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Overview of Ongoing Projects: Success Stories and Lessons Learned

Exploiting Pharmacogenetic Discovery to Improve Patient Care: Why Aren't We There Yet?

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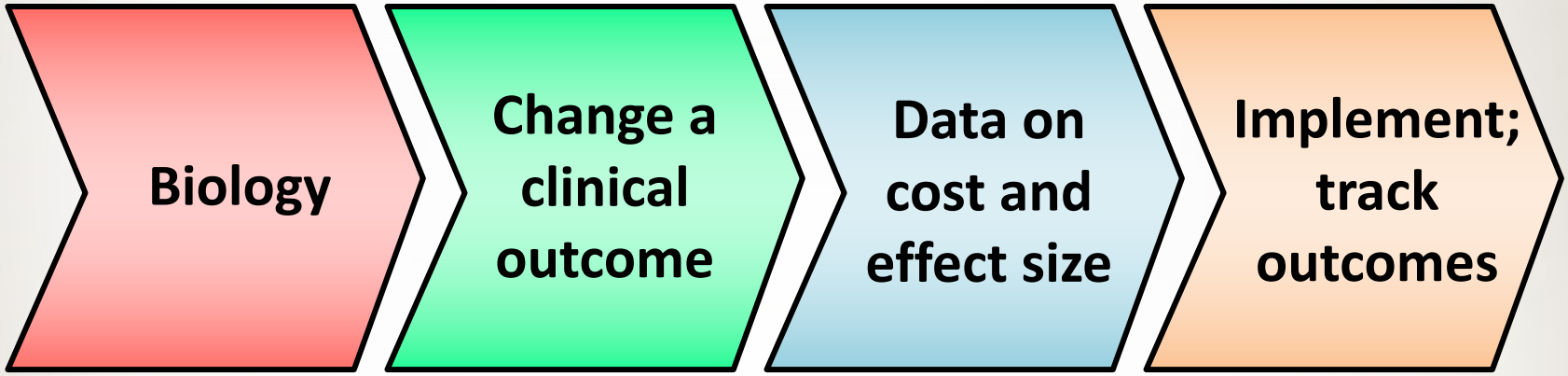
Senior Vice President for Personalized Medicine

Vanderbilt University Medical Center

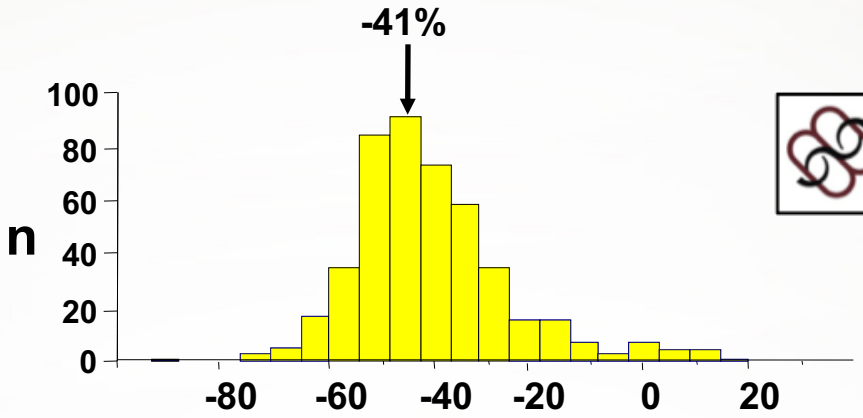
The spectrum of pharmacogenetic research



Outline

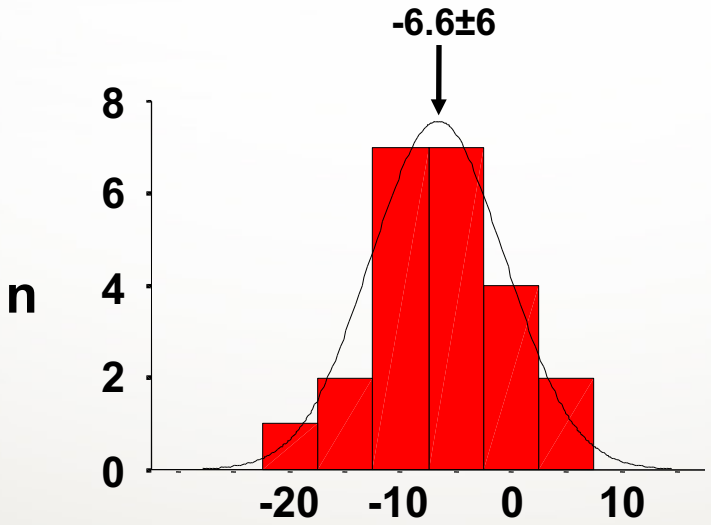
- Principles of Clinical Pharmacology and PGx
- What have we learned and are learning from warfarin, abacavir, carbamazepine, azathioprine…
- A few implementation thoughts

The general problem of variable drug response



PharmacoGenomics Research Network

%Δ LDL cholesterol with simvastatin 40 mg



Δ diastolic BP with HCTZ (AA population)

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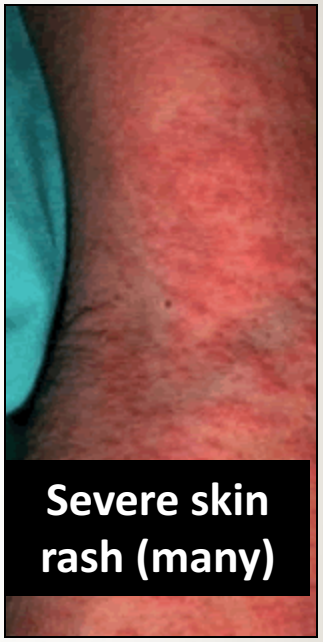
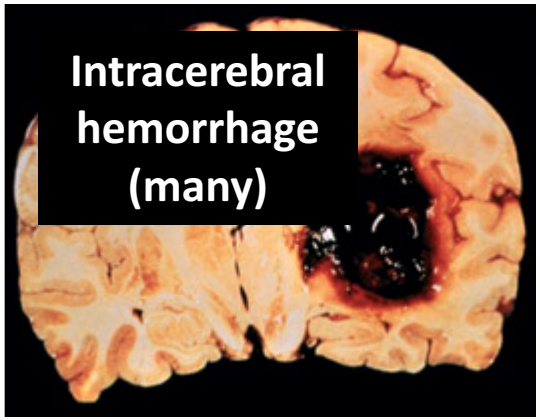
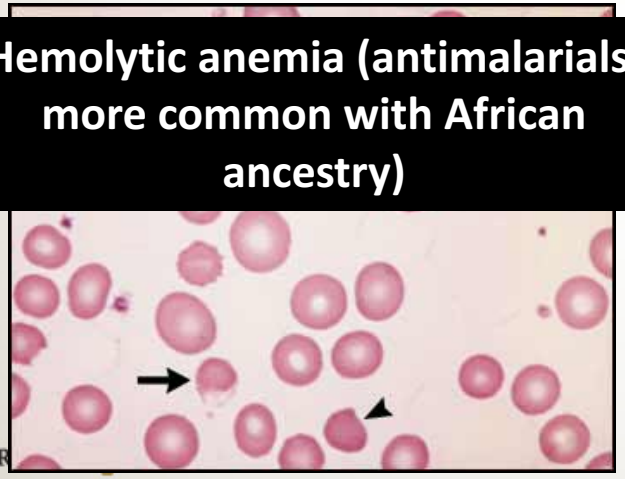
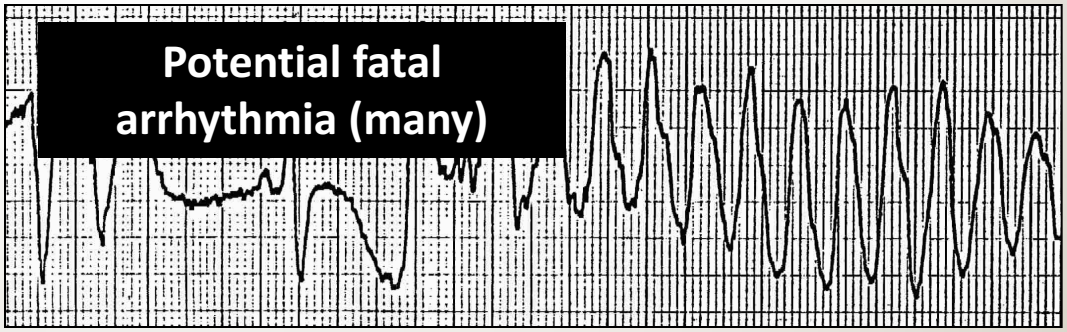
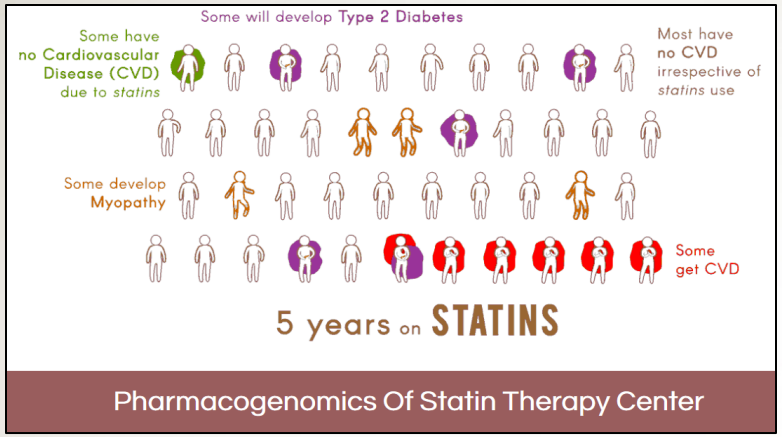
Rare serious adverse drug effects



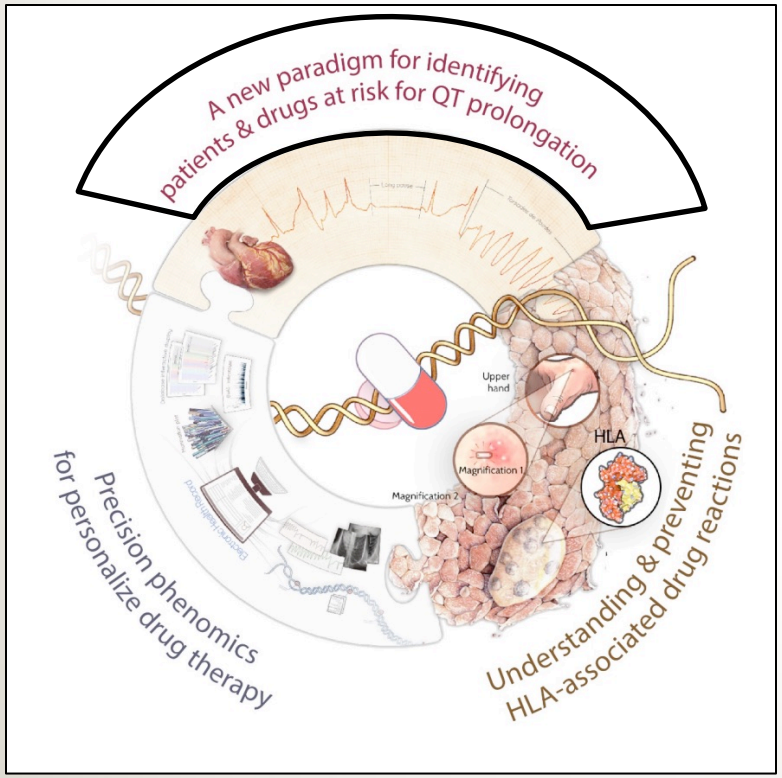




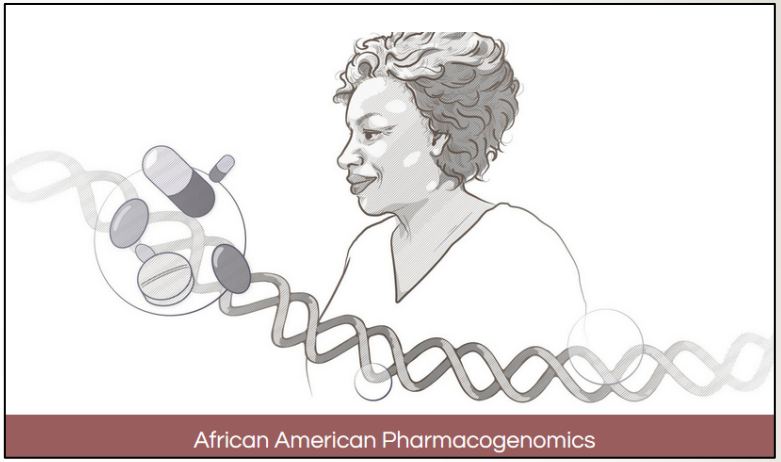




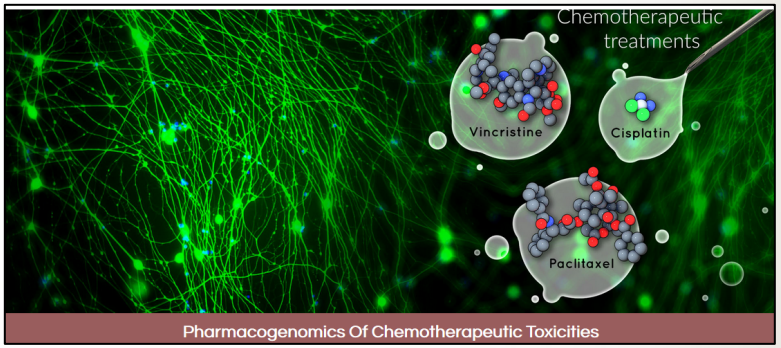
Pharmacogenomics Of Statin Therapy Center



PGRN



African American Pharmacogenomics



Pharmacogenomics Of Chemotherapeutic Toxicities

Biomarkers For Metformin Response

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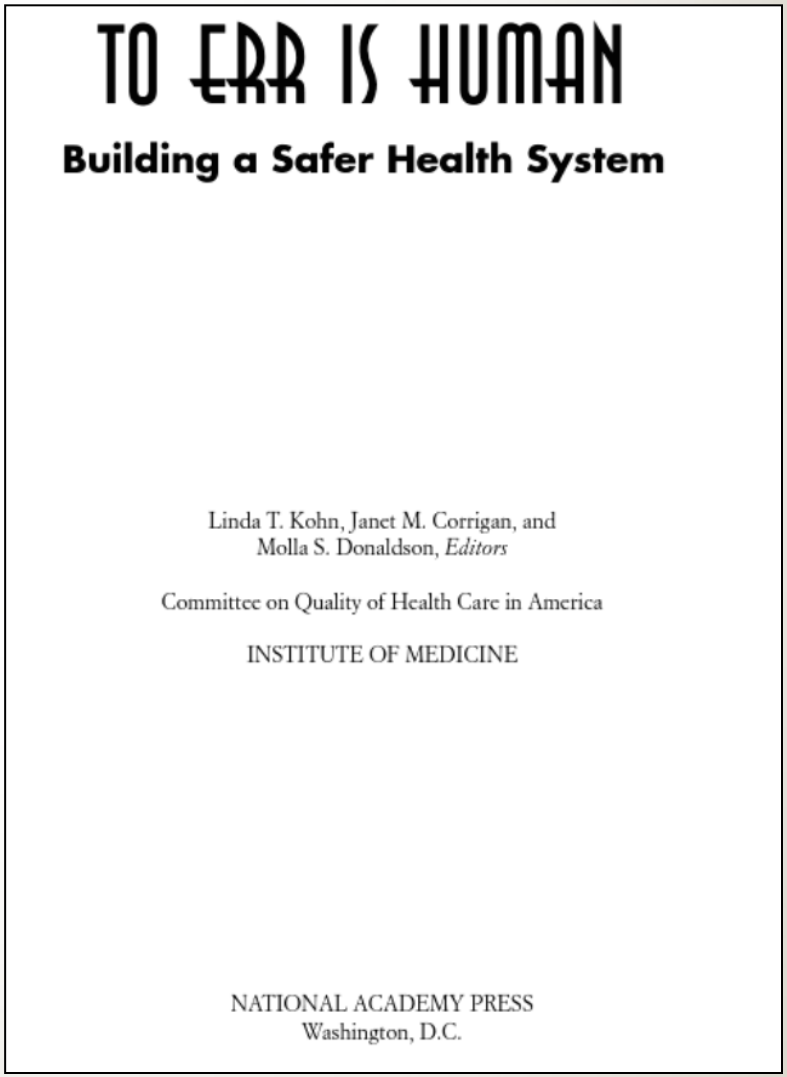
US mortality from adverse drug reactions

1998 estimate:

- 2.2 million adverse drug effects in hospitalized patients
- 106,000 deaths, the 4th – 6th leading cause of death in the US

Lazarou et al



US mortality from adverse drug reactions

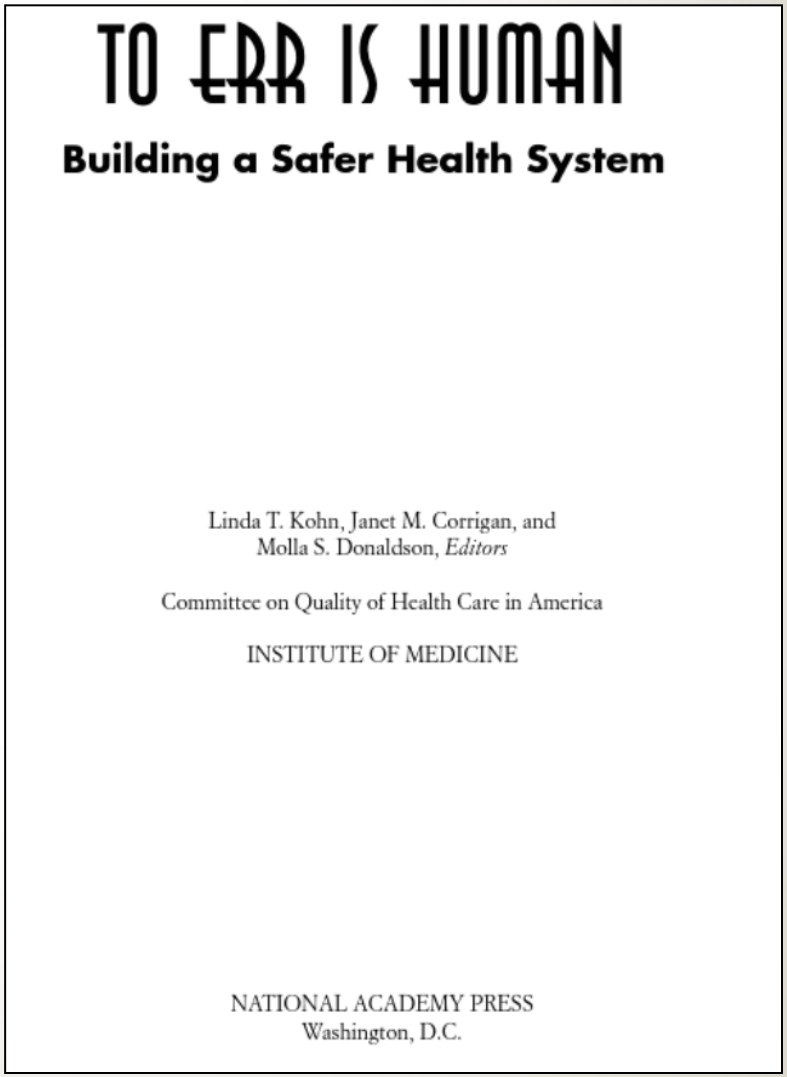
1998 estimate:

- 2.2 million adverse drug effects in hospitalized patients
- 106,000 deaths, the 4th – 6th leading cause of death in the US

Lazarou et al

- 2010: no evidence of change over time

Landrigan et al



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Daily US mortality from adverse drug reactions

Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

Munir Pirmohamed, Sally James, Shaun Meakin, Chris Green, Andrew K Scott, Thomas J Walley, Keith Farrar, B Kevin Park, Alasdair M Breckenridge

6.5% of all admissions associated with an ADR

Table 4 Drugs causing adverse drug reactions

Drug group/drug			ns
NSAIDs			emorrhagic npairment,
Diuretics			lectrolyte
Warfarin			R, haematoma
ACE inhibitors/ AII receptor anta			lectrolyte
Antidepressants			tion, GI bleed,
β blockers			sion, wheezing
Opiates			, urinary retention
Digoxin	36 (2.9)	—	Symptomatic toxic digoxin levels
Prednisolone	31 (2.5)	—	Gastritis, GI bleeding, hyperglycaemia, osteoporotic fracture
Clopidogrel	29 (2.4)	—	GI bleeding

?20-30% have a prominent genetic etiology

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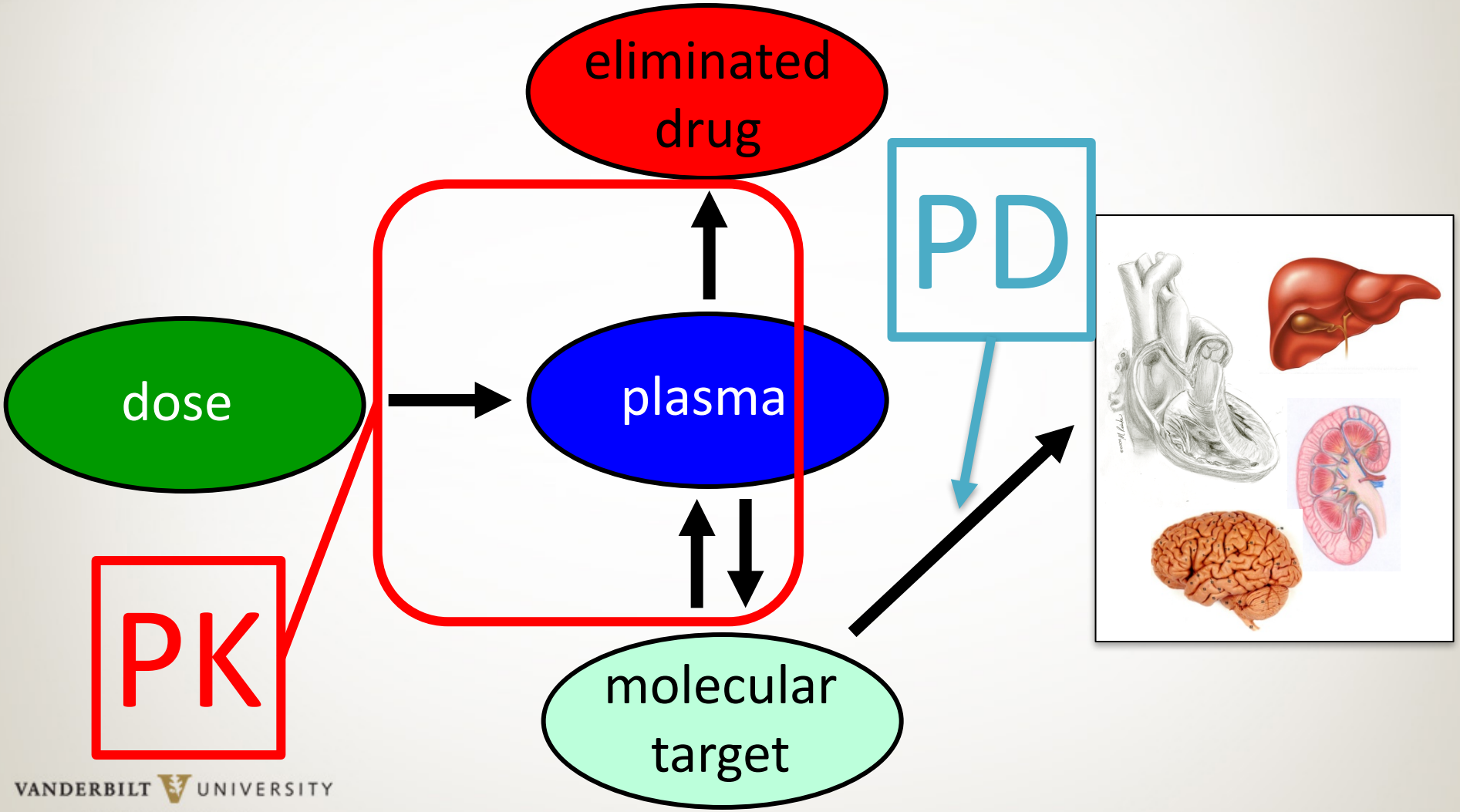
A framework to analyze variable drug actions

Is there a consistent relationship among dose, concentrations, and effects? If not, why not?



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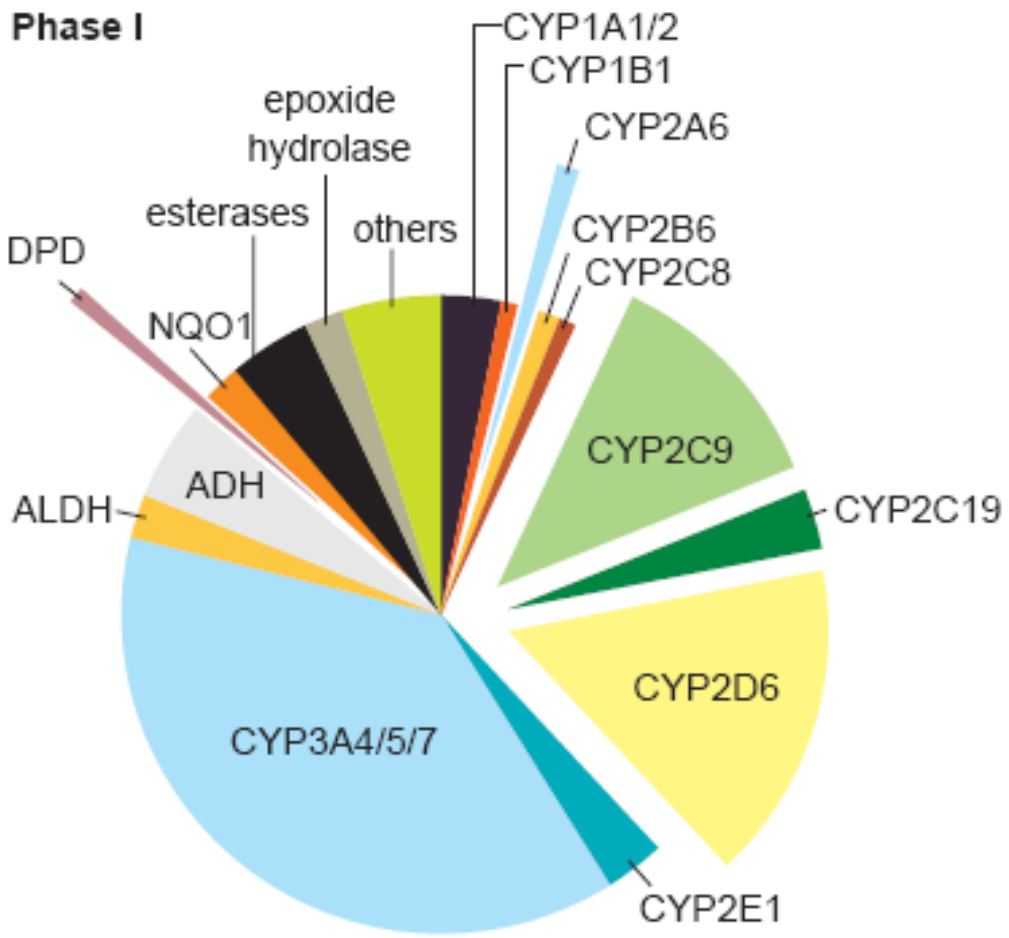
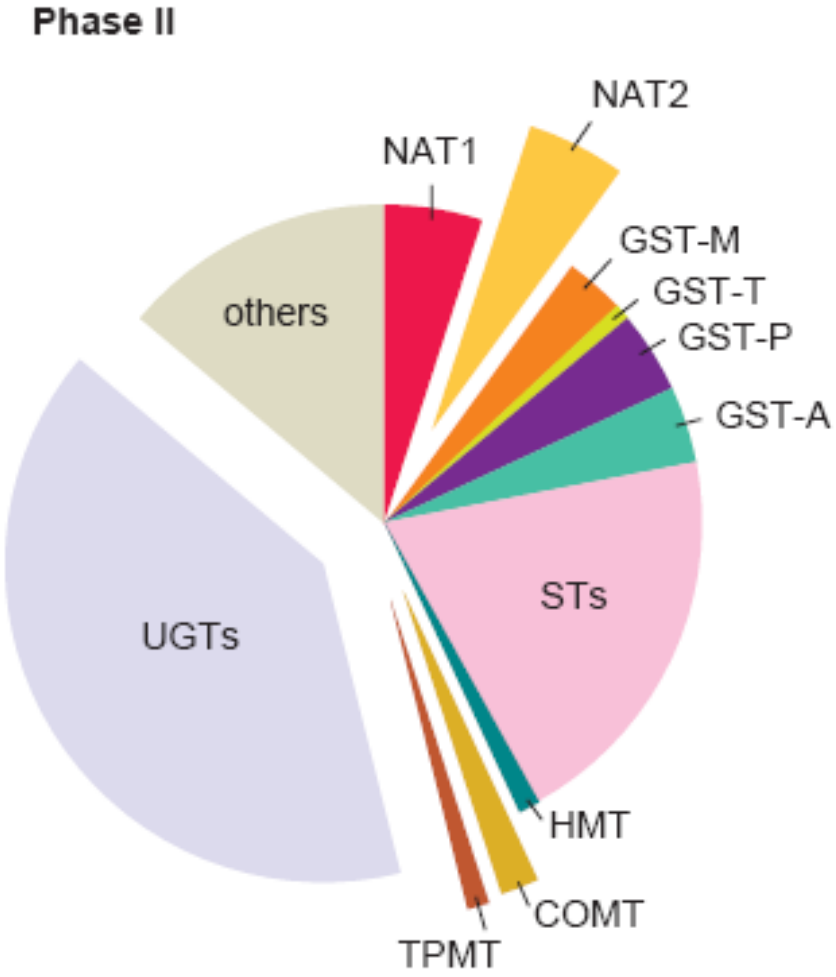
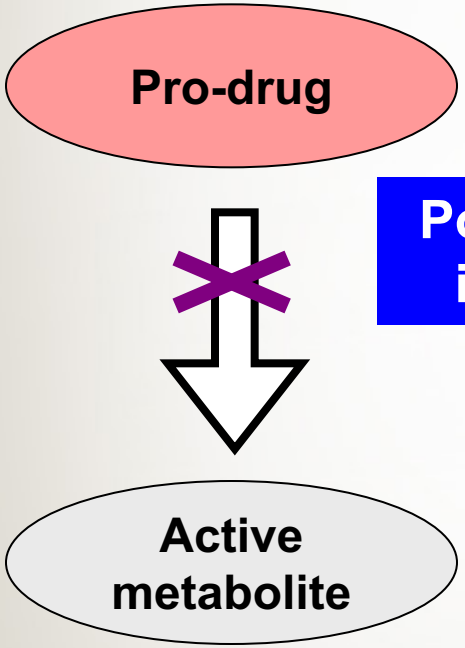




Relling and Evans, 1999

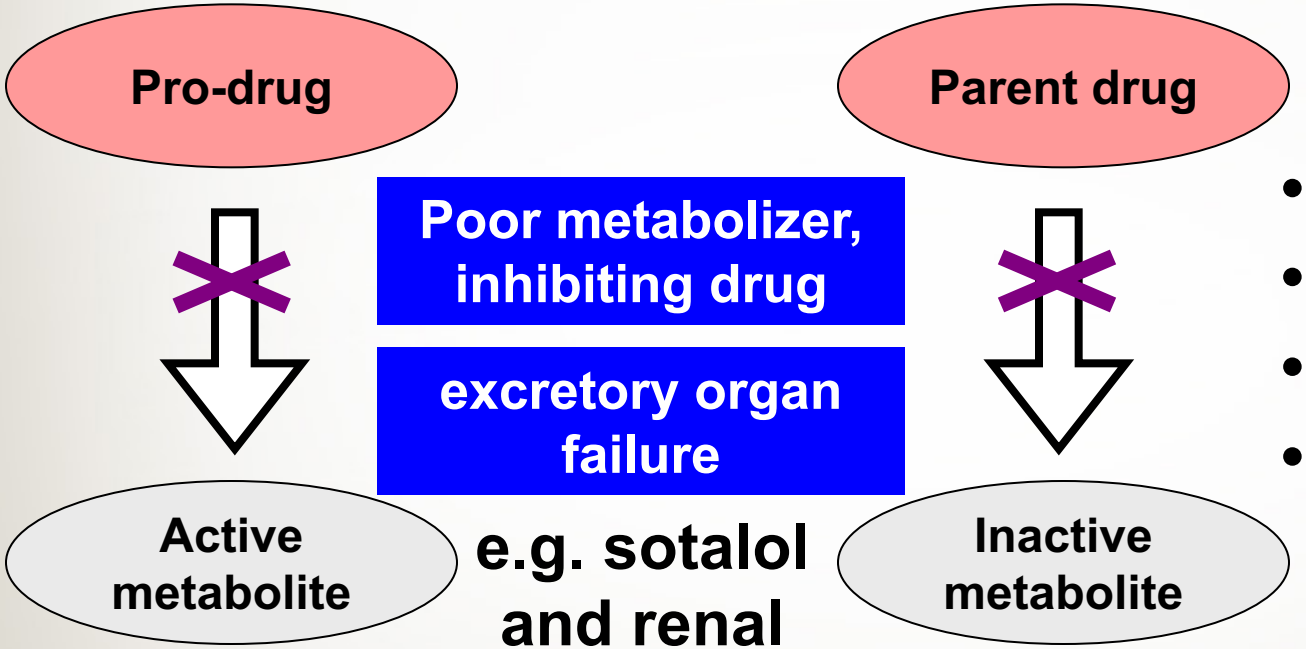
Single pathway to bioactivation:
High-risk pharmacokinetics



- encainide
- **clopidogrel**
- **tamoxifen**
- **codeine**

Narrow therapeutic index + Single pathway to elimination:

High-risk pharmacokinetics (2)



- debrisoquine
- warfarin
- irinotecan
- azathioprine

0090-9556/89/1703-0265$02.00/0
DRUG METABOLISM AND DISPOSITION
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CHARACTERIS **MAN LIVER**

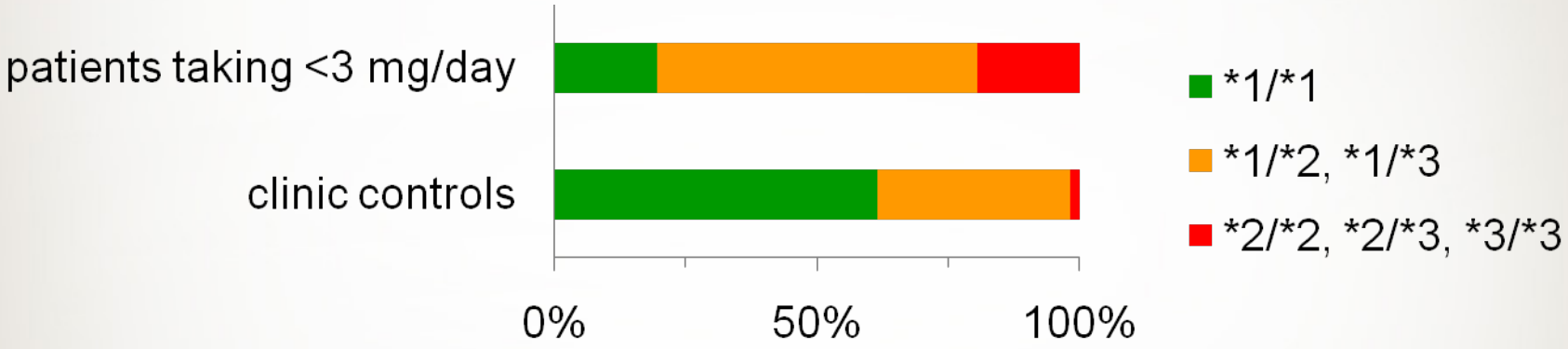
ALLAN E. F . TRAGER

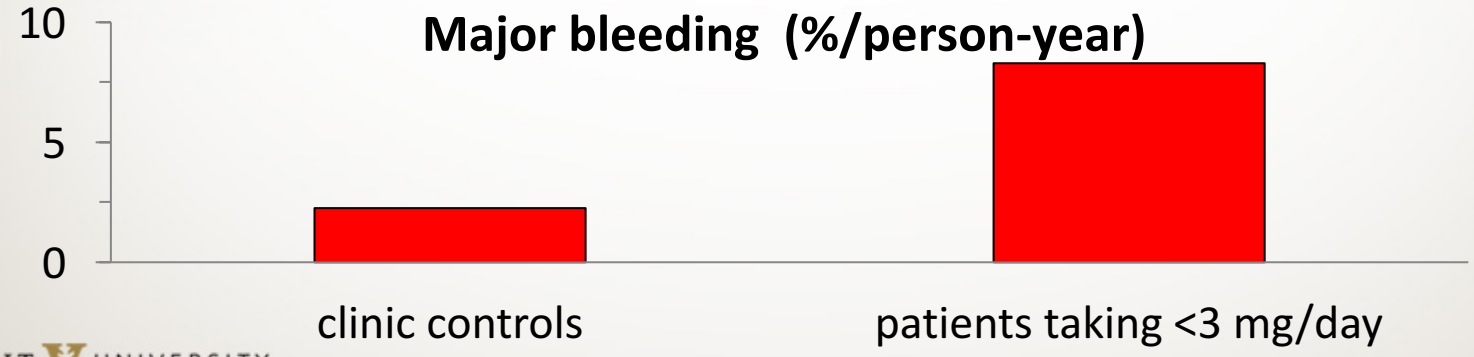
Pharmacogenetics (1994) 4, 39–42

Short communication

Impaired (*S*)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9

Allan E. Rettie,[1]* Larry C. Wienkers,[1] Frank J. Gonzalez,[2] William F. Trager[1] and Kenneth R. Korzekwa[2]





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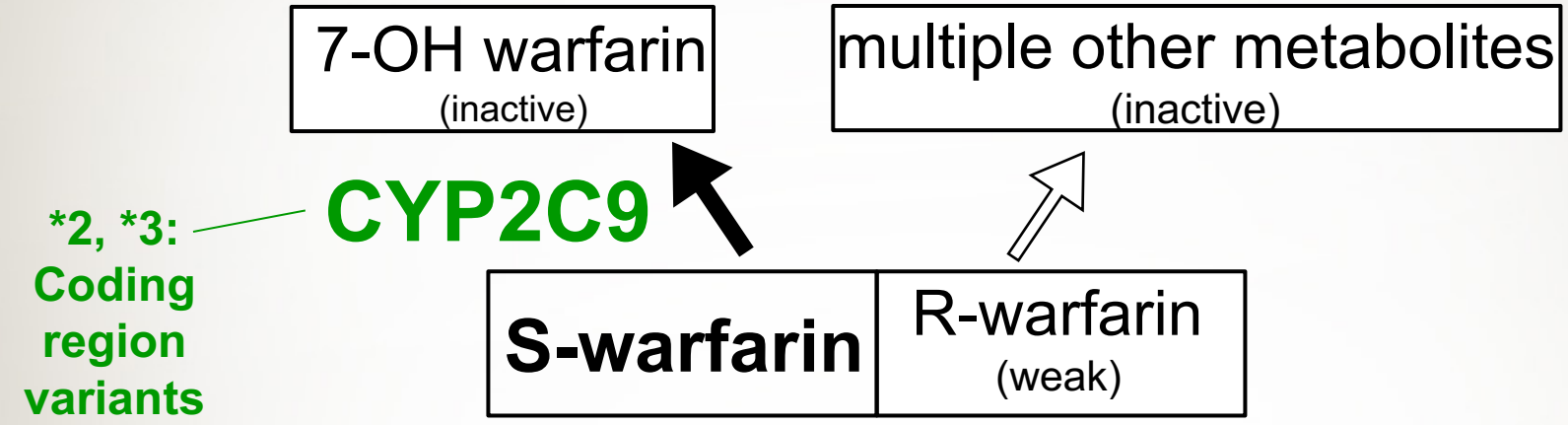
Aithal et al., Lancet 1999

Multiple gene effect

The warfarin pathway



Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2

Simone Rost[1,2*], Andreas Fregin[1*], Vytautas Ivaskevicius[3], Ernst Conzelmann[4], Konstanze Hörtnagel[2], Hans-Joachim Pelz[5], Knut Lappegard[6], Erhard Seifried[3], Inge Scharrer[7], Edward G. D. Tuddenham[8], Clemens R. Müller[1], Tim M. Strom[2,9] & Johannes Oldenburg[1,3]

letters to nature

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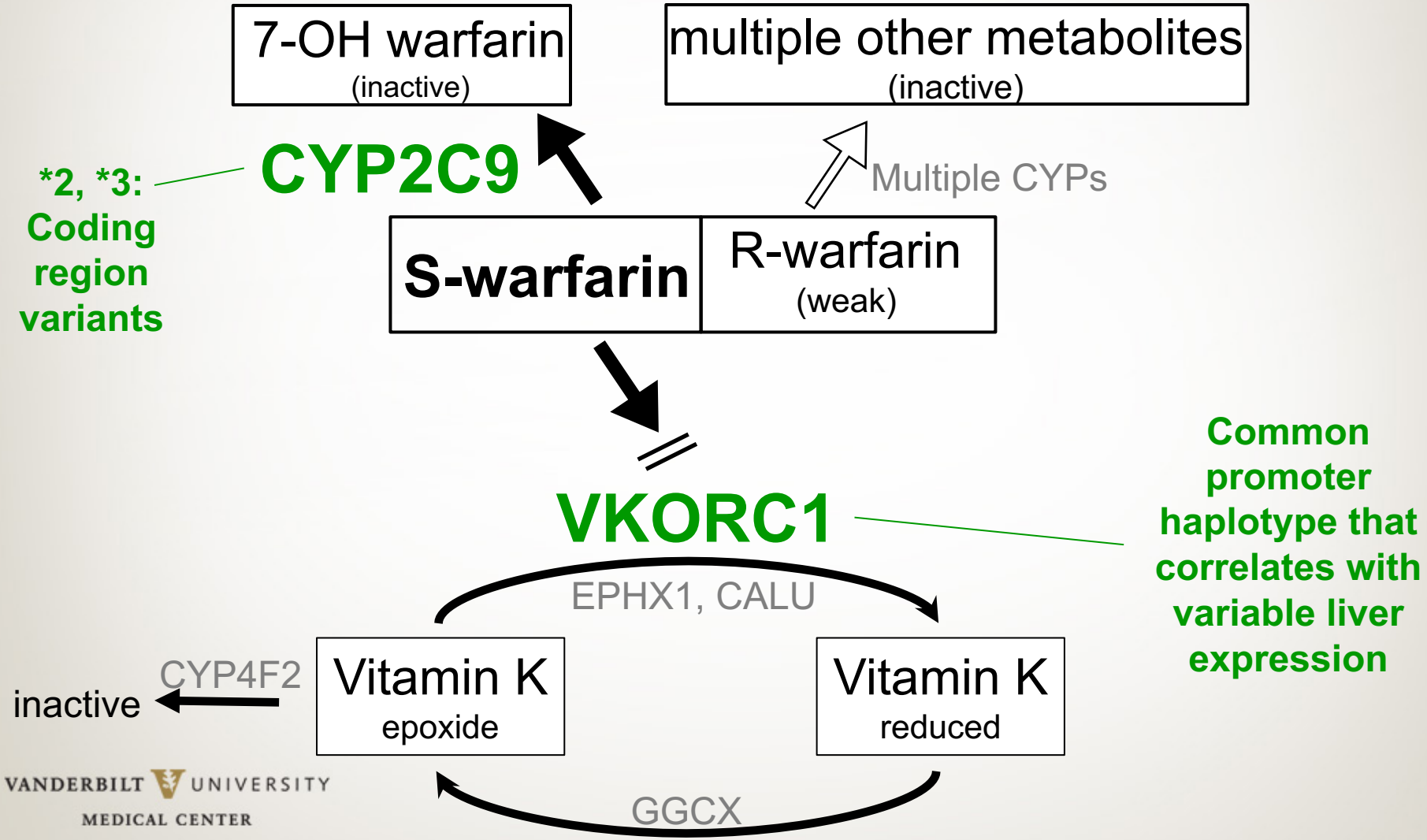
Multiple gene effect

The warfarin pathway



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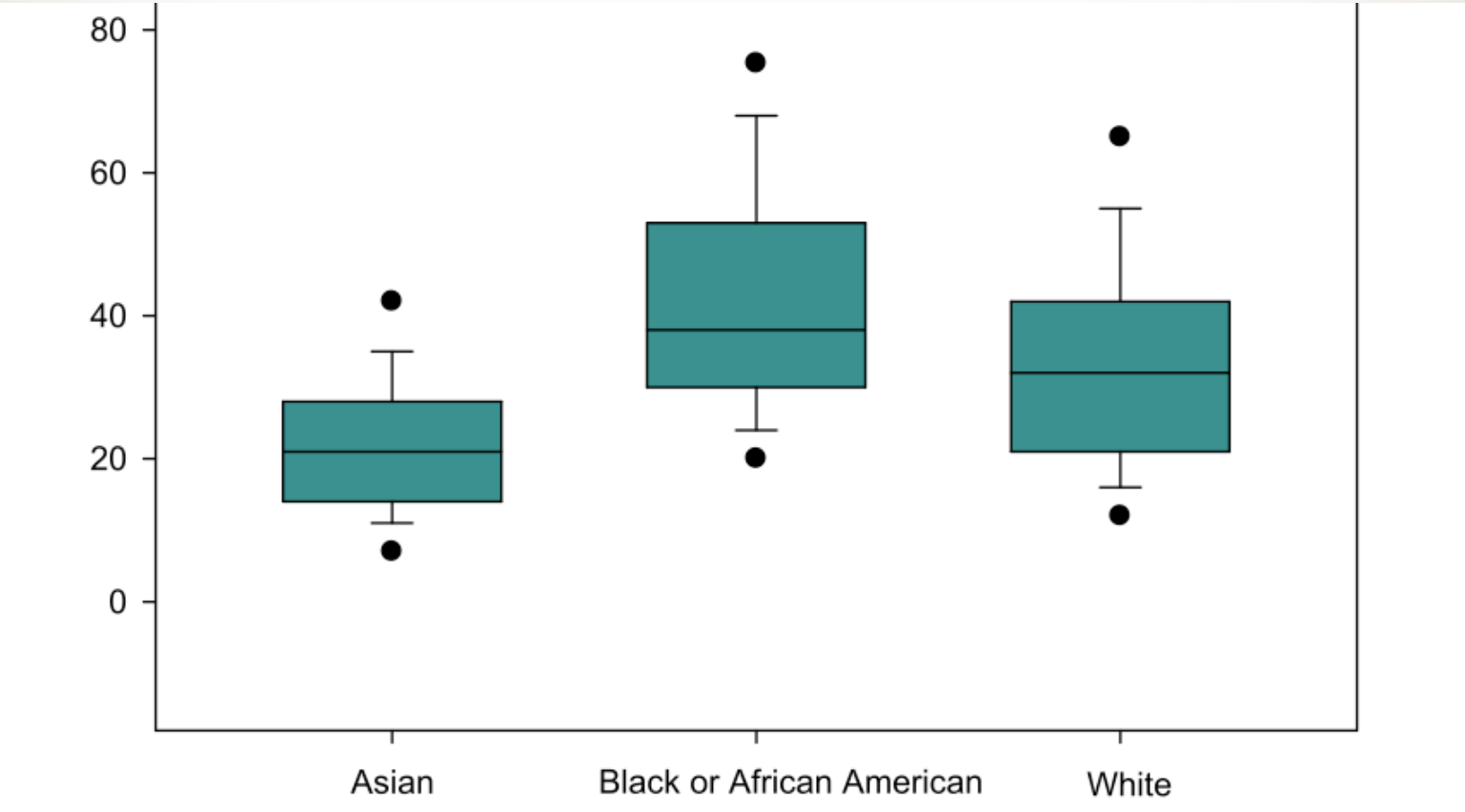
The International Warfarin Pharmacogenomics Consortium

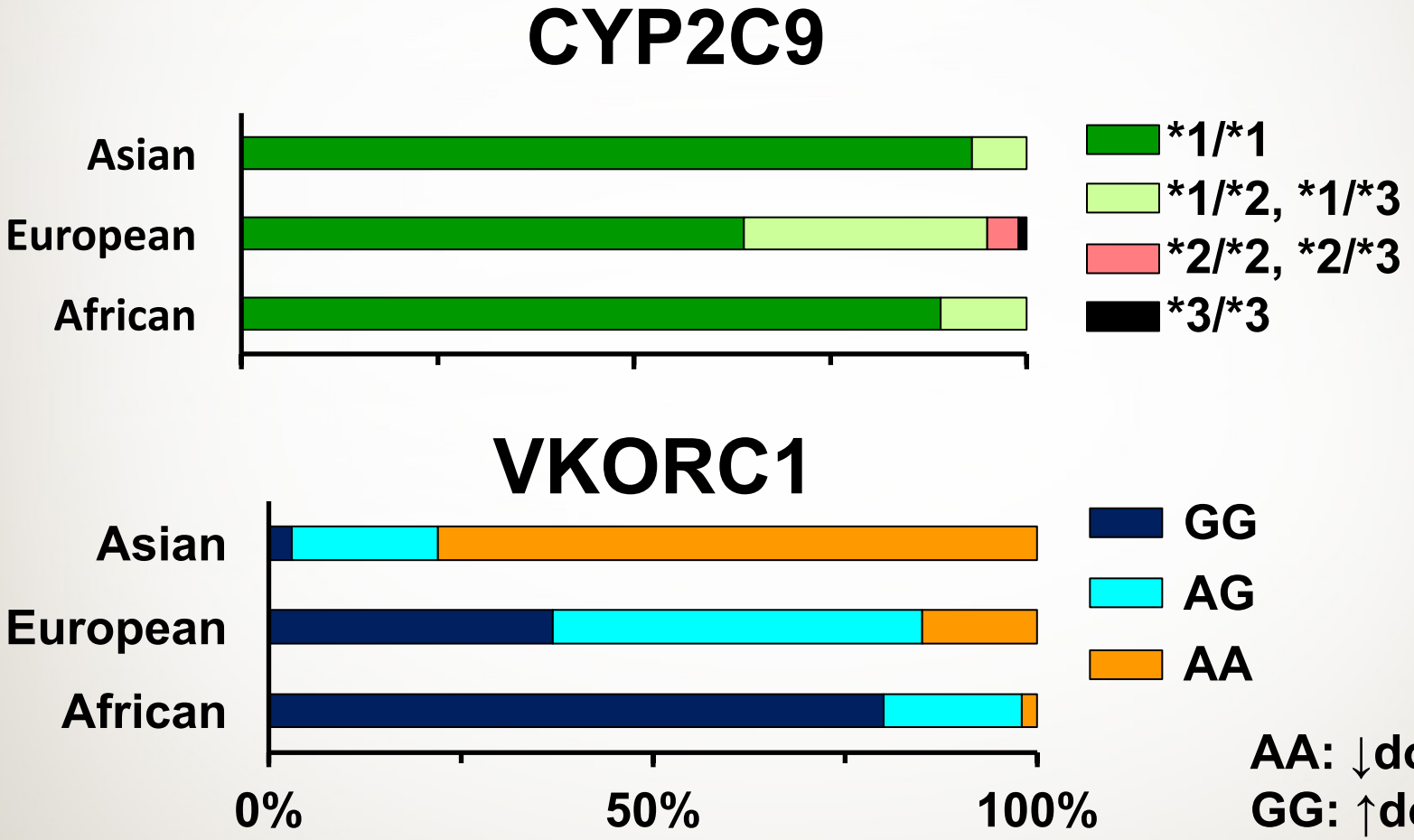
>5000 patients with genetic information and outcomes

- 55% Caucasian
- 10% African
- 31% Asian

Average weekly warfarin doses for stable INR



CYP2C9 and VKORC1 genotypes vary by ethnicity



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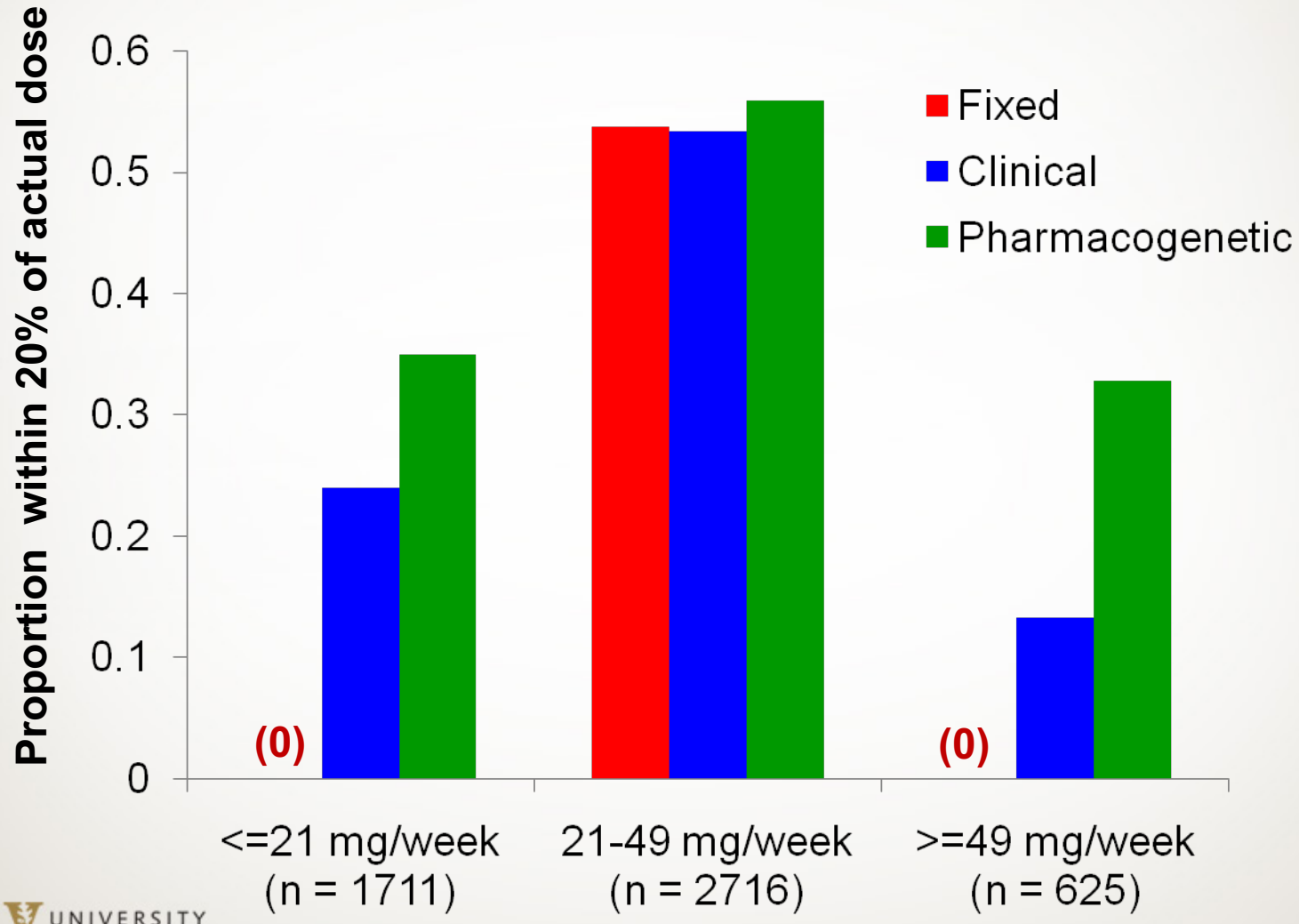
Comparing dosing algorithms

For most patients, average dosing is OK



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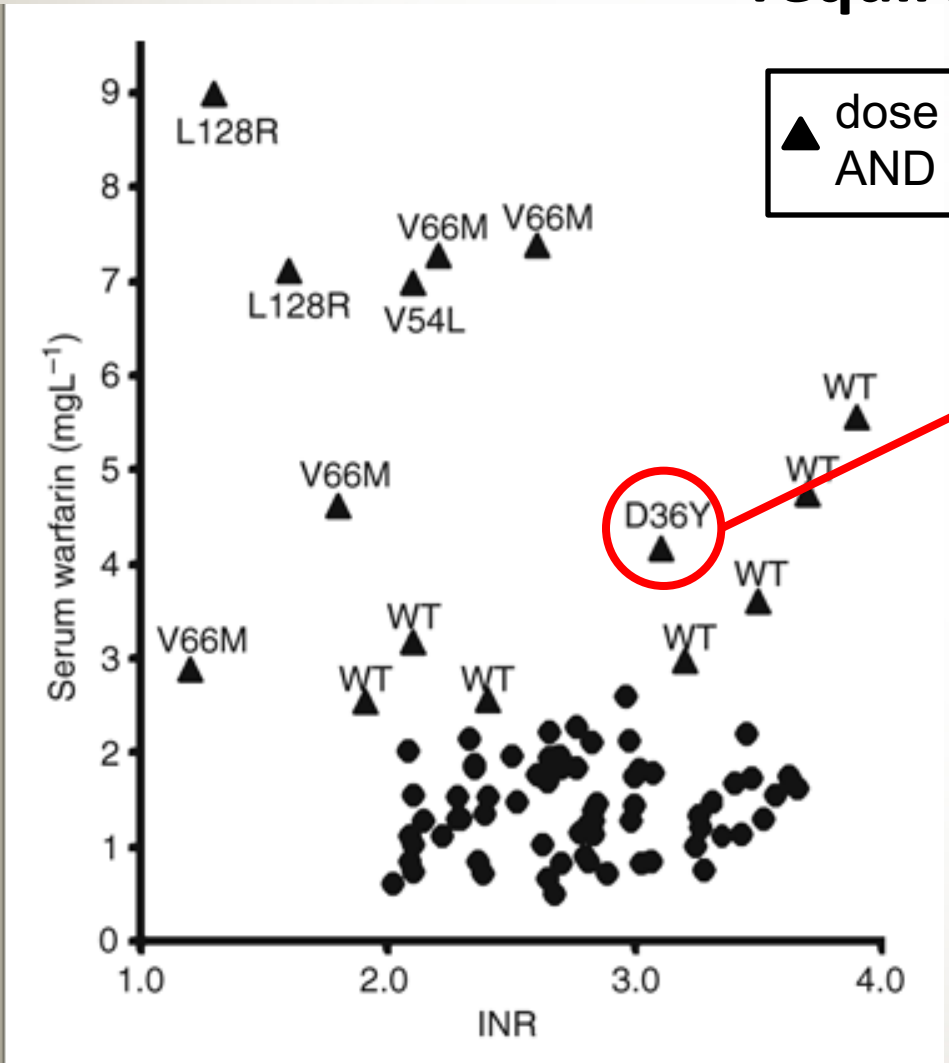
Warfarin: not so simple….

Rare variants in VKORC1 associated with high dose requirements



▲ dose requirement >20 mg/day
AND serum warfarin >2.3

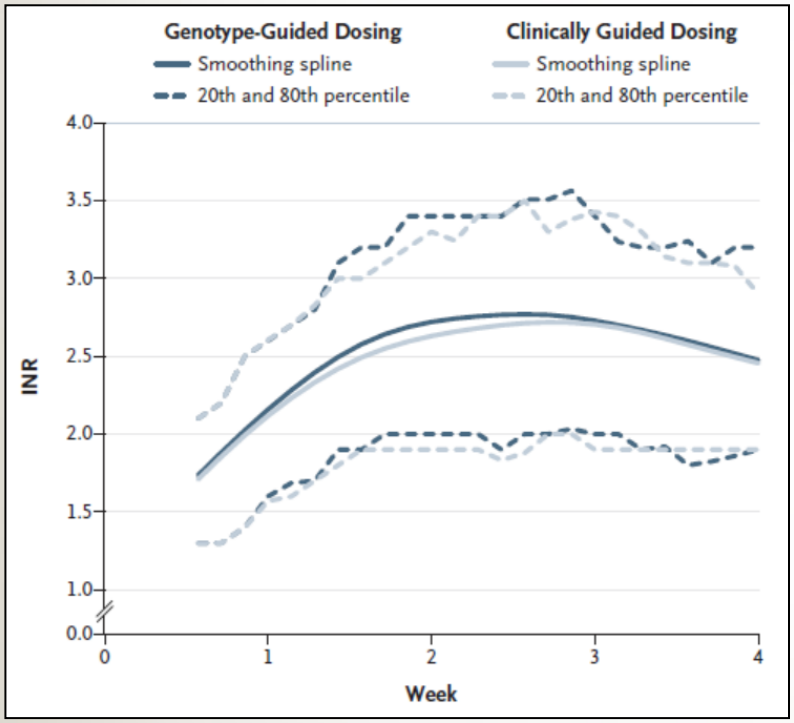
identified in 8/15 Ashkenazi patients requiring >11 mg/day

May 2017: 231 non-synonymous variants in *VKORC1* in gnomAD

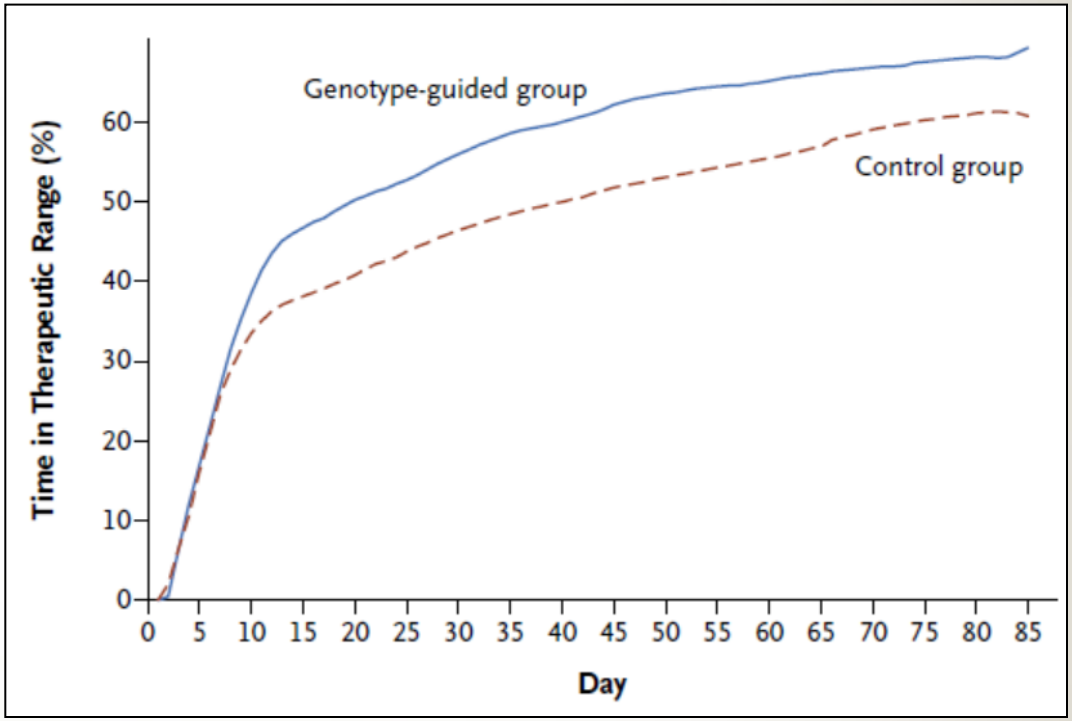
Harrington et al., 2008

RCTs comparing genotype-guided vs conventional dosing for warfarin

time in INR range during drug initiation



Kimmel et al, 2013



Pirmohamed et al, 2013

RCTs comparing genotype-guided vs conventional dosing for warfarin

time in INR range during drug initiation

Table 3. Adverse Events through Day 28 of Warfarin Therapy.

Outcome	Genotype-Guided Group (N=514)	Clinically Guided Group (N=501)	Hazard Ratio (95% CI)*	P Value
	no. (%)			
Any INR ≥4, major bleeding, or thromboembolism†	105 (20)	103 (21)	1.01 (0.77–1.33)	0.93
Any INR ≥4	100 (19)	92 (18)	1.08 (0.81–1.44)	0.59
Major bleeding‡	4 (1)	10 (2)	0.41 (0.13–1.31)	0.13
Thromboembolism	5 (1)	4 (1)	1.27 (0.34–4.73)	0.72
Clinically relevant nonmajor bleeding§	13 (3)	20 (4)	0.62 (0.30–1.27)§	0.18
Death from any cause	2 (<1)	1 (<1)	2.09 (0.19–23.22)	0.55

Kimmel et al, 2013

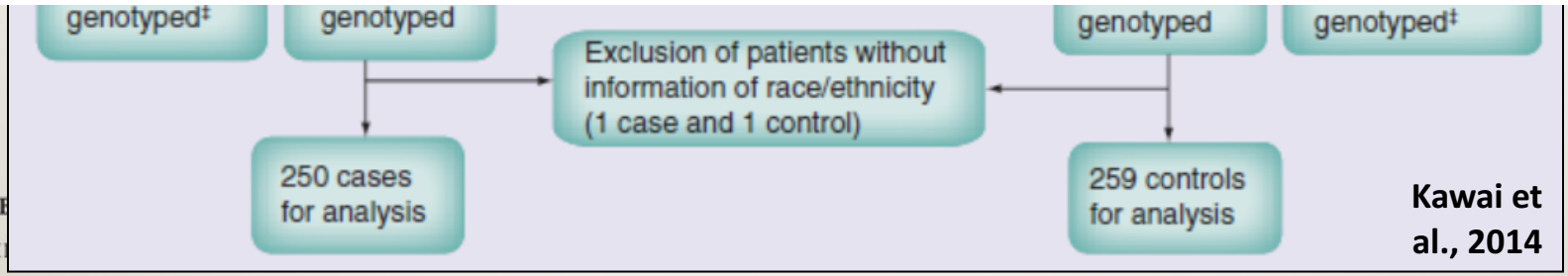
Bleeding during long-term therapy

- Patient ≥18 years old
- Warfarin or coumadin mentioned in EMR with associated dose within 7 days of admission date
- Admitted after 01/01/2006

Table 4. Genotype and risk of major bleeding.

Genotype	Simple model, OR (95% CI)	Full model, OR (95% CI)
VKORC1 rs9923231	0.98 (0.75,1.29)	0.96 (0.72,1.27)
*CYP2C9*2* carrier	0.82 (0.57,1.20)	0.84 (0.57,1.24)
*CYP2C9*3* carrier	1.94 (1.08,3.49)	1.75 (0.95,3.21)
CYP4F2	0.83 (0.63,1.10)	0.85 (0.64,1.14)
*CYP2C9 *2 +*3*†	1.07 (0.77,1.48)	1.02 (0.73,1.43)

Simple model: Adjusted for age, sex, race, body surface area, log[time on warfarin].
Full model: Adjusted for the same covariates as in the simple model + *VKORC1*, *CYP2C9*2*, *CYP2C9*3*, *CYP4F2* genotype, number of warfarin inhibitors, number of warfarin potentiators, use of antiplatelet agents and nonsteroidal anti-inflammatory drugs, previous bleeding without warfarin and atrial fibrillation and venous thromboembolism as indication for warfarin.
†Additive model where 0 allele = 0, 1 allele = 1 and 2 allele = 2 (e.g., **1/*1* = 0, **1/*2* = 1, **1/*3* = 1, **2/*2* = 2, **2/*3* = 2, **3/*3* = 2).
OR: Odds ratio.



Kawai et al., 2014

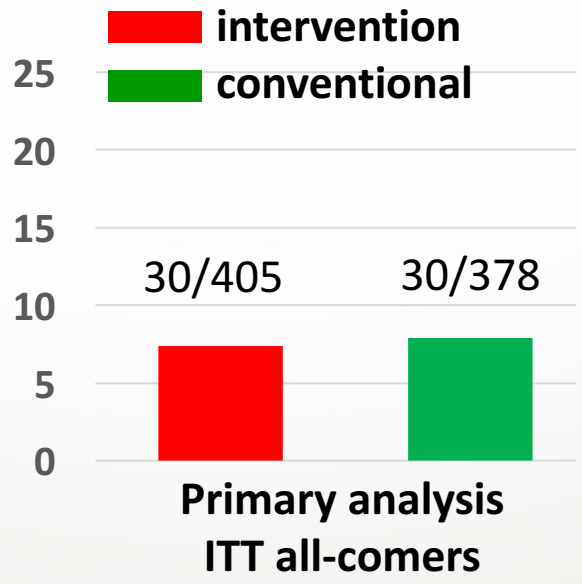
Genetics Informatics warfarin Trial (GIFT): what we know

- 1650 patients post hip/knee surgery and receiving warfarin randomized to PGx or conventional guided therapy. INR targets randomized to 1.8 or 2.5 in each group.
- Composite primary outcome: Major bleeding at 30 days, INR≥4 at 30 days, death within 30 days, VTE within 60 days of surgery.
- Genetics beat conventional: 10.8% vs. 14.7%; RR = 0.73; 95% CI, 0.56-0.95

Added value of PGx (TPMT) for azathioprine in IBD

- conventional = 378; Intervention = 405
- Intervention: dose adjustment in heterozygous and homozygous variant carriers
- No difference in disease activity across groups

% with hematologic ADR



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Coenen et al., Gastroenterology 2015

The Stevens-Johnson syndrome

A terrible adverse drug reaction

The Stevens-Johnson syndrome

A terrible and predictable adverse drug reaction

	Abacavir hypersensitive (n=18)	Abacavir tolerant (n=167)	Odds ratio (95% CI)	p_c
*HLA-B*5701*	14 (78%)	4 (2%)	117 (29–481)	<0·0001
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73 (20–268)	<0·0001
*HLA-B*5701, HLA-DR7, HLA-DQ3*	13 (72%) ..	0 (0%) ..	822 (43–15 675)	<0·0001 ..

Mallal et al., Lancet 2002

The Stevens-Johnson syndrome

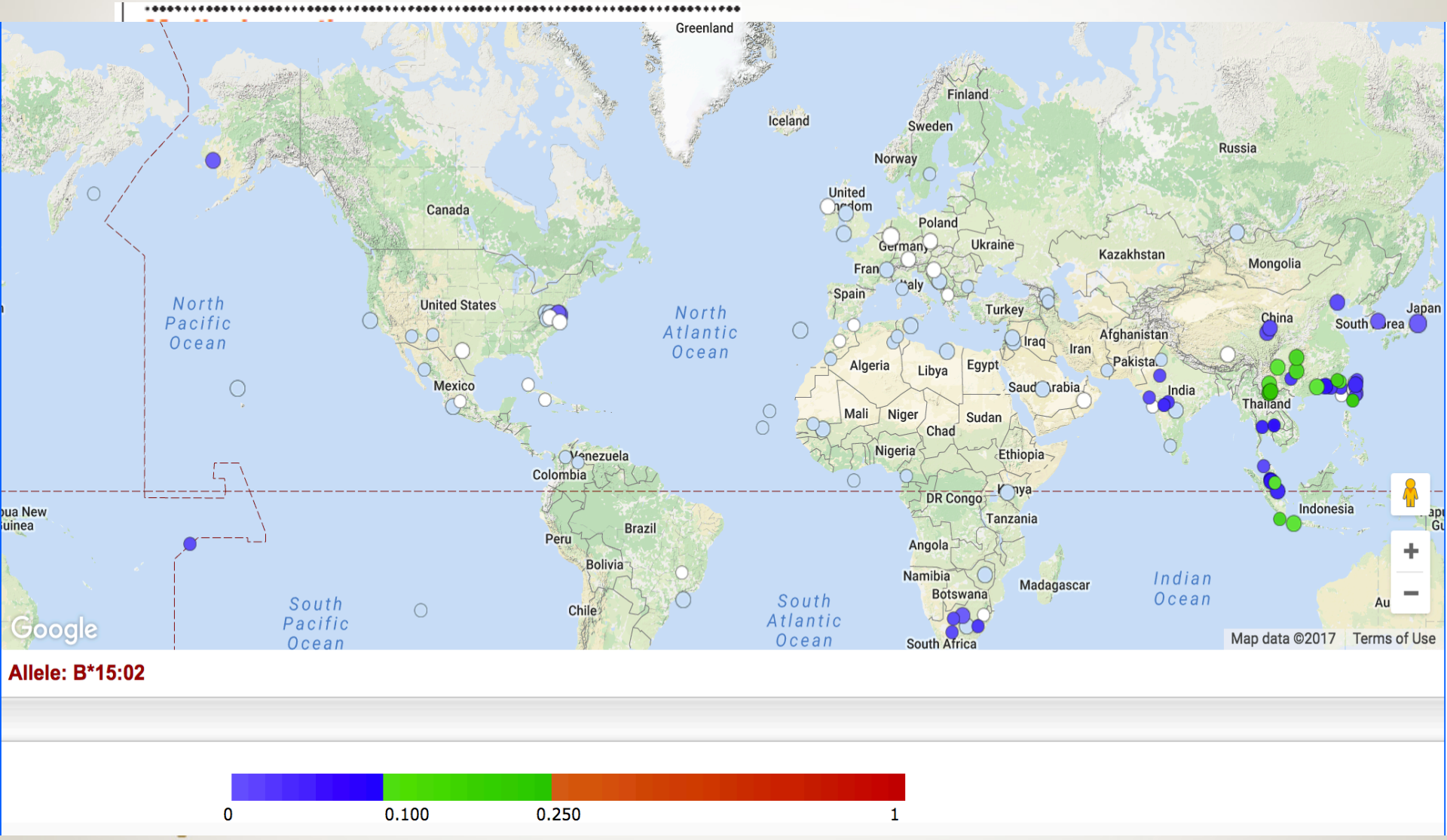
A terrible and predictable and preventable adverse drug reaction

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

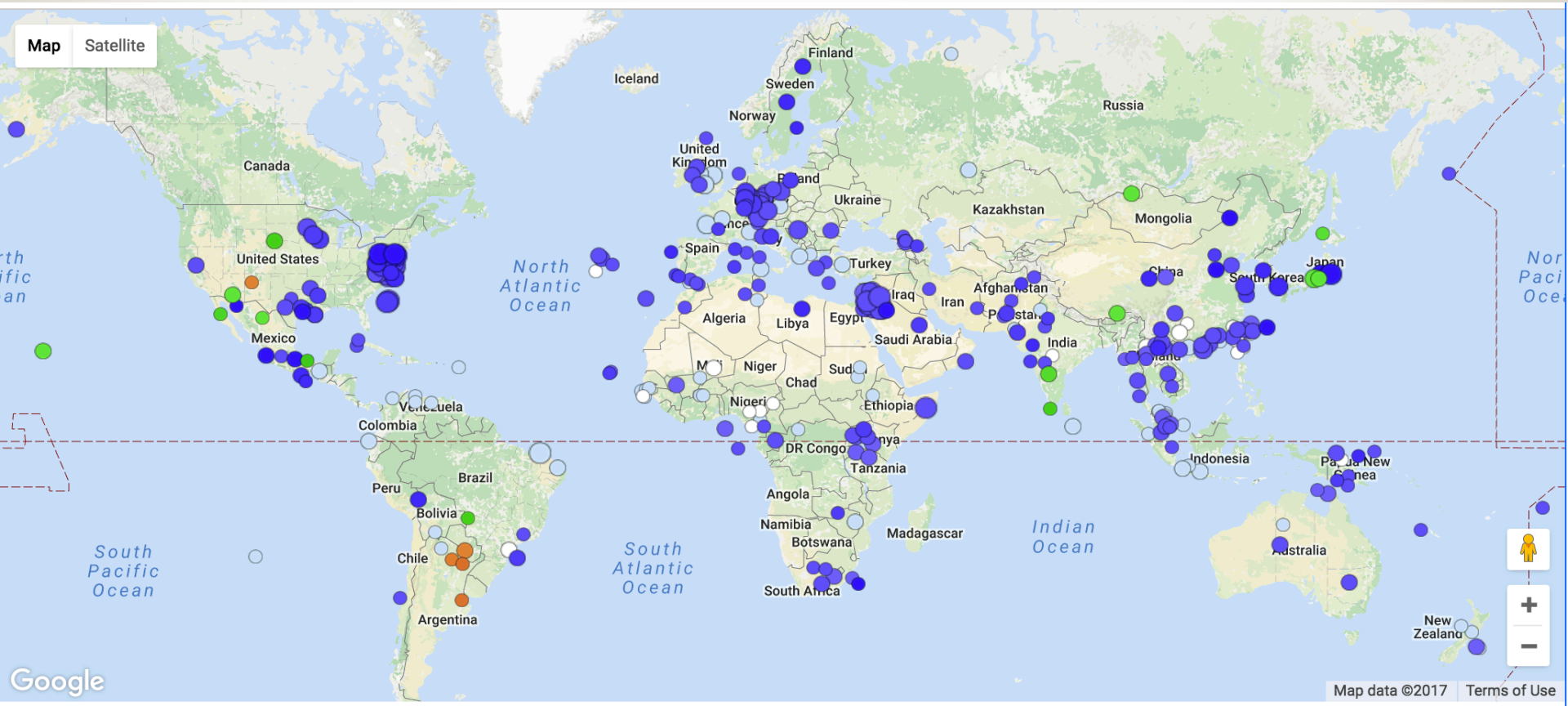
Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

Mallal, Phillips et al., NEJM 2008

Distribution of HLA-B*15:02



Distribution of HLA-A*31:01



Allele: A*31:01

The Hong Kong carbamazepine experience after implementing a genetic testing policy

Chen et al., Neurology 2014

- New prescriptions for carbamazepine fell from 16.2% (10,077/62,056) to 2.6% (1,910/74,606) ($p < 0.001$)
- SJS/TEN related to carbamazepine fell from 0.24% (20/8,284) to 0% (0/1,076; $p = 0.027$)
- Prescriptions for other antiepileptic drugs increased.
- SJS/TEN induced by phenytoin increased (0.15% [18/11,839] vs 0.26% [33/12,618], $p = 0.058$)
- Overall incidence of SJS/TEN remained unchanged (0.09% [42/45,832] vs 0.07% [39/55,326], $p = 0.238$).
- **Implementation requires education**

Implementing pharmacogenetics

"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

82 year old man on sotalol for paroxysmal AF develops renal failure and torsades

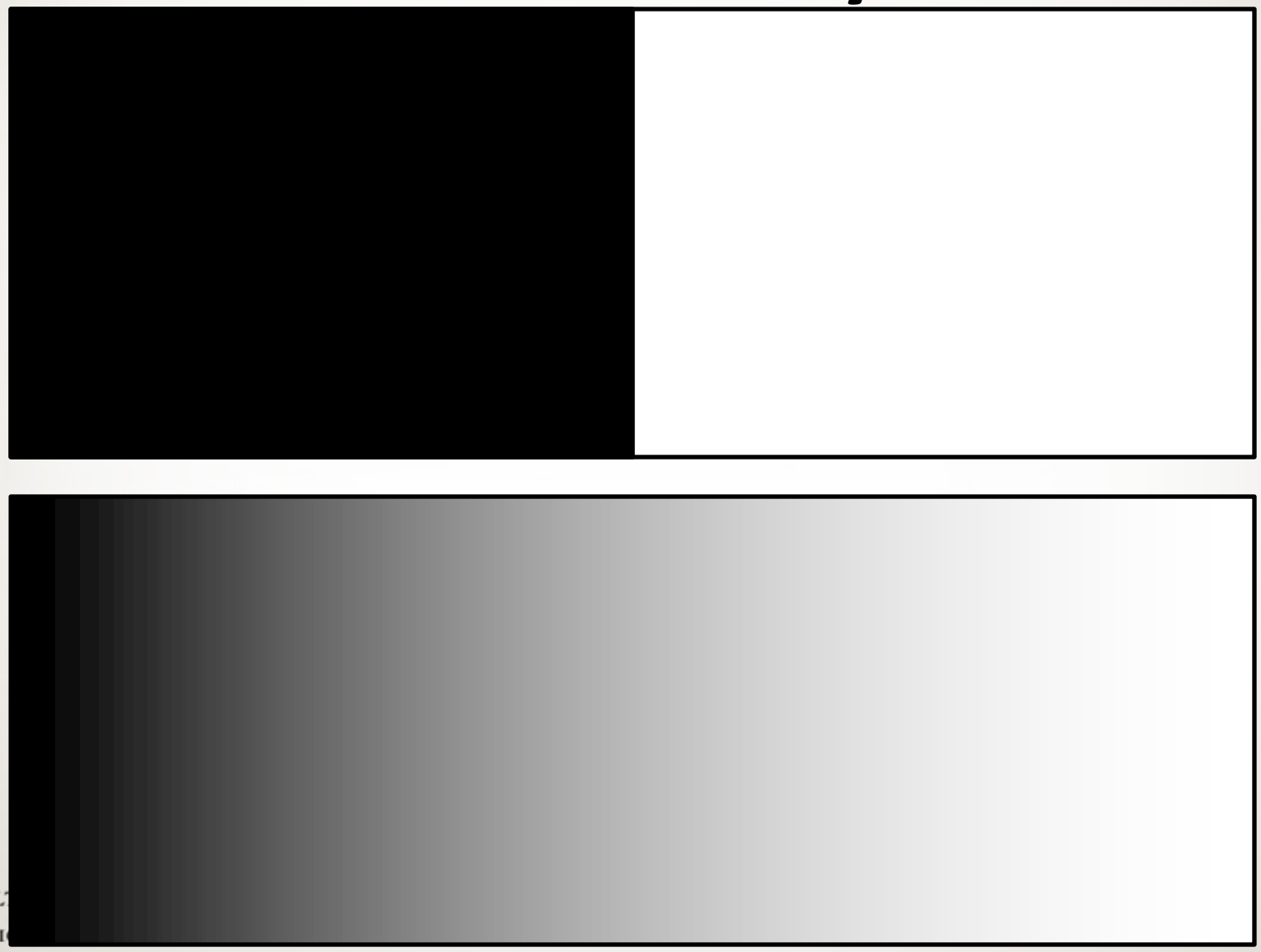
DOSAGE IN RENAL IMPAIRMENT

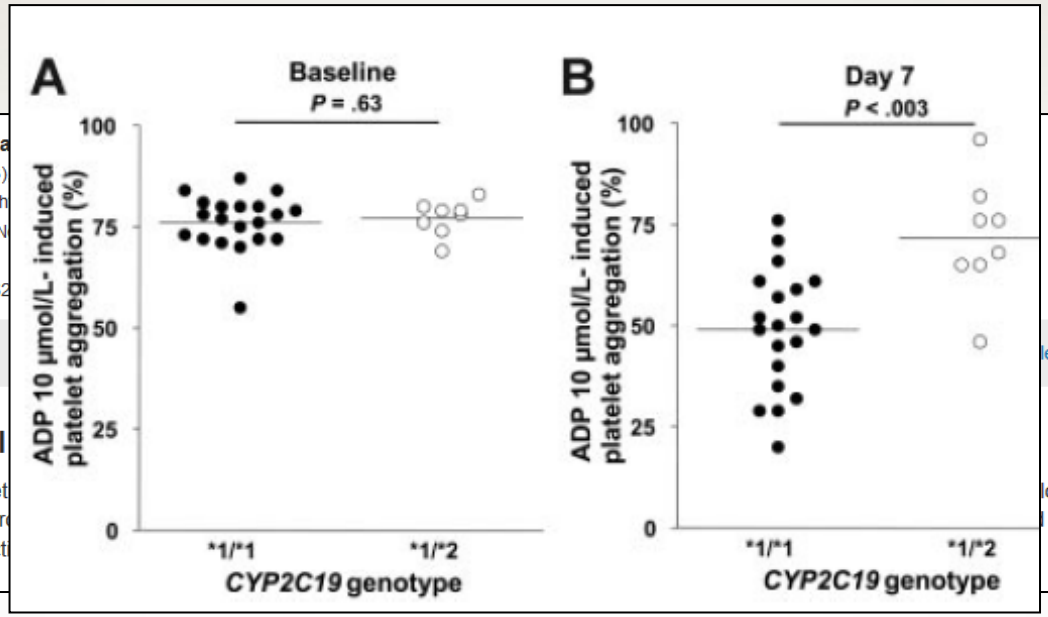
Adults

Because sotalol is excreted predominantly in urine and its terminal elimination half-life is prolonged in conditions of renal impairment, the dosing interval (time between divided doses) of sotalol should be modified (when creatinine clearance is lower than 60 mL/min) according to the following table.

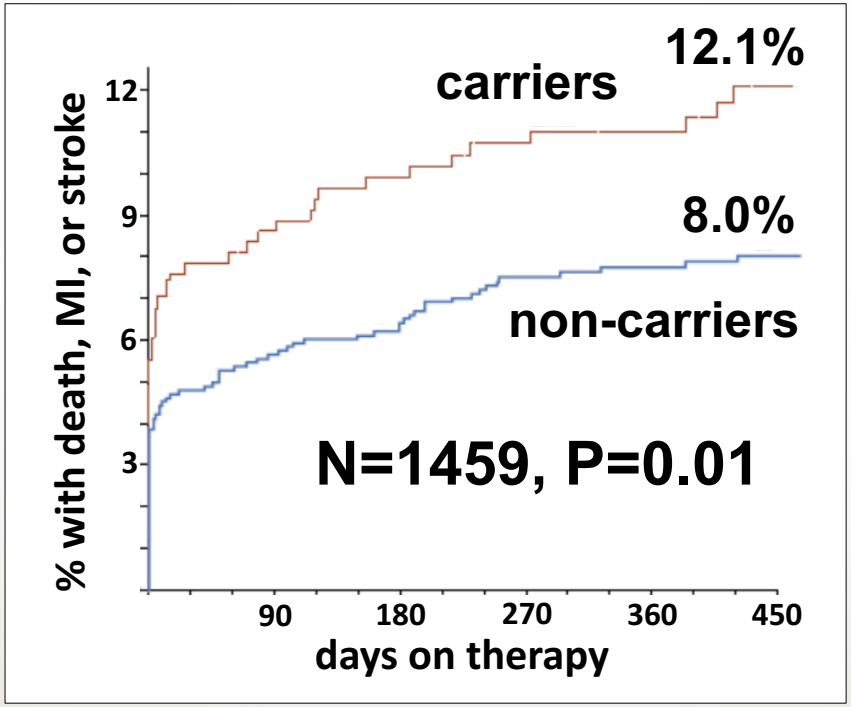
There is no randomized clinical trial to support this recommendation

Genetic data, prediction, and "actionability"



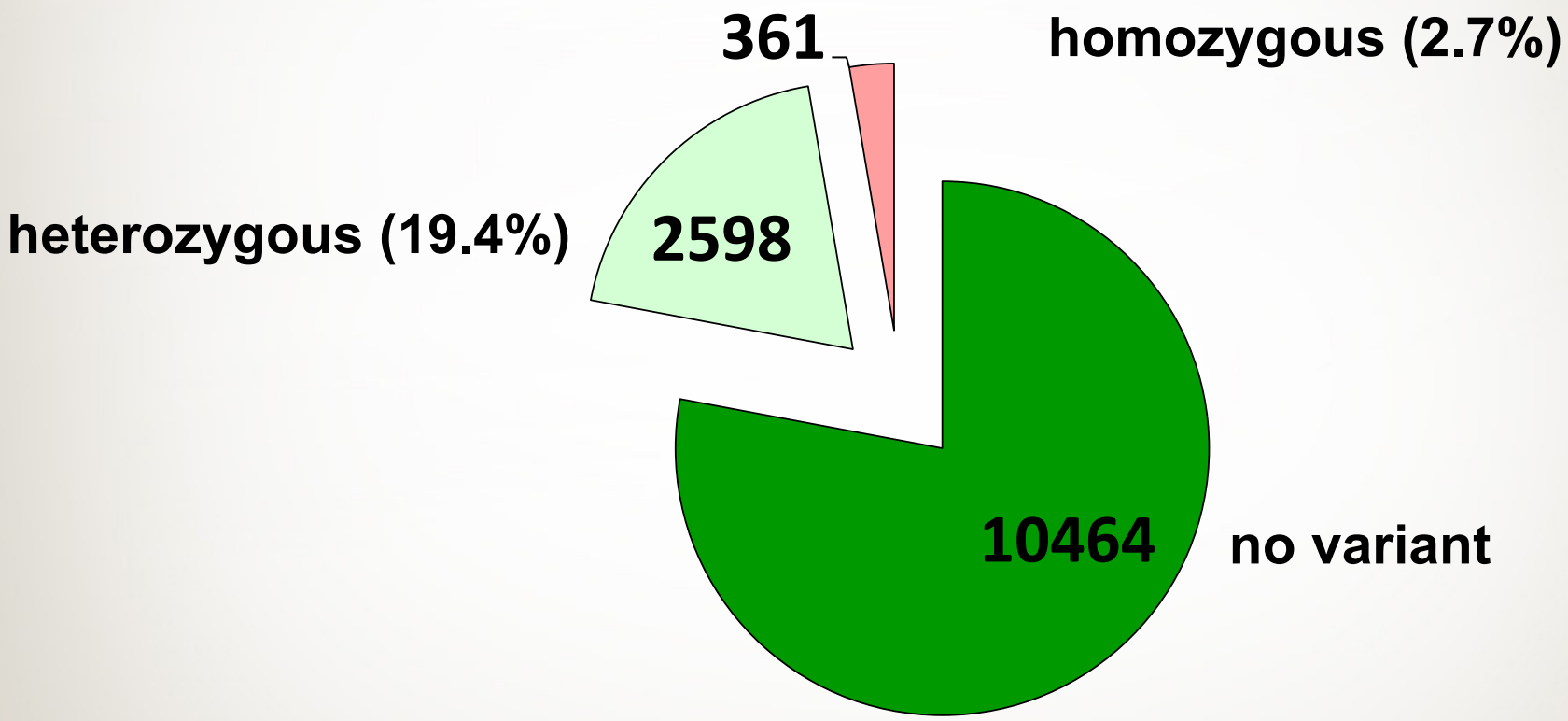


Hulot et al., 2006



Mega et al., 2009

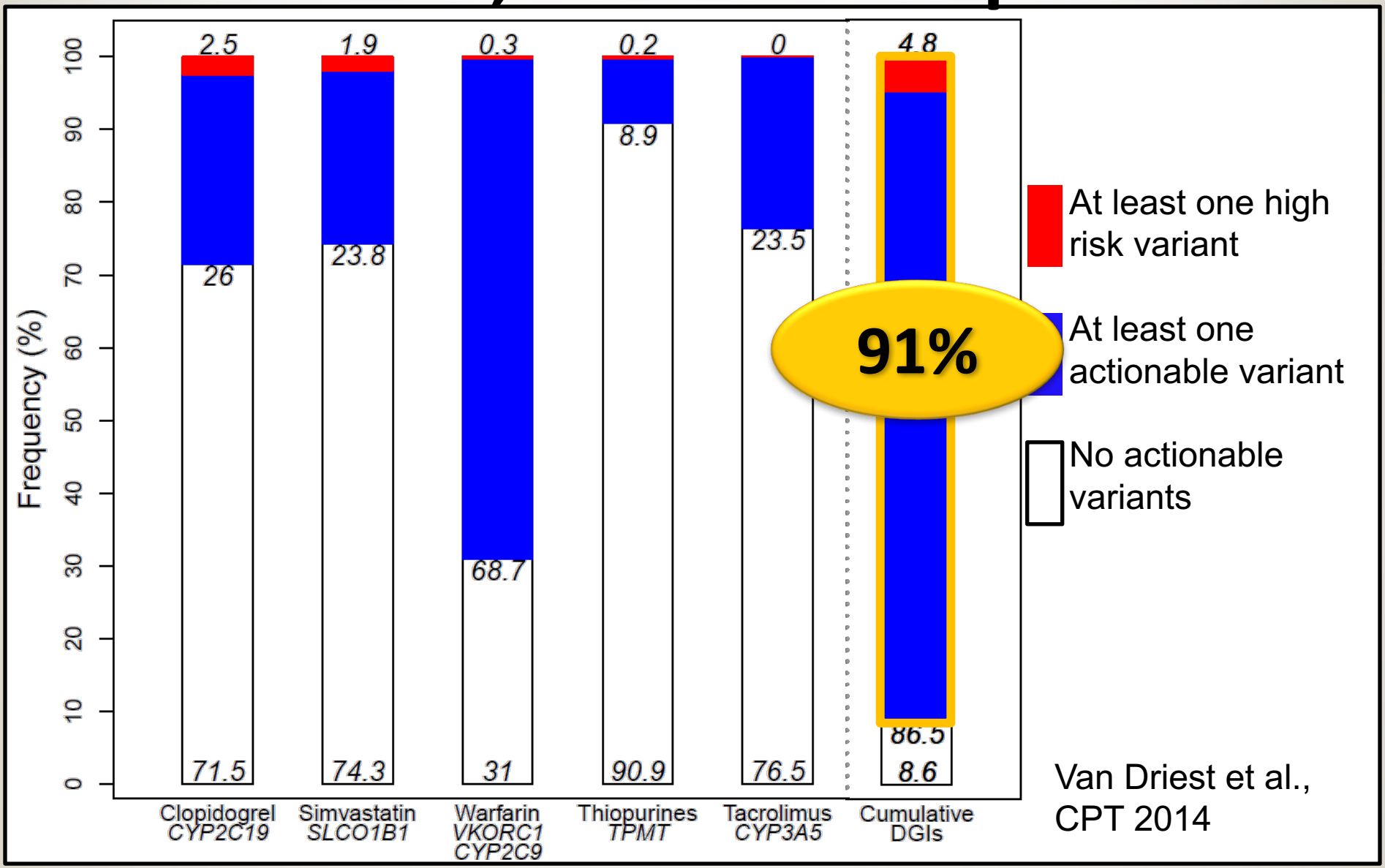
CYP2C19 genotypes in 13,423 patients in the Vanderbilt PREDICT program



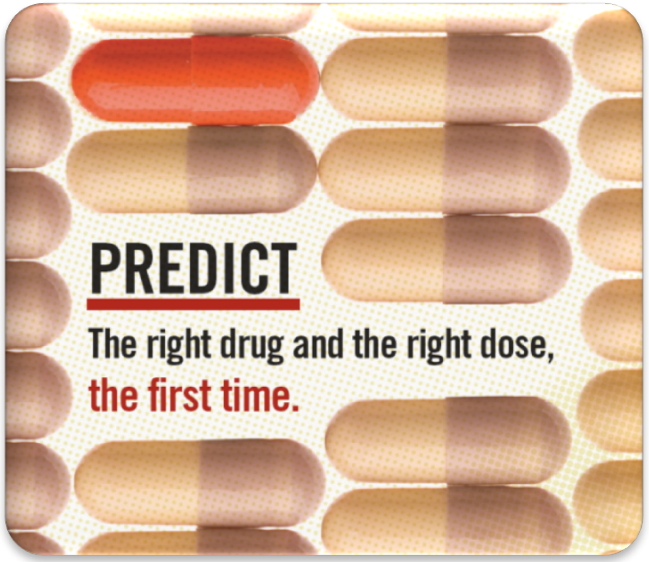
(*2, *3, *4, *6, *8)

VANDERBILT UNIVERSITY MEDICAL CENTER

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



Van Driest et al., CPT 2014



St. Jude Children's Research Hospital

PG4KDS: Clinical Implementation of Pharmacogenetics

Original article

Preemptive Genotyping for Personalized Medicine: Design of the Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment Protocol

Suzette J. Bielinski, PhD, MEd[a], Janet E. Olson, PhD[a], Jyotishman Pathak, PhD[a], Richard M. Weinshilboum, MD[b, c], Liewei Wang, MD, PhD[b], Kelly J. Lyke[a], Euijung Ryu, PhD[a],
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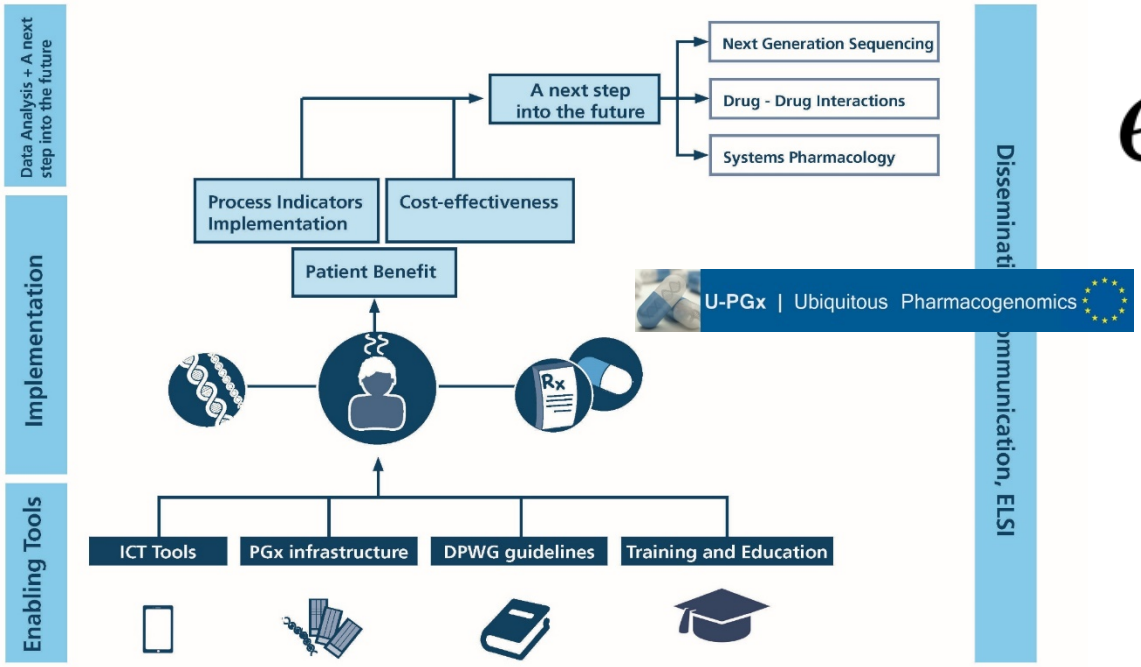

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What do we need?

- Comprehensive biology
- Methods to identify, accumulate, and study outliers
- Accurate tests; functional genomics
- Guidelines on how to use test results
- IT infrastructure
- Data on efficacy of diverse approaches: point of care versus panel/preemptive
- Education
- Medical and economic outcomes
- Engaging multiple partners: patients, payers, users,

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