*1/*1
Intermediate metabolizer (~18-45%)	one reduced and one nonfunctional allele	*1/*2, *1/*3
Poor metabolizer (~2-15%)	no functional alleles	*2/*2, *2/*3, *3/*3

Scott et al. Clin Pharm Ther (2013)



THE LANCET

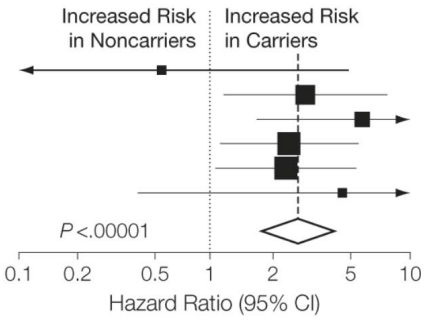


The NEW ENGLAND JOURNAL of MEDICINE

Number at risk							
CYP2C19 reduced-function carrier and *ABCB1* 3435 TT	125	110	108	105	90	83	58
CYP2C19 reduced-function non-carrier and *ABCB1* 3435 TT	288	266	263	256	220	193	142
CYP2C19 reduced-function carrier and *ABCB1* 3435 CC/CT	268	252	250	241	214	185	123
CYP2C19 reduced-function non-carrier and *ABCB1* 3435 CC/CT	773	740	733	721	649	562	400

A Carriers of 1 or 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

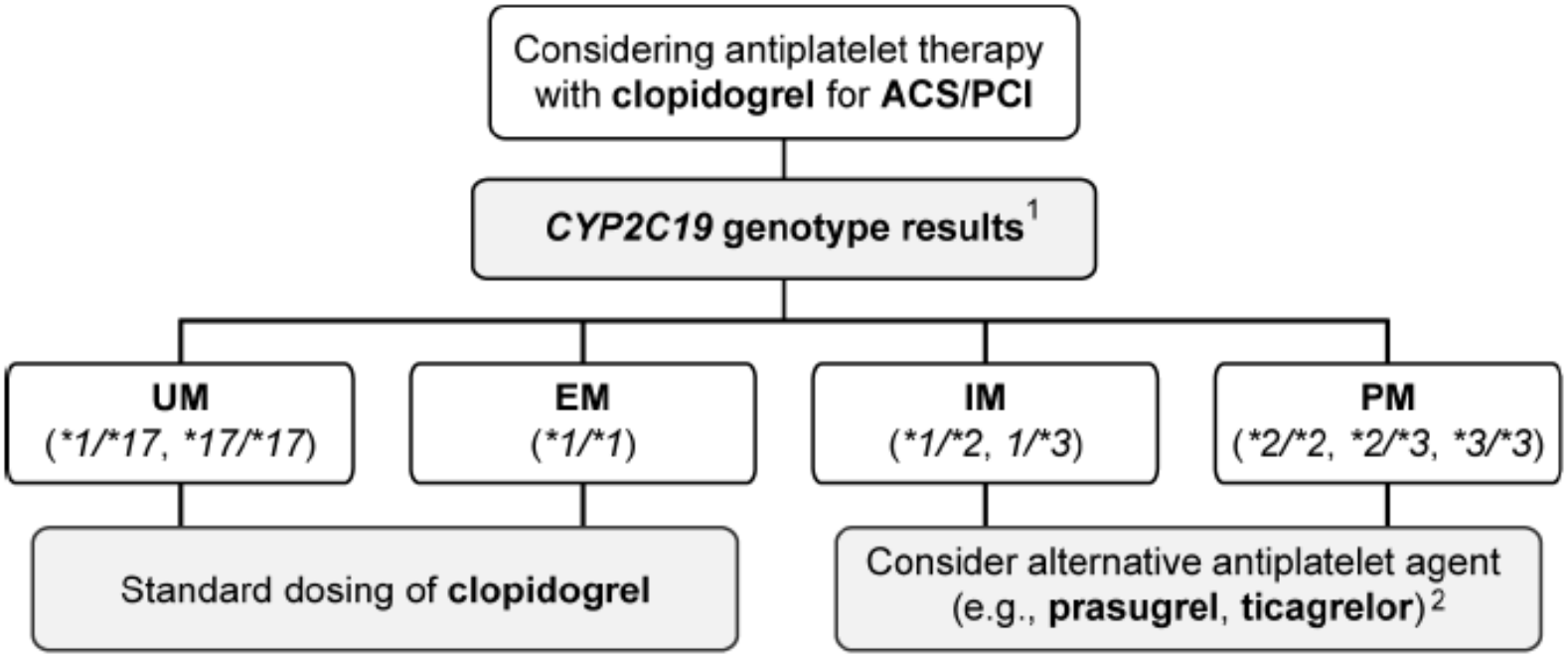
	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	1 or 2	None	
EXCELSIOR	1/243	4/554	0.57 (0.06-5.09)
TRITON-TIMI 38	9/375	8/1014	3.09 (1.19-8.00)
AFIJI	8/61	4/162	6.04 (1.75-20.82)
RECLOSE	13/247	11/525	2.55 (1.14-5.70)
ISAR	11/680	12/1805	2.45 (1.08-5.55)
CLEAR-PLATELETS	2/68	1/160	4.78 (0.43-52.69)
Overall	44/1674	40/4420	2.81 (1.81-4.37)



JAMA The Journal of the American Medical Association

Mega JL et al. Lancet 2010:1312–1319
Mega JL et al. JAMA. 2010;304(16):1821-1830
Mega JL et al. N Engl J Med 2009;360:354-362

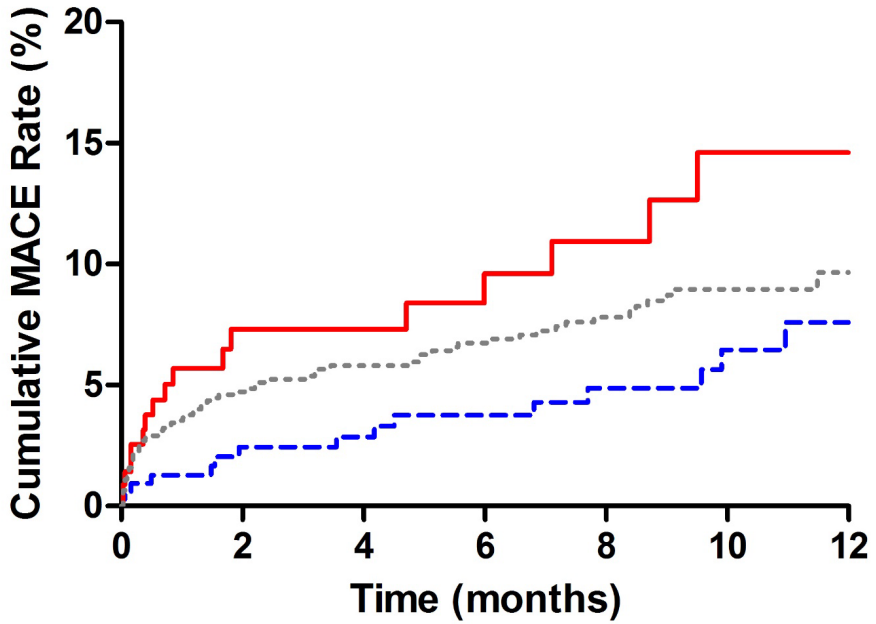
CPIC: Clinical recommendations for *CYP2C19* and clopidogrel



- CPIC recommendations if genotype is already available
- ACC/AHA recommend case by case genotyping
- Not supported by RCTs

Scott et al. Clin Pharm Ther (2013)

Emerging Data: *CYP2C19* and outcomes with clopidogrel

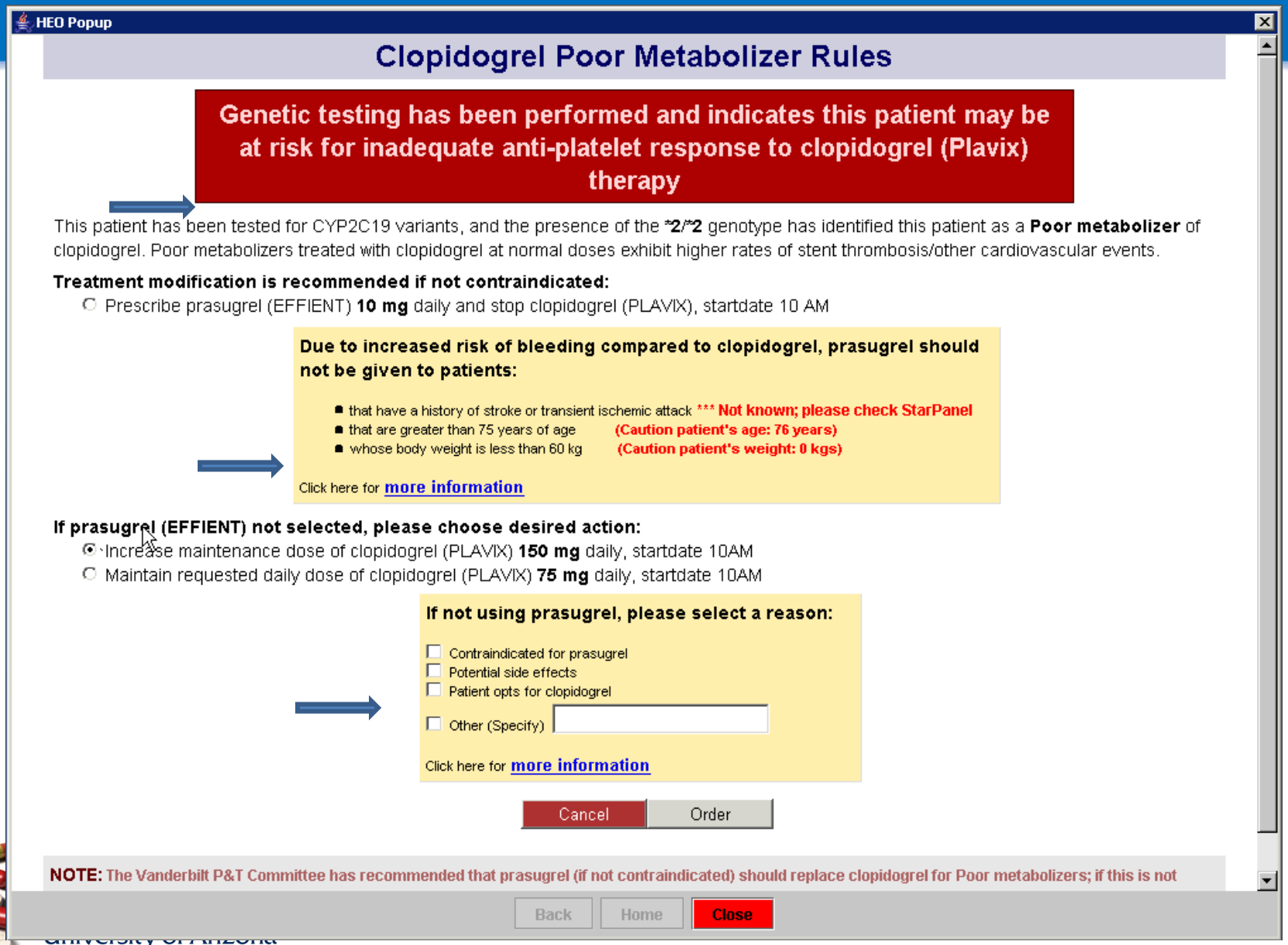


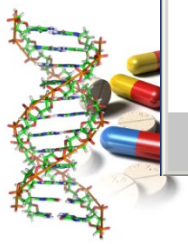
NO. at risk							
LOF_CLOP	226	112	89	76	63	39	3
NON-LOF	1243	759	636	577	451	293	28
LOF_ALT	346	245	221	195	161	112	9

LOF = Loss of function

Adjusted Hazard Ratio
LOF-CLOP vs LOF ALT: 2.21 (1.13-4.33) p=0.021
LOF-ALT vs non-LOF: 0.81 (0.48-1.35) p=0.41

Clinical implementation

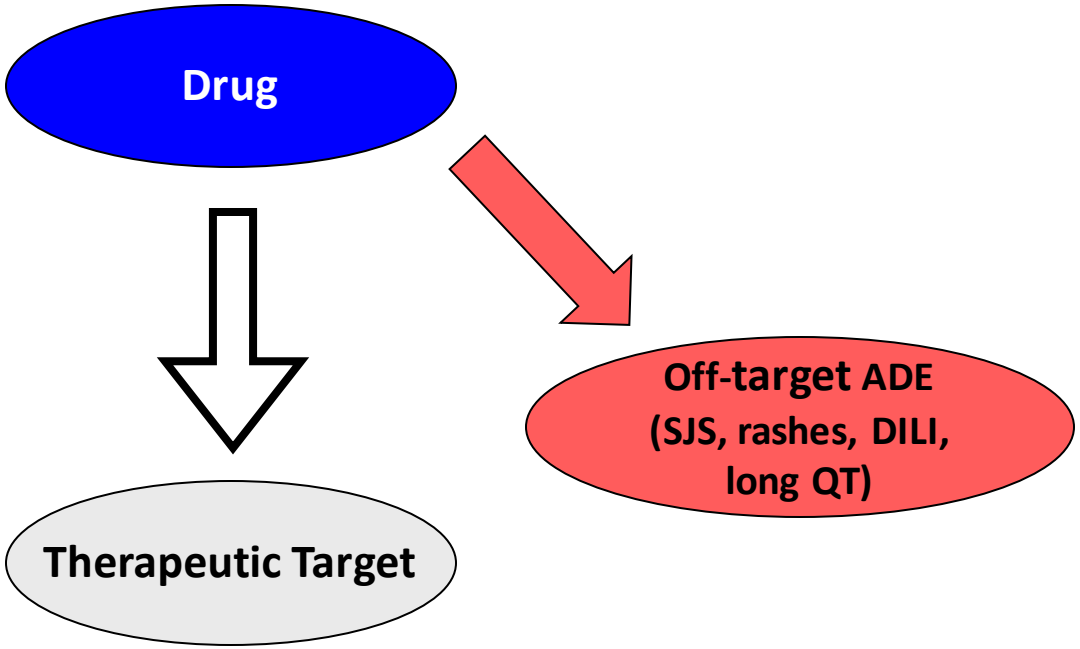




lth Sciences

Where pharmacogenomics matters

Off-target serious adverse effects



- simvastatin
- carbamazepine
- clozapine
- haloperidol
- abacavir
- antibiotics

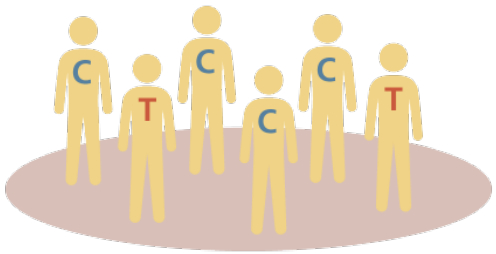
Simvastatin and muscle toxicity

- Statins have wide therapeutic index and severe ADRs relatively uncommon
- Most common statin-related ADR is skeletal muscle toxicity
  - Myalgias (pain) – 1-5% patients
  - Myopathy (pain with evidence of muscle degradation) – 1 in 1,000 patients
  - Rhabdomyolysis (severe muscle damage with acute kidney injury), 1 in 100,000 patients
- Risk factors: age, statin dose, concomitant fibrates

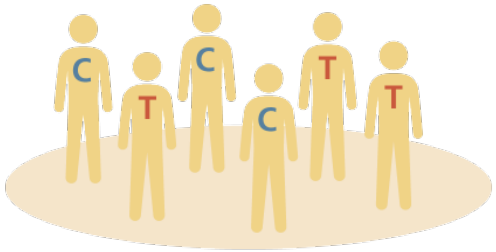
Wilke et al. Clin Pharm Ther (2012)

Genome-wide association study (GWAS)

Identify cases and controls



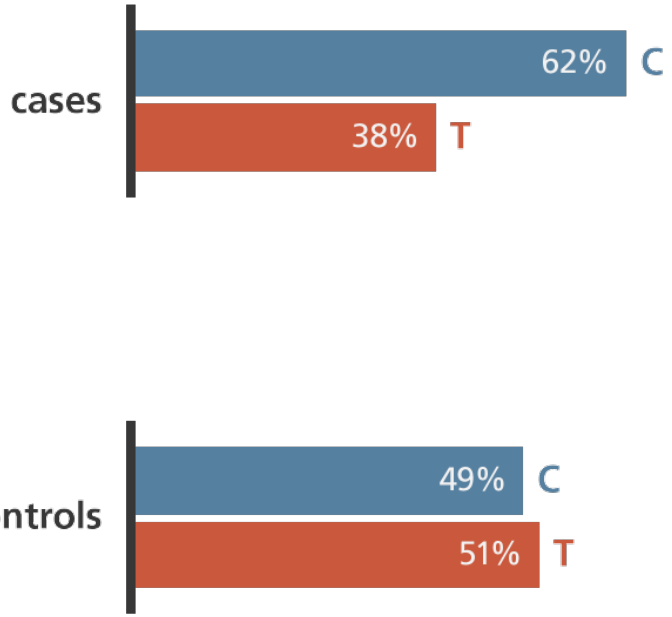
cases (n=1,000)
people with heart disease



controls (n=1,000)
people without heart disease

Genotype a million SNPs across the genome

Statistical analysis for SNPs association with case

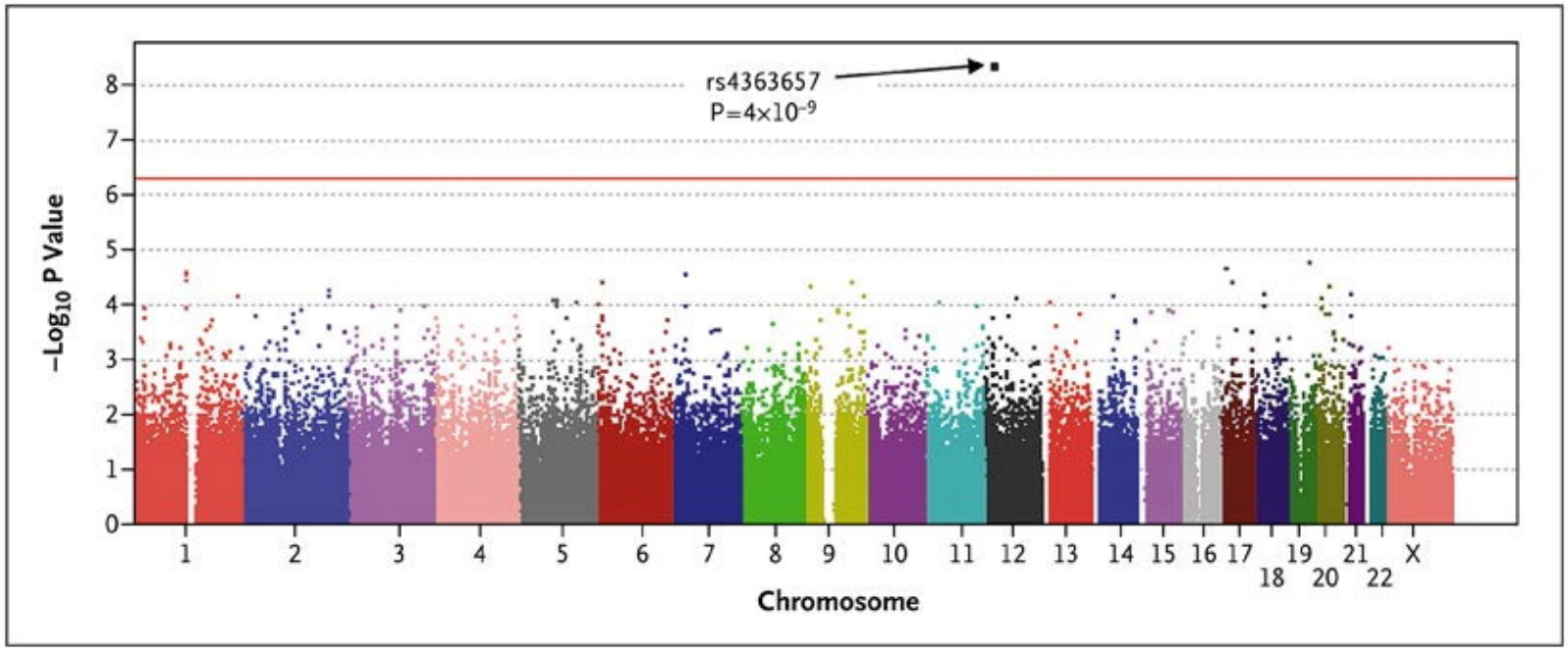


A case-control genome-wide association study investigating genetic variants associated with heart disease.

The University of Arizona Health Sciences

Image credit: Genome Research Limited

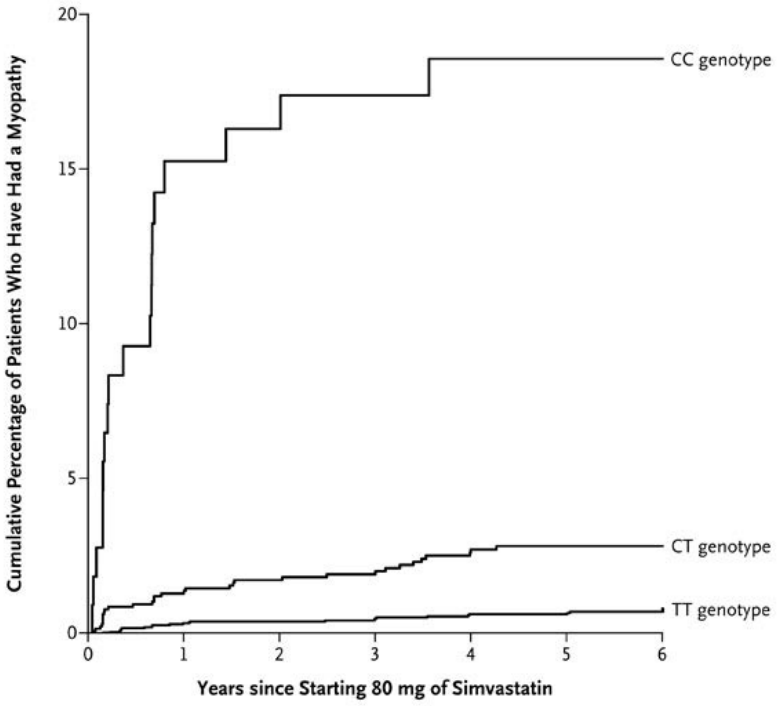
SLCO1B1 Variants and Statin-Induced Myopathy



- Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study.
- x axis is –log(p value) so a dot (representing a SNP) at 8 on the x axis has a p value of $p=1x10^{-8}$ or p=0.00000001

The SEARCH Collaborative Group. N Engl J Med 2008;359:789-799

Risk of myopathy associated with 80 mg daily simvastatin by *SLCO1B1* rs4149056 genotype



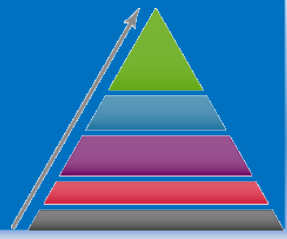
Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy							
		Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

The University of Arizona Health Sciences

The SEARCH Collaborative Group. N Engl J Med 2008;359:789-799

The NEW ENGLAND JOURNAL of MEDICINE

CPIC: Clinical recommendations



- Simvastatin metabolized primarily by CYP3A4 and transported into liver primarily by SLCO1B1 (OATP1B1)
- Avoid 80 mg simvastatin in all patients (FDA)
  - Exception in patients taking this dose for over a year without signs/symptoms of muscle toxicity
- *SLCO1B1* genotyping may apply to other statins, but not currently sufficient evidence
- Simvastatin-induced muscle toxicity can still occur in absence of rs4149056

Table 2 Dosing recommendations for simvastatin based on SLCO1B1 phenotype

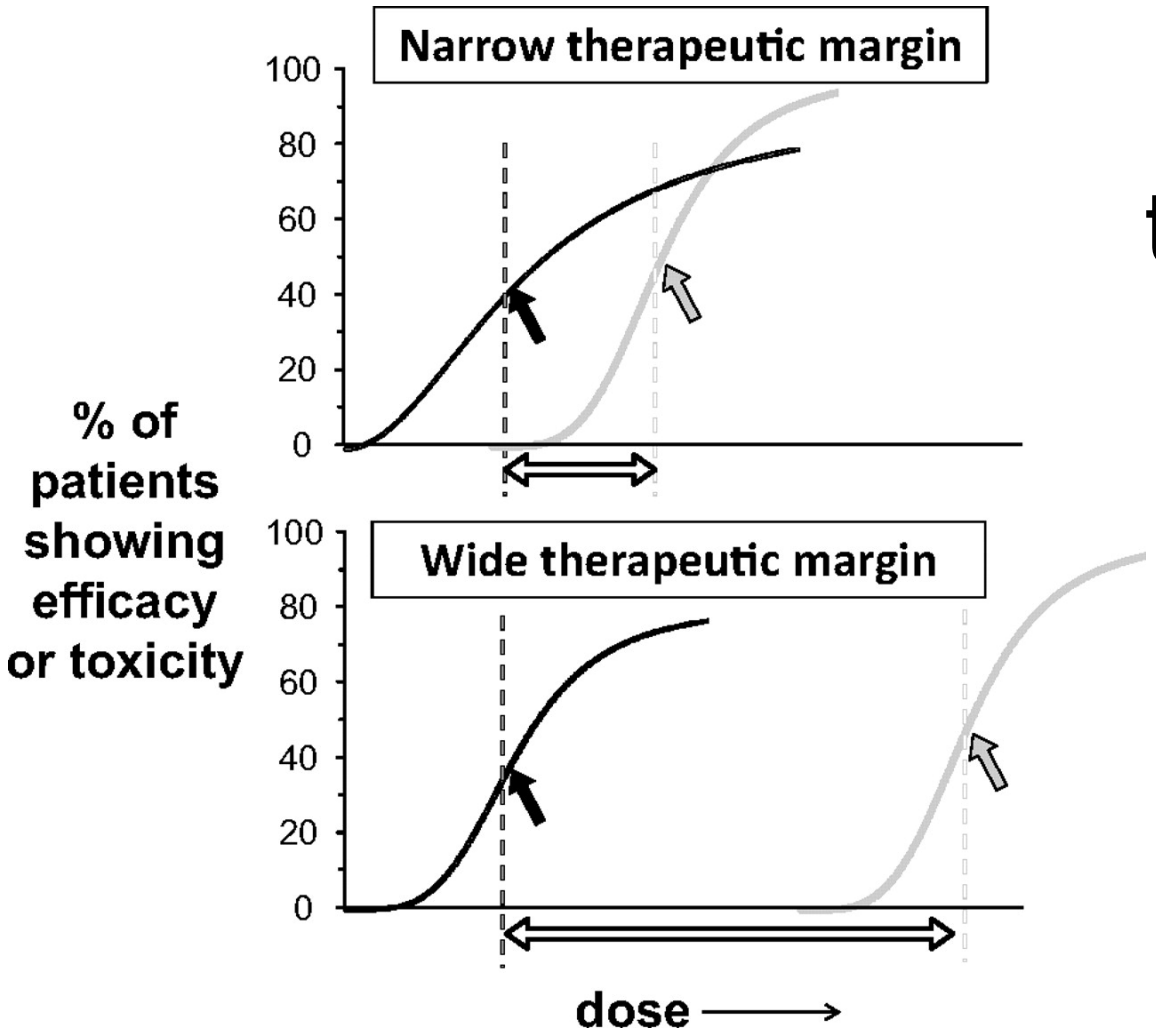
Phenotype	Implications for simvastatin	Dosing recommendations for simvastatin[a,b]	Classification of recommendations[c]
Normal function	Normal myopathy risk	Prescribe desired starting dose[b] and adjust doses of simvastatin based on disease-specific guidelines	Strong
Intermediate function	Intermediate myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong
Low function	High myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong

CK, creatine kinase.

[a]In all cases, the potential for drug–drug interaction should be evaluated before initiating a prescription. [b]The US Food and Drug Administration recommends against 80 mg (unless already tolerated for 12 months). [c]See the **Supplementary Material** online (text section titled "Levels of Evidence") for additional details regarding the three-tiered system used to grade the quality of evidence.

Ramsey et al. Clin Pharm Ther (2014)

Where Pharmacogenomics Matters

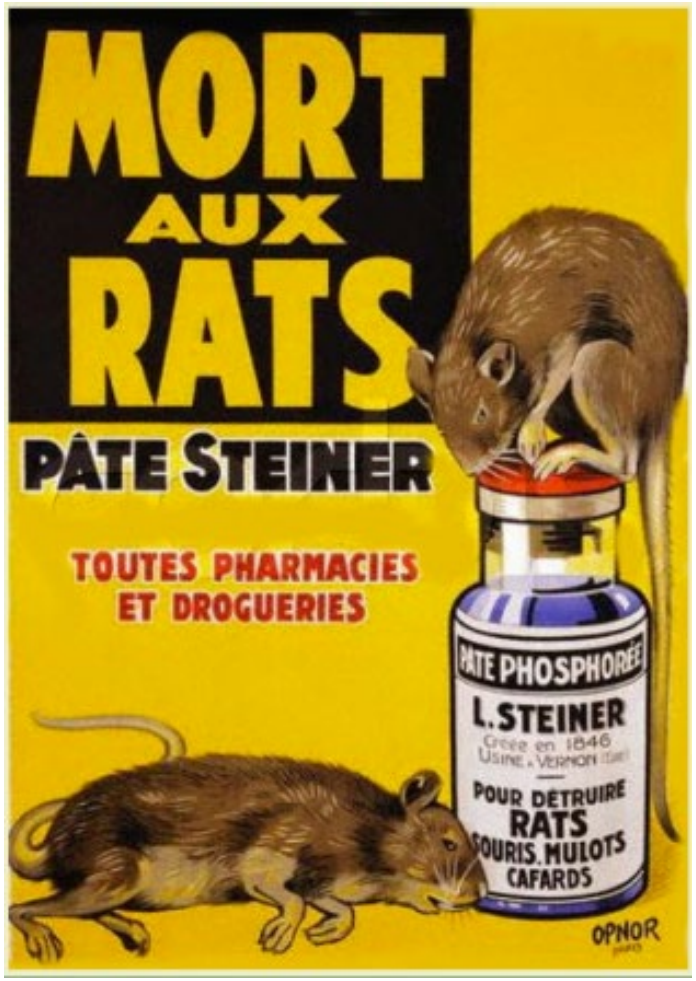


Drugs with narrow therapeutic windows

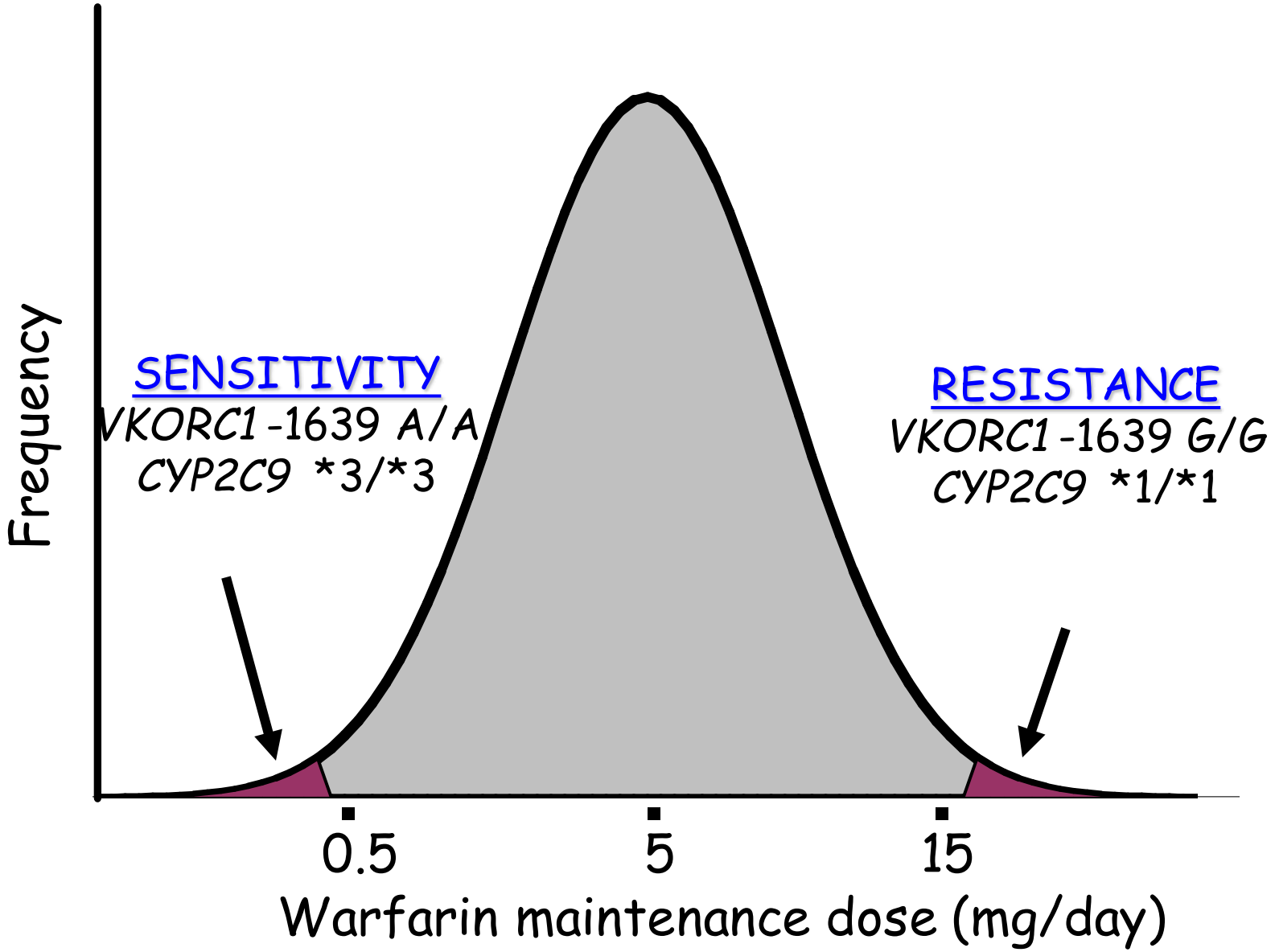
- **warfarin**
- **lithium**
- **digoxin**
- **some antibiotics (vancomycin)**

Warfarin


Later's
WARFARIN
BAIT
KILLS NORWAY (SEWER) RATS, ROOF RATS & MICE
EFFECTIVE CONTROL FOR RATS AND MICE IN AND AROUND THE HOUSE
500 g
SEALED BAIT BAGS


MORT AUX RATS
PÂTE STEINER
TOUTES PHARMACIES ET DROGUERIES
PÂTE PHOSPHORÉE
L. STEINER
Créée en 1846
POUR DÉTRUIRE
RATS
SOURIS, MULOTS
CAFARDS
OPNOR

Inter-individual variability in warfarin dose



Gage et al.

Warfarin package insert

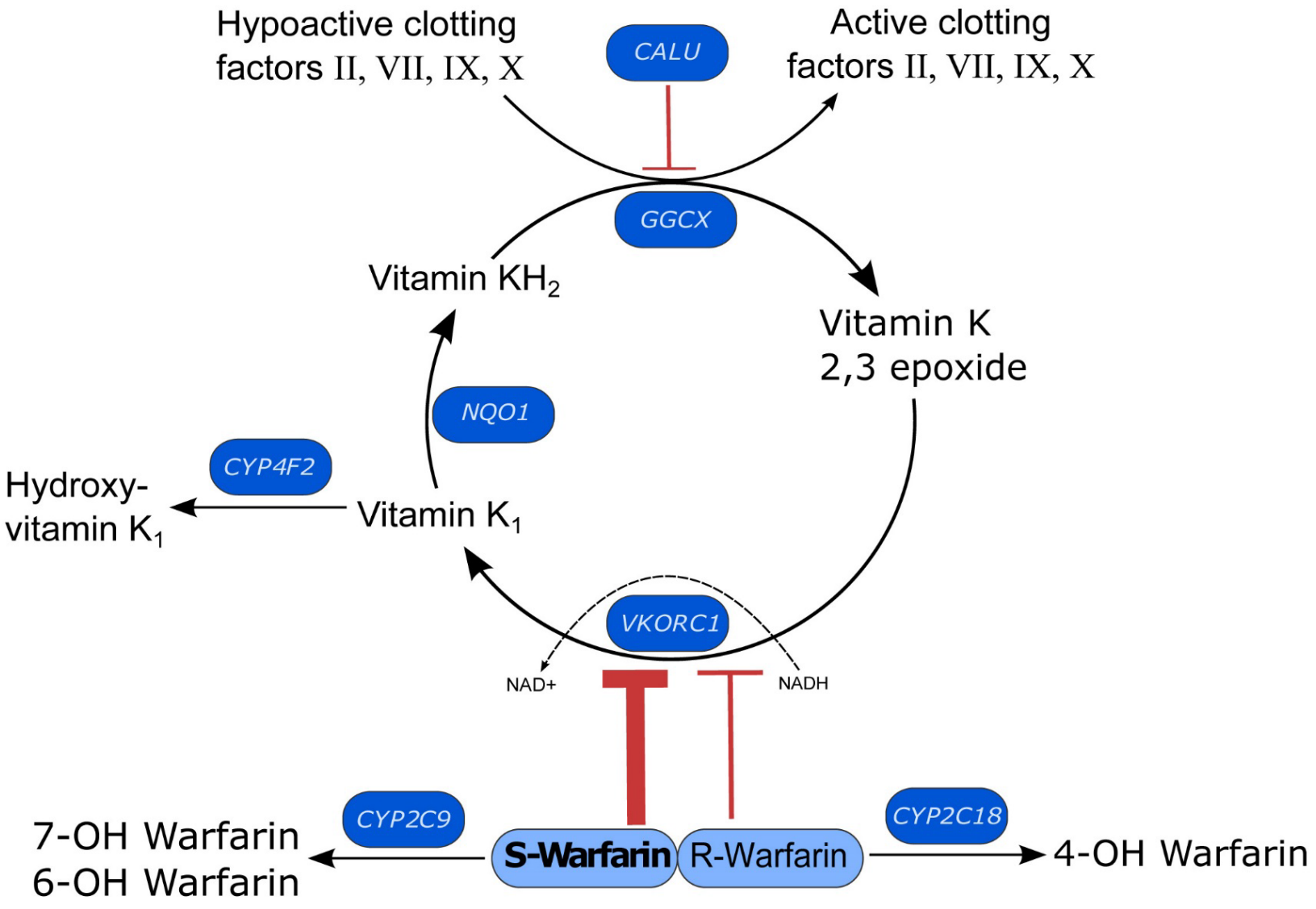
Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

FDA. Coumadin package insert

Multiple genes affecting warfarin dose



WARFARINDOSING

www.WarfarinDosing.org

- Warfarin Dosing
- Clinical Trial
- Outcomes
- Hemorrhage Risk
- Patient Education
- Contact Us
- References
- Glossary
- About Us

User:
Patient:
Version 2.40
Build : April 05, 2013

Required Patient Information

Age: [ ] **Sex:** -Select- **Ethnicity:** -Select-

Race: -Select-

Weight: [ ] lbs **or** [ ] kgs

Height: ([ ] feet and [ ] inches) **or** ([ ] cms)

Smokes: -Select- **Liver Disease:** -Select-

Indication: -Select-

Baseline INR: [ ] **Target INR:** [ ] ☐ Randomize & Blind

Amiodarone/Cordarone® Dose: [ ] mg/day

Statin/HMG CoA Reductase Inhibitor: -Select-

Any azole (eg. Fluconazole): -Select-

Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: -Select-

Genetic Information

VKORC1-1639/3673: Not available/pending

CYP4F2 V433M: Not available/pending

GGCX rs11676382: Not available/pending

CYP2C9*2: Not available/pending

CYP2C9*3: Not available/pending

CYP2C9*5: Not available/pending

CYP2C9*6: Not available/pending

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› ESTIMATE WARFARIN DOSE

The He

Randomized controlled trials for warfarin pharmacogenomic testing

Study	Sample size (n)	Control group dosing algorithm	Clinical Factors included in algorithm(s)	Comparator Group (% TTR)	Genotype-Guided Group (% TTR)**	p value
Pirmohamed et al. 2013 (EU-PACT)	454	Fixed dose*	Age, Height, Weight, Amiodarone	60.3%	67.4%	<0.001
Kimmel et al. 2013 (COAG)	955 700 (non-AA) 255 (AA)	Clinically-derived dose	Age, Race, Smoking status, BSA, Amiodarone, Target INR,	45.4% 46.1% (non-AA) 43.5% (AA)	45.2% 48.8%(non-AA) 35.2% (AA)	0.91 0.15 (non-AA) 0.0003 (AA)
Verhoef et al. 2013 (EU-PACT)***	548	Clinically-derived dose	Age, Sex, Height, Weight, Amiodarone	60.2%	61.6%	0.52

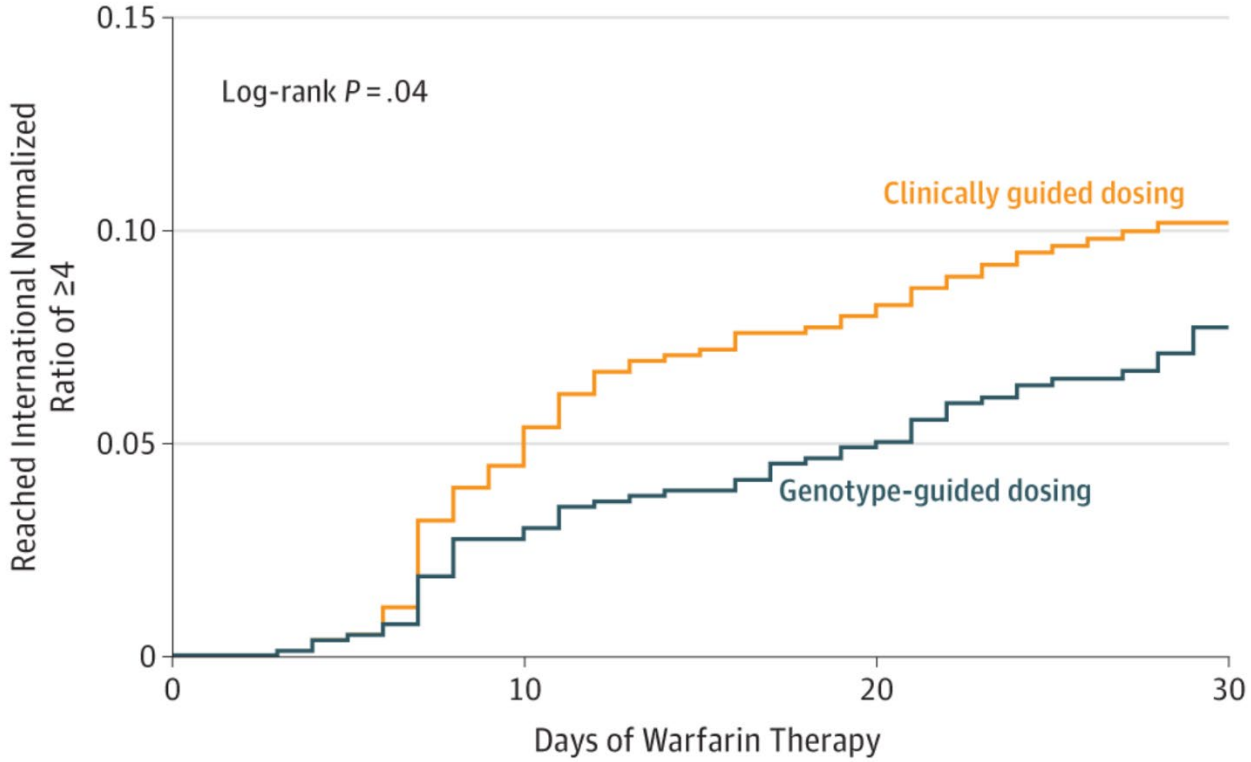
*Fixed dose algorithm used no clinical factors and started with 10mg (day 1) and 5mg (days 2 and 3).

** All genotype-guided algorithms included clinical factors and genetic factors *CYP2C9 *2,*3,* and *VKORC1 -1639A* (or *VKORC1 1173T).*

***Study administered warfarin derivatives acenocoumarol and phenprocoumon.

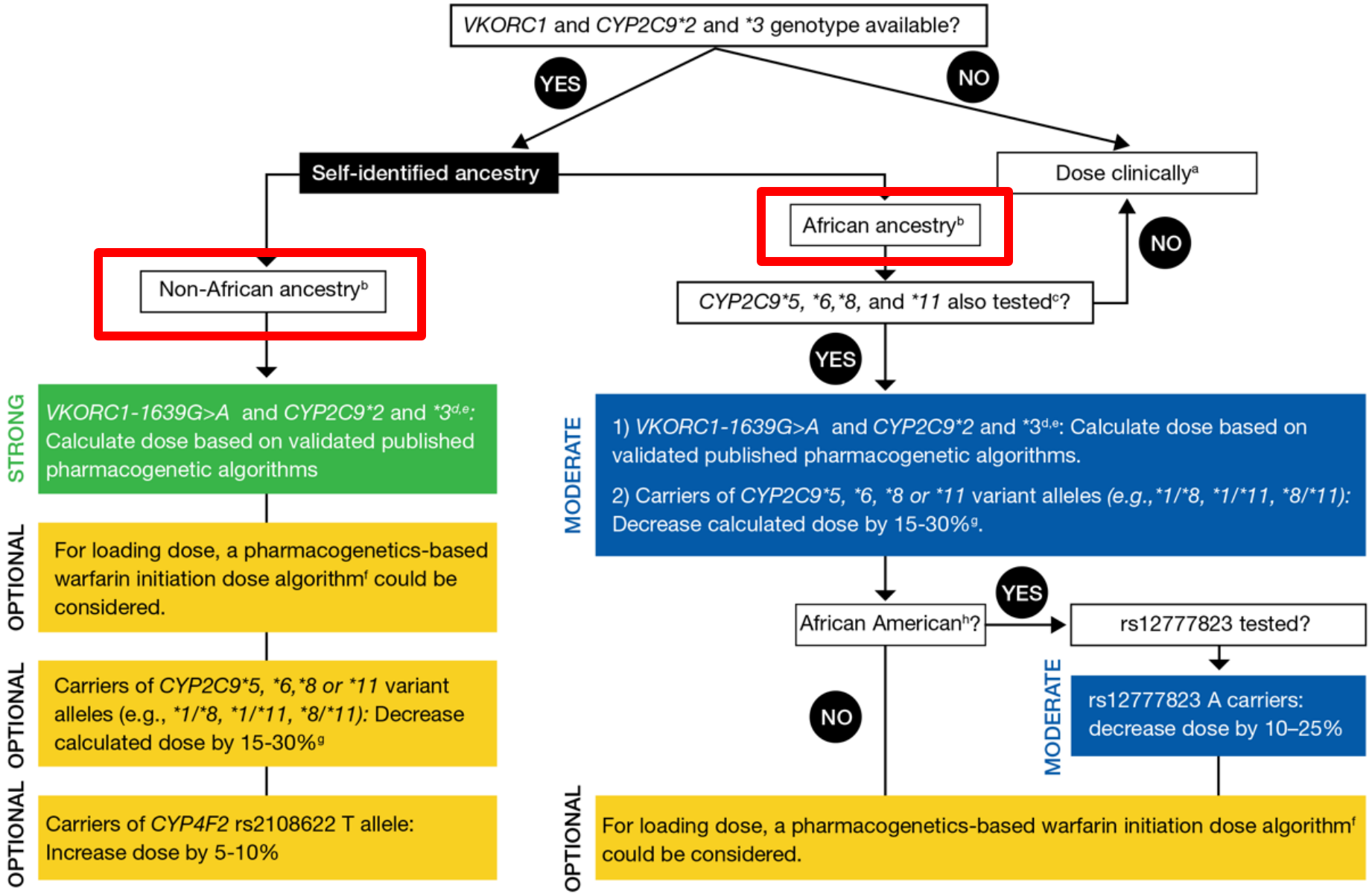
From: **Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee ArthroplastyThe GIFT Randomized Clinical Trial**

JAMA. 2017;318(12):1115-1124. doi:10.1001/jama.2017.11469



No. of patients				
Clinically guided dosing	789	737	698	209
Genotype-guided dosing	808	771	739	216

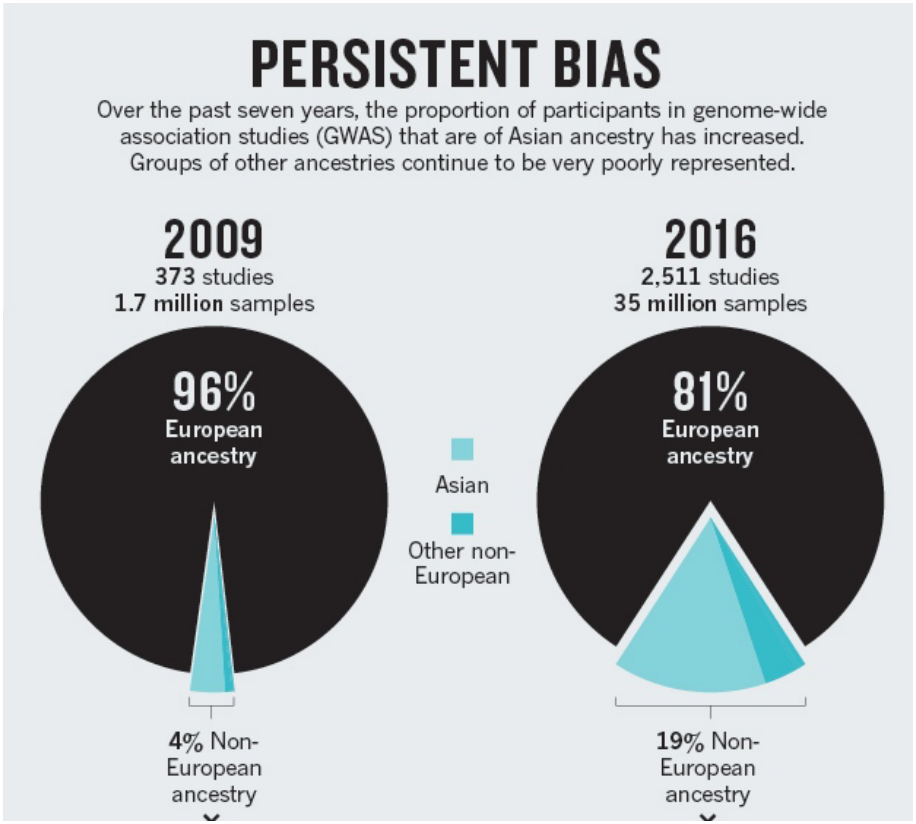
CPIC: Clinical Recommendations (2017)



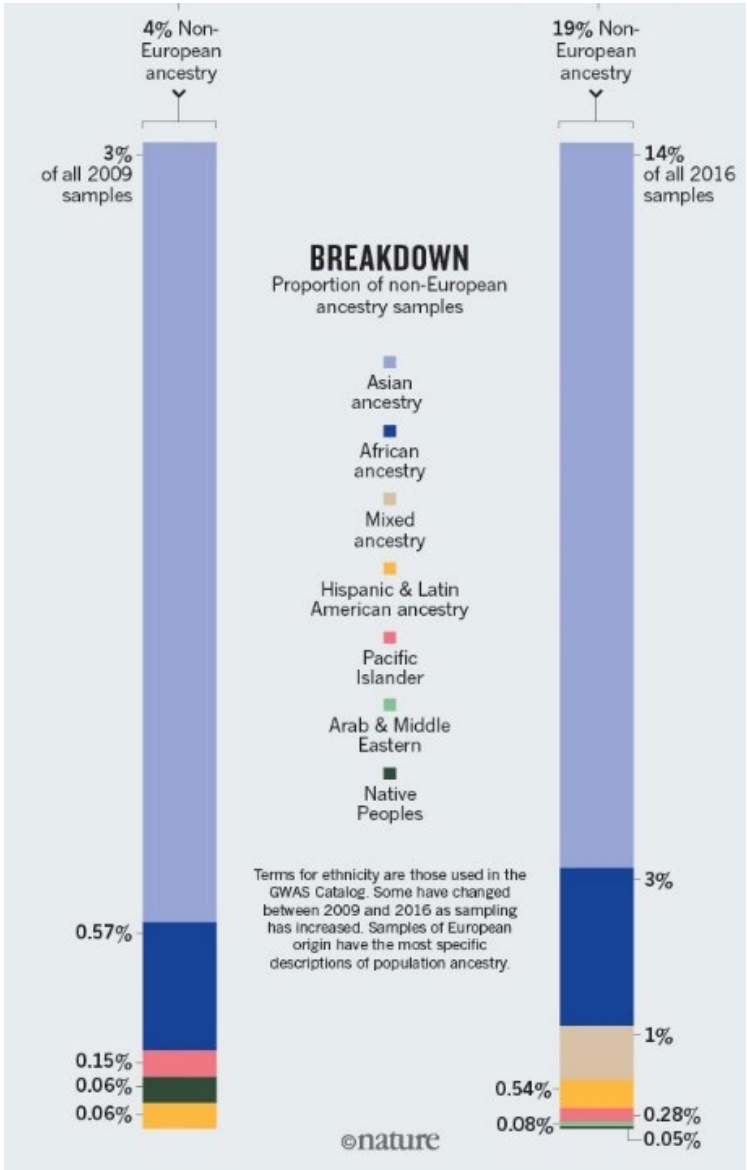
Health Sciences

Johnson et al. Clin Pharm Ther (2017)

Genomics is failing on diversity



- Studies in whites may not be valid in other race/ethnic groups
- Without research, clinical testing may not be useful for non-whites



Popejoy and Fullerton. Nature 2016

All of Us RESEARCH PROGRAM

Mission and Objectives

Nurture relationships
with one million or more participant partners, from all walks of life, **for decades**

Our mission

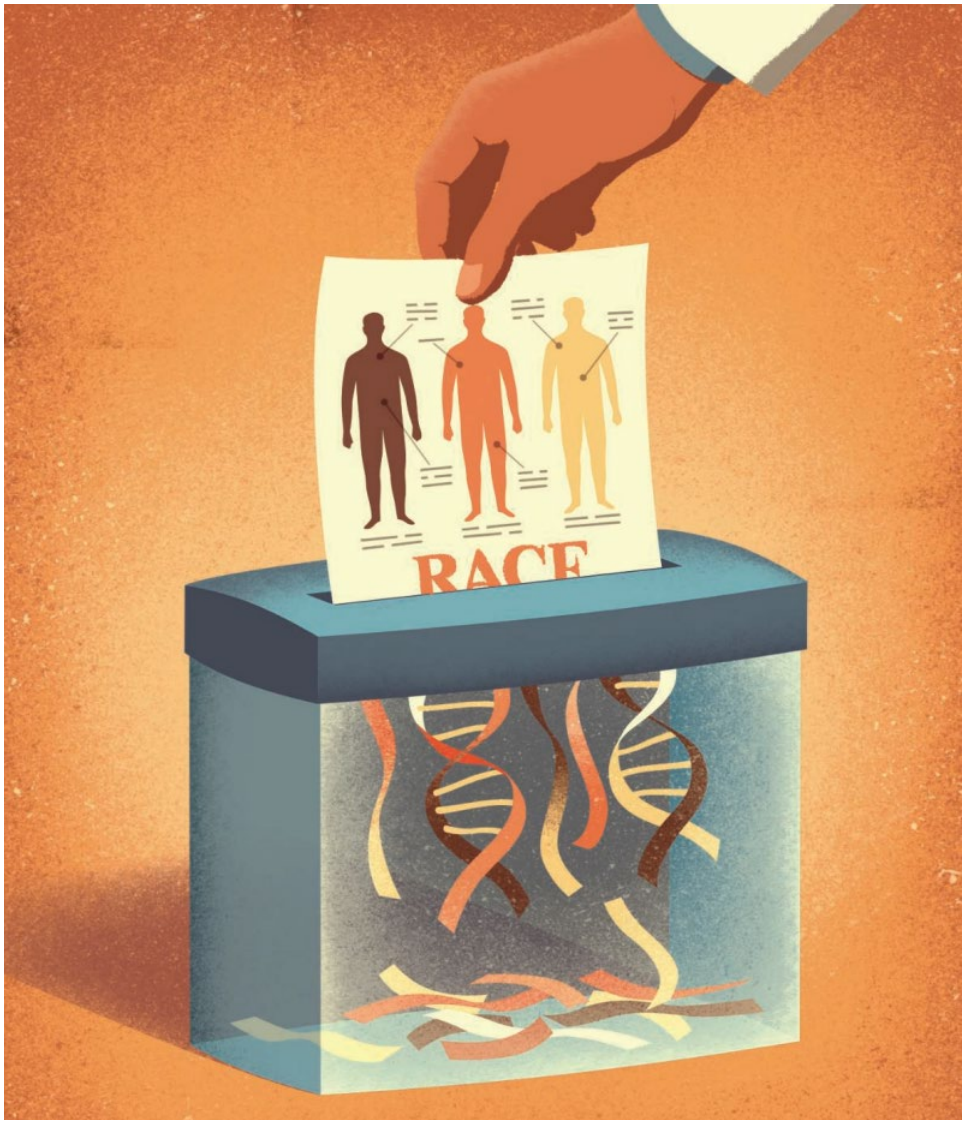
To accelerate health research and medical breakthroughs, **enabling individualized** prevention, treatment, and **care for all of us**

Deliver one of the largest, richest biomedical datasets ever
that is easy, safe, and **free to access**

Catalyze the robust ecosystem
of researchers and funders hungry to use and support it

Goal of 50% of participants under-represented in biomedical research

Questions?



Yudell et al. Science (2016)