Personalized medicine: what does it mean to pharmacists?

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Montreal Heart Institute

June 7th, 2012

Disclosures

- I have received grants or been an co-investigator of grants from AstraZeneca, Pfizer, Hoffman-Laroche, Novartis et Johnson et Johnson

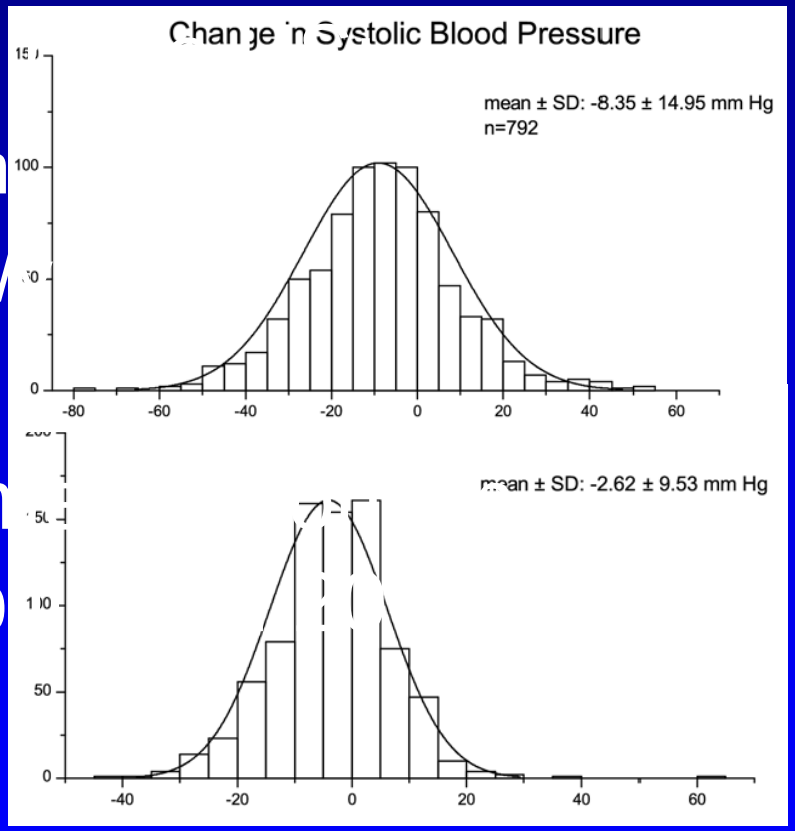
Plan of the presentation

- Why personalized medicine?
- How will personalized medicine change clinical practice?
- Will personalized medicine impact our notion of evidence-based practice?
- Will personalized medicine change pharmacy education?

Why personalized medicine?

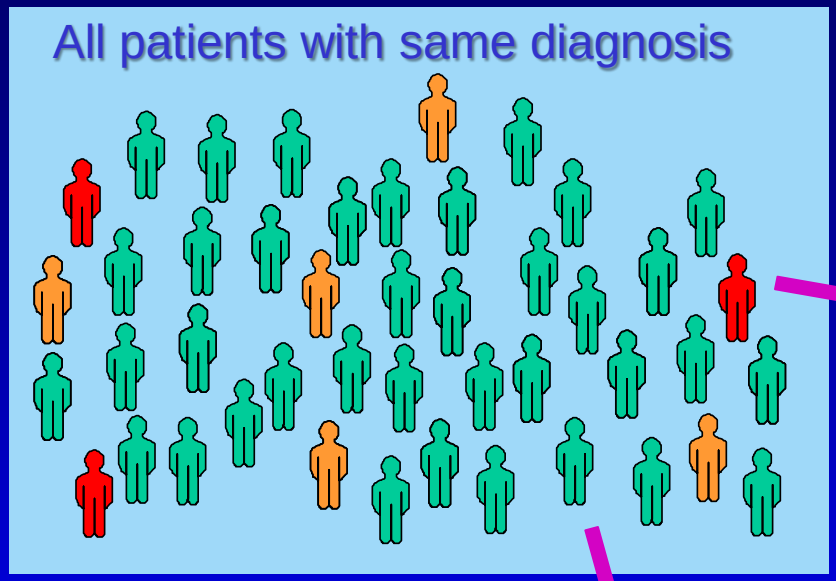
Why personalized medicine?

- Variable response to drugs
- Adverse drug reactions
  - 4th to 6th cause of death
  - 2 million hospitalisations/
  - Up to $160 billion/year
- The annual cost of CV n
  Canada surpassed $5 b



Brunner M, et al. Am J Cardiol. 2007;99:1549-54. Gandhi TK, et al. NEJM 2003;348:1556-64. Lazarou J, et al. JAMA. 1998;279:1200-05. Evans WE, McLeod HL. NEJM 2003;348:538-49. Jackevicius, C. A. et al. CMAJ 2009;181:E19-E28

Potential of personalized medicine

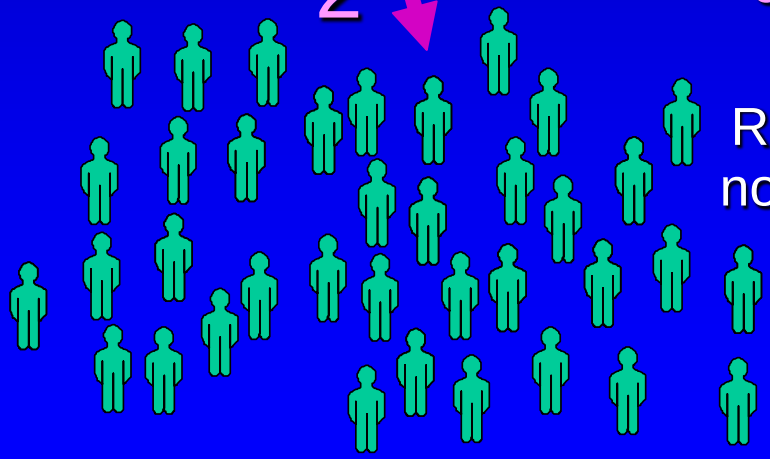


1

Non-responders and toxic responders

Treat with alternative dose or agent

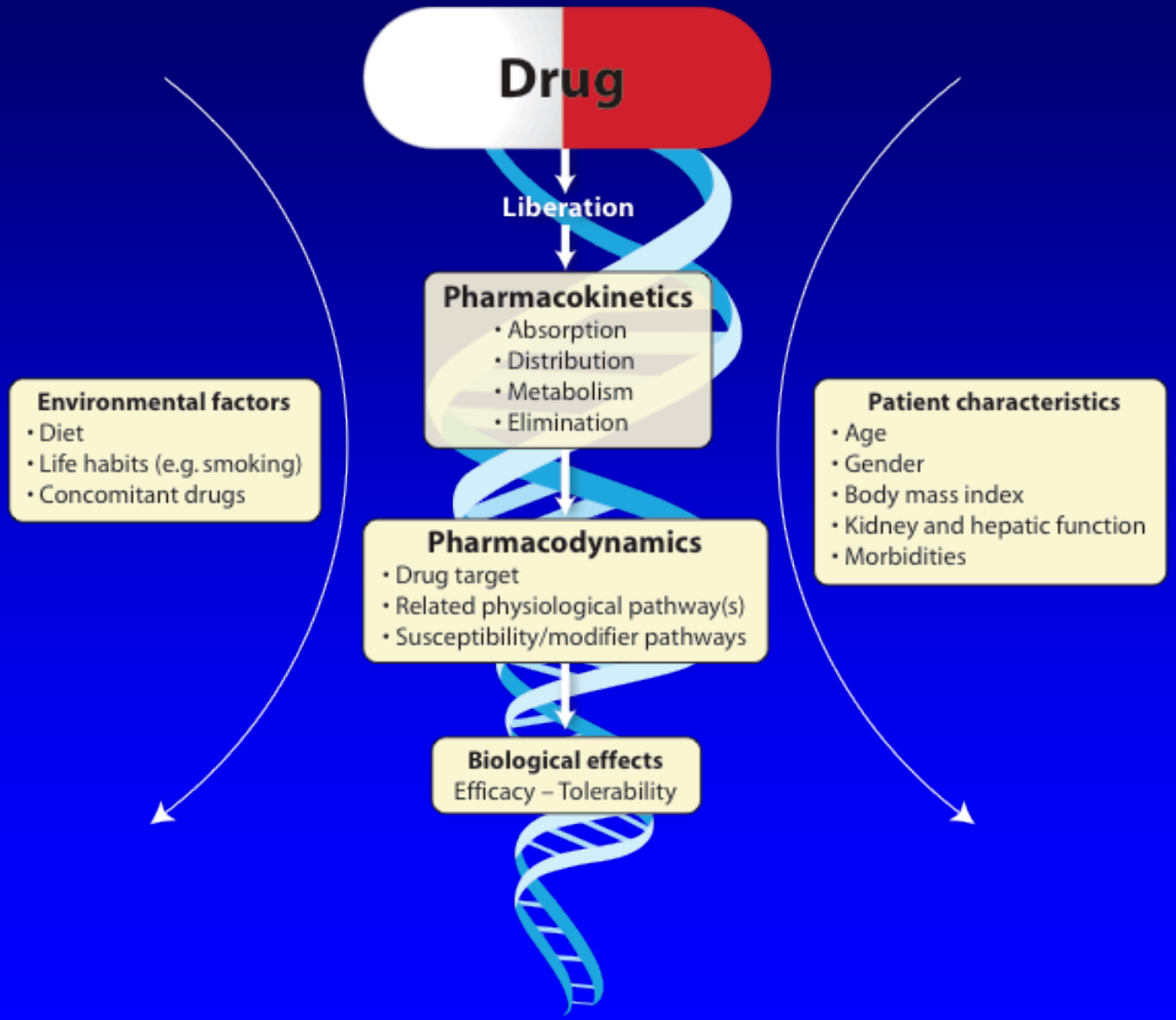
2



Responders and patients not predisposed to toxicity

Treat with conventional drug or dose

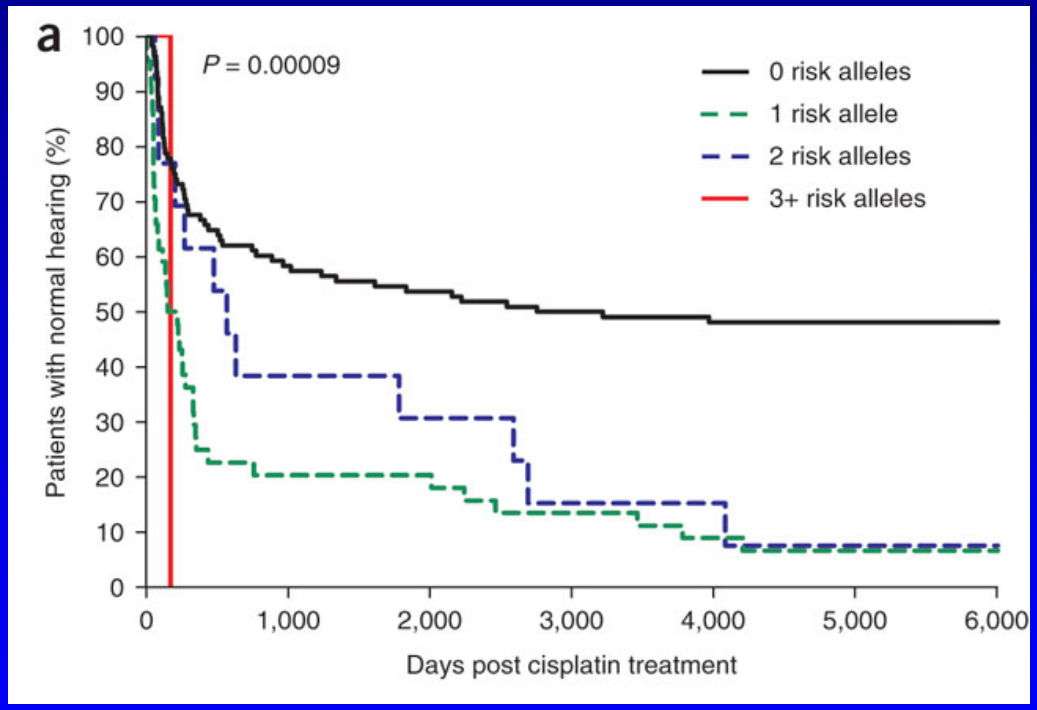
Pharmacogenomics



de Denus S, Phillips MS, Tardif JC. Pharmacogenomics. R Brugada, ed. Spinger;2010:273-287.

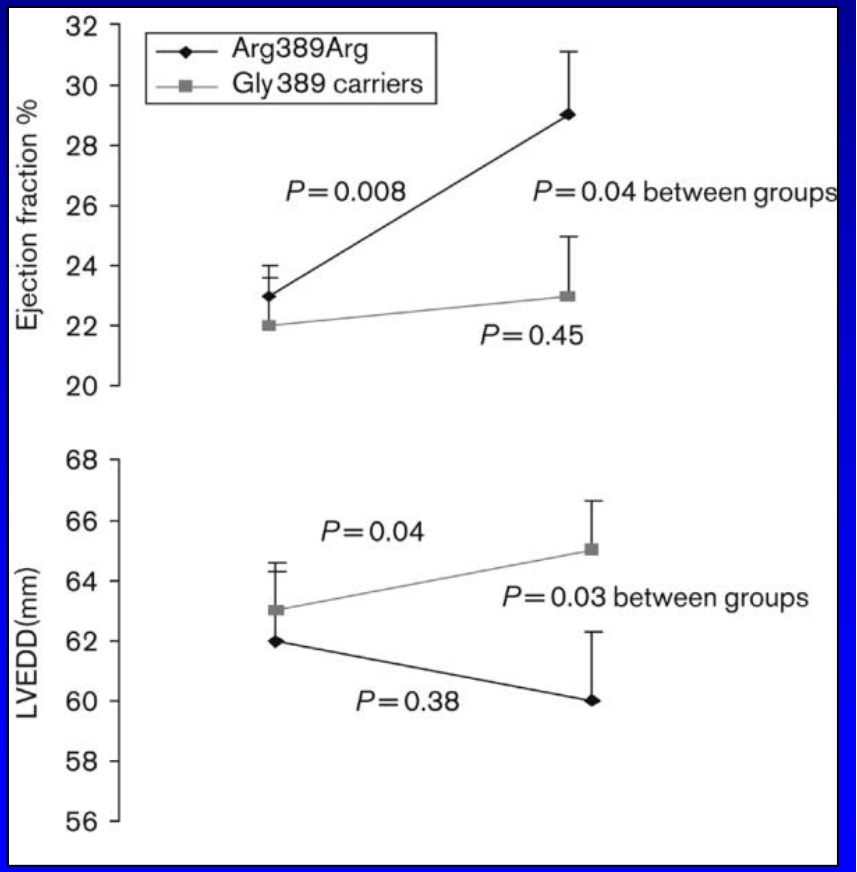
Selected examples

TPMT and *COMT* cisplatin-induced hearing loss



Ross CJ, et al. Nat Genet. 2009;41:1345-9.

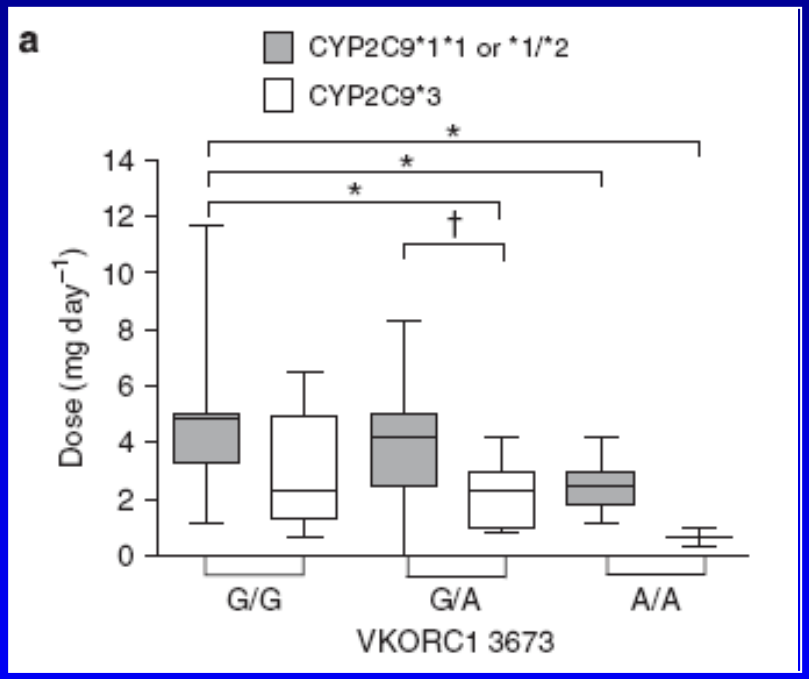
ADRB1 Arg389Gly and left ventricular remodelling with metoprolol



Terra SG, et al. Pharmacogenet Genomics 2005 ;15:227-34.

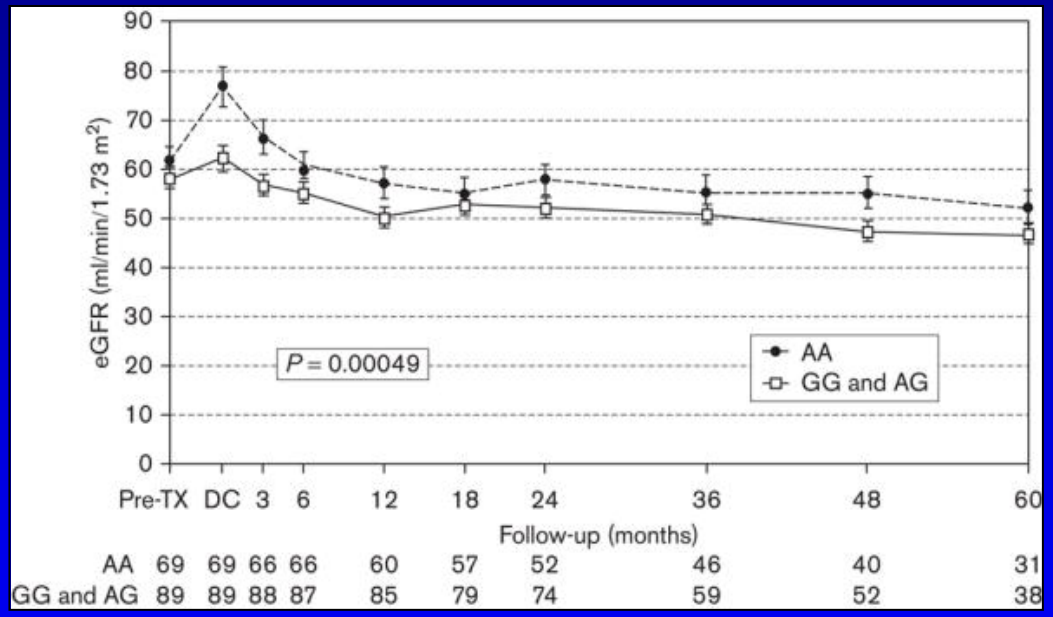
Selected examples

Warfarin and CYP2C9 and VKORC1



Michaud V, et al. Clin Pharmacol Ther. 2008;83:740-8.

PRKCB1 and CNI-induced renal dysfunction



Lachance K, et al. Pharmacogenet Genomics. 2012 ;22:336-43.

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- Fluorouracil
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Research shows that of all the clinical factors such as age, sex, weight, general health and liver function that alter a patient's response to drugs, genetic factors account for a significant proportion. This information becomes even more crucial when you consider the fact that adverse reactions to prescription drugs are killing about 106,000 Americans each year- roughly three times as many as are killed by automobiles. This makes prescription drugs the fourth leading killer in the U.S., after heart disease, cancer, and stroke.

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Click here to view a list of drugs for which DNA testing may be helpful.

Approximately half of all Americans have genetic defects that affect how they process these drugs. There are four different types of metabolizers, and we all fall into one of these categories for the variable pathways in Cytochrome P450 (this Cytochrome is responsible for creating the enzymes that process chemicals of all kinds through our bodies.) The easiest way to understand this is to picture a two lane highway.

ACCP COMMENTARY

Recommended Basic Science Foundation Necessary to Prepare Pharmacists to Manage Personalized Pharmacotherapy

American College of Clinical Pharmacy

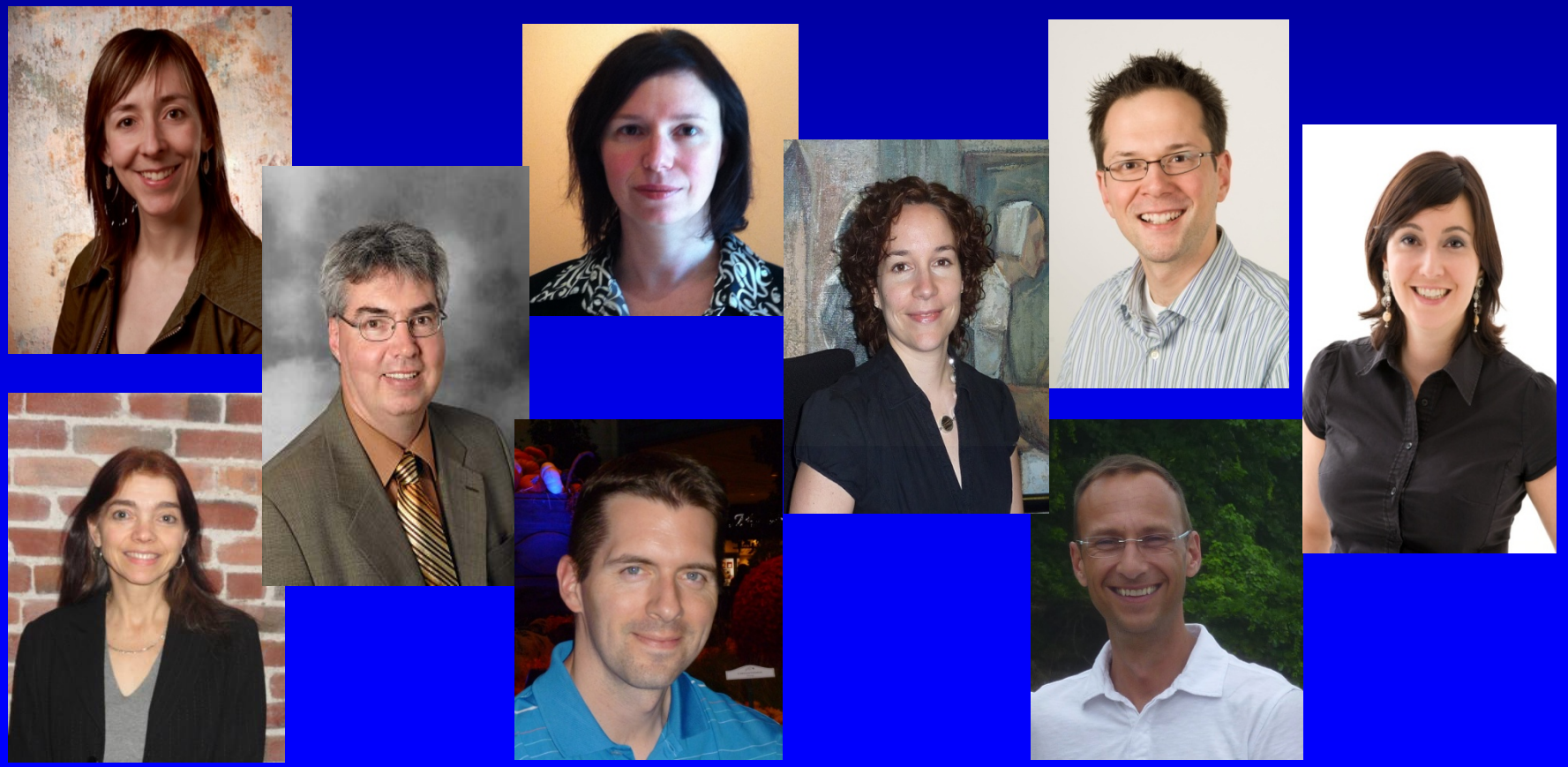
Larisa H. Cavallari, Pharm.D., Brian R. Overholser, Pharm.D., Douglas Anderson, Pharm.D., Eric Boyce, Pharm.D., Larry Buie, Pharm.D., Christine M. Formea, Pharm.D., Jason C. Gallagher, Pharm.D., Mary S. Hayney, Pharm.D., M.P.H., and Julie Oestreich, Pharm.D., Ph.D.

- *« As experts in pharmacotherapy, pharmacists may well provide an increasingly valuable service in dealing with the complexities of the drug decision process in the era of personalized medicine. »*

Groupe d'action pour la
pharmacothérapie personnalisée

Who are we?

- « A group of health care professionals who aim at promoting and educating other health care professionals and the public regarding personalized pharmacotherapy.»



How will personalized medicine change clinical practice?

How will personalized medicine change clinical practice?

New terminology

Linkage disequilibrium

Exon

Haplotype

Single nucleotide polymorphism

Genomewide association study

Point-of-care genotyping

Allele

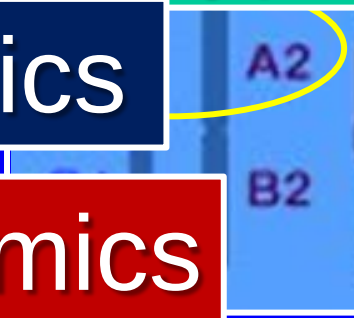
Wild-type

Proteomics

Metabolomics

Next-generation Sequencing

Transcriptomics



N Engl J Med 2010;362:2001-11.

How will personalized medicine change clinical practice?

Potential ethical considerations

Genetic information vs other biomakers

- Unique to each individual → part of a person's identity.
- Does not change with time, accompanies a person throughout their life.
- Not only relevant for an individual, but also their family members.

Ravitsky V, et al. AJOB 2006;6:8-17. Renegar G, et al. Bioethics 2006;20:24-36.

Patient case

- Gene Gray, 48-year-old woman.
  - Diagnosis : New-onset heart failure
  - New prescription:
    - Furosemide 40 mg po qd
    - Ramipril 1.25 mg qd
    - Metoprolol 25 mg po bid

Patient Name: Gene Gray

Date of Birth: 16-02-1964 Laboratory # 12345

Go to www.GeneMedRx.com/dnalogin to determine interaction risk before prescribing medication to this patient. The patient's genetic information listed below impacts response to the majority of medications.

DST-CYP2D6 *4/*5 Poor Metabolizer

DST-CYP2C19 *2/*3 Poor Metabolizer

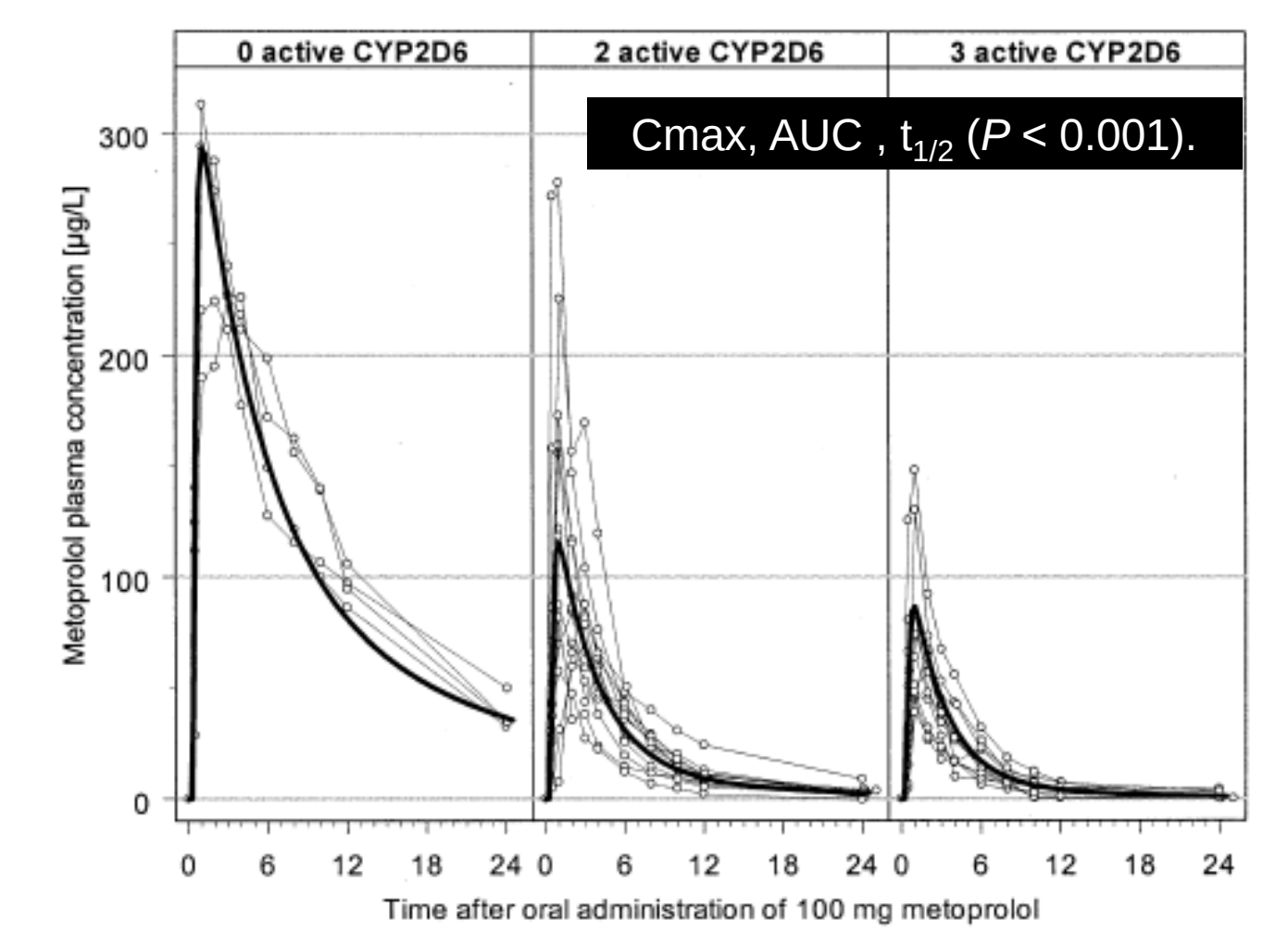
DST-CYP2C9 *1/*1 Normal Metabolizer

DST-VKORC1 A/A High sensitivity to warfarin

genelex

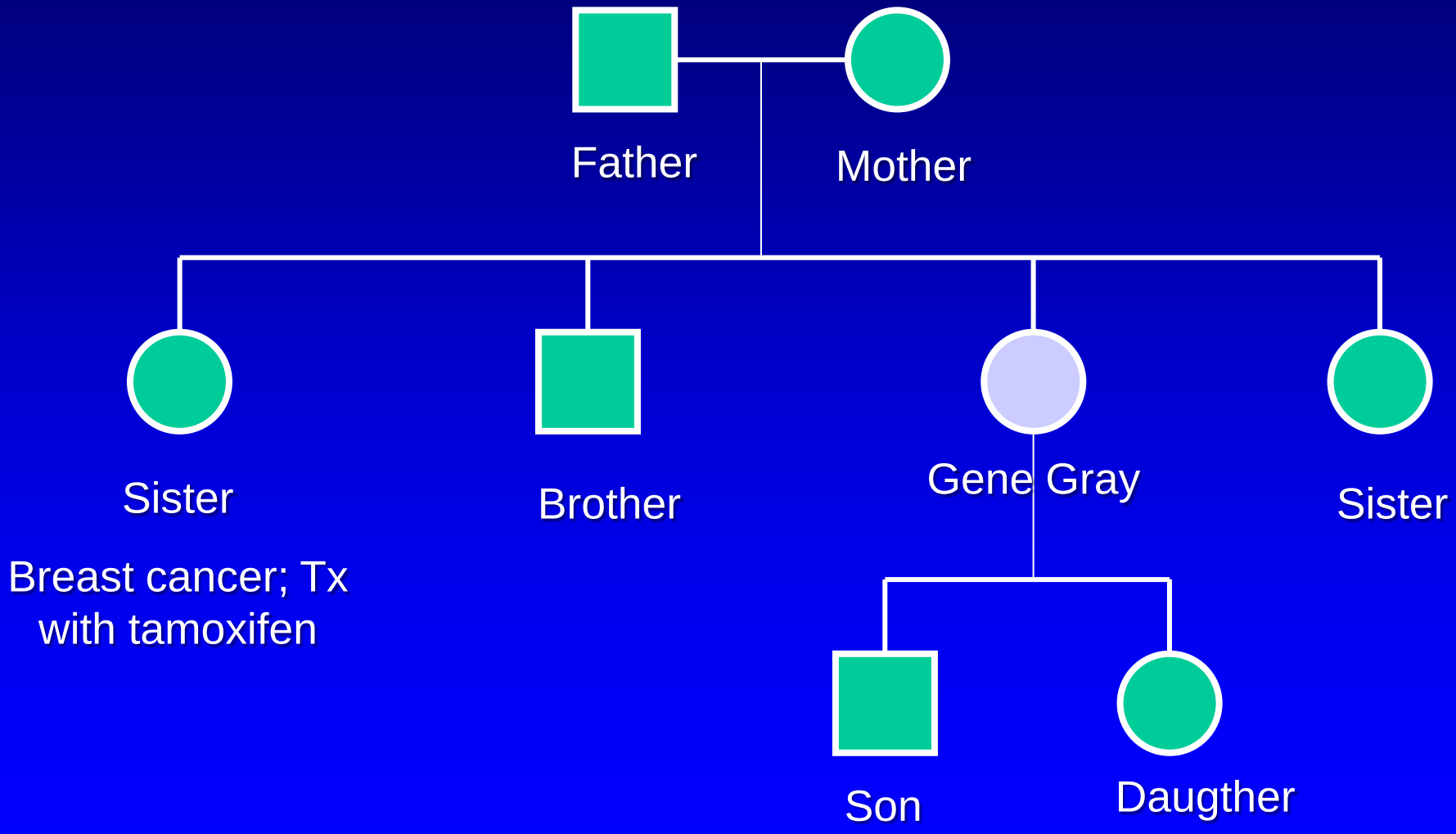
Questions? – Call 800 TEST-DNA

CYP2D6 and Metoprolol in HF



Kirchheiner J, et al. Clin Pharmacol Ther 2004;76:302-12.

Family tree

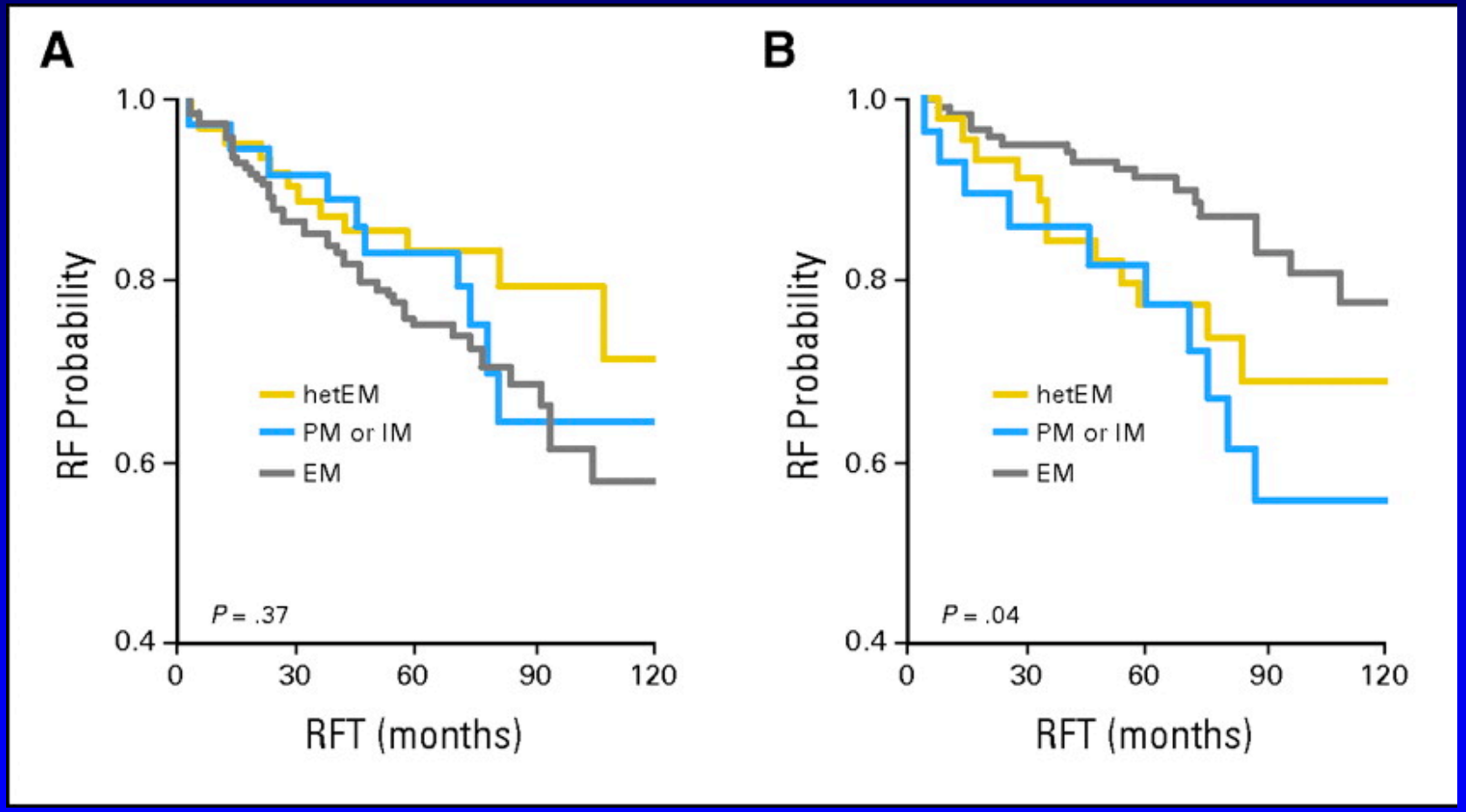


Adapted from Laura Robb

CYP2D6 and tamoxifen

No tamoxifen

Tamoxifen



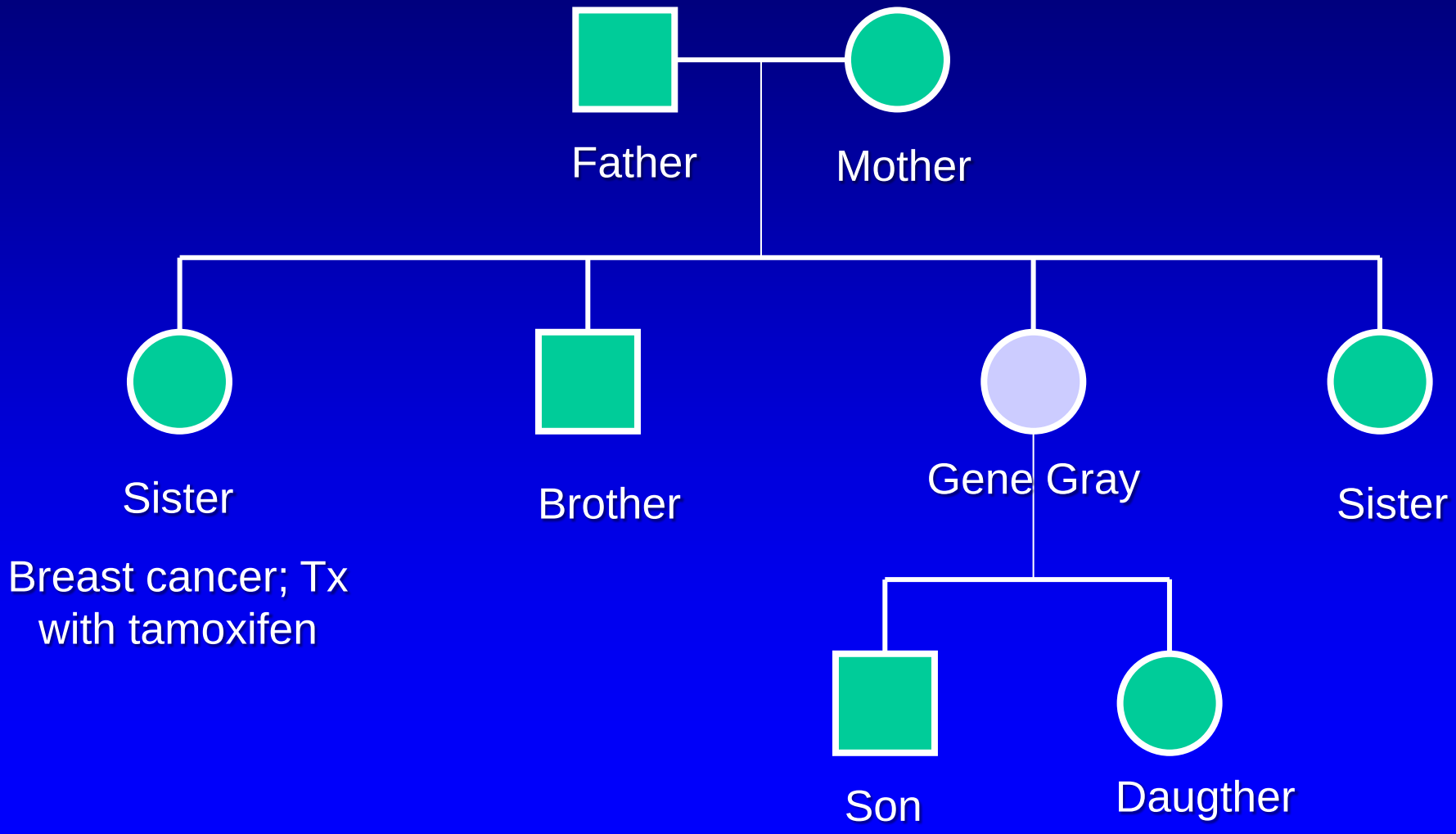
RFT: Relapse-free time

EM: extensive metabolizer
PM: poor metabolizer

JCO 2007;25:5187-93

Adapted from Nathalie Letarte

Family tree



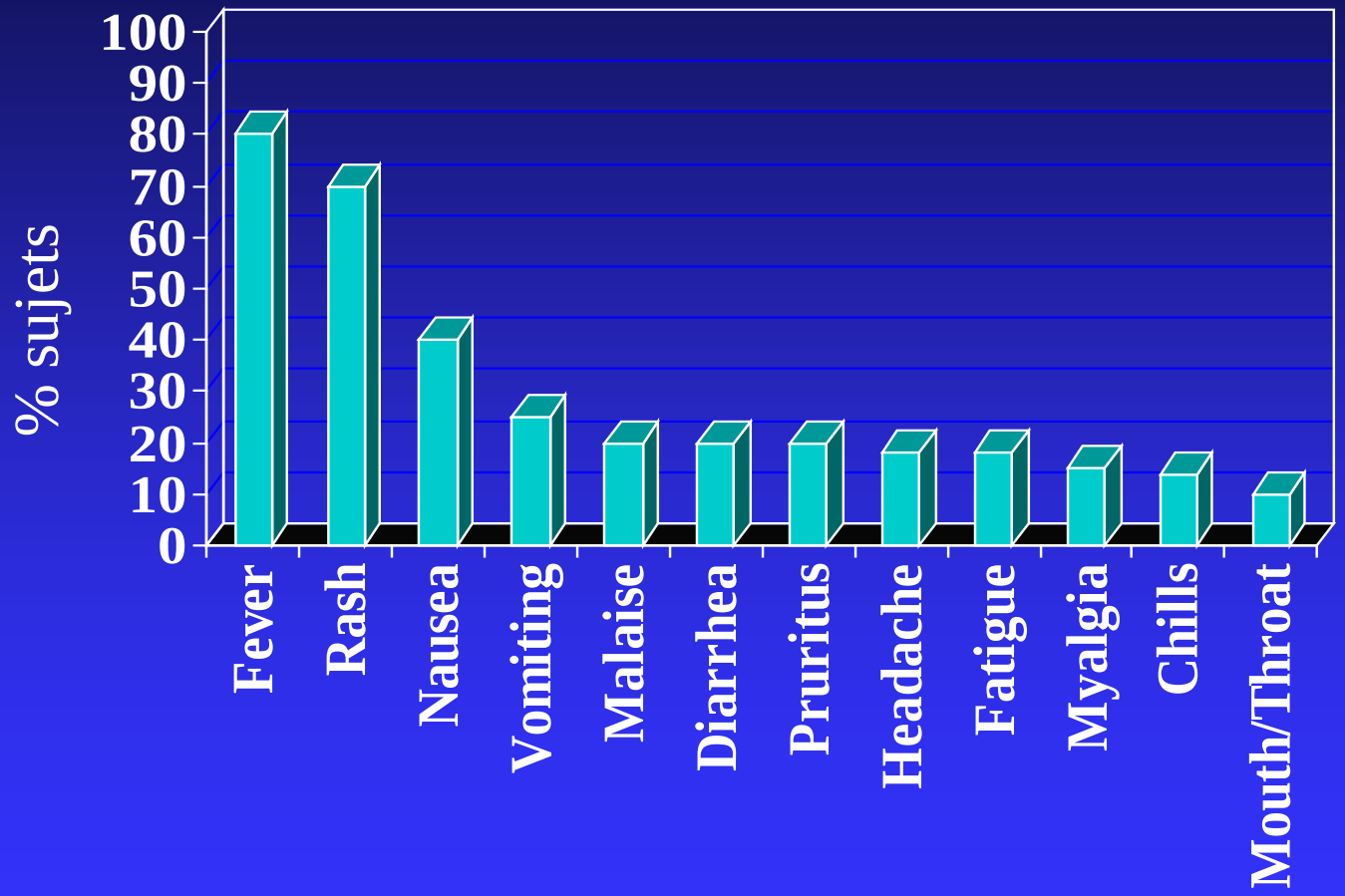
Adapted from Laura Robb

How will personalized medicine change clinical practice?

Selected examples

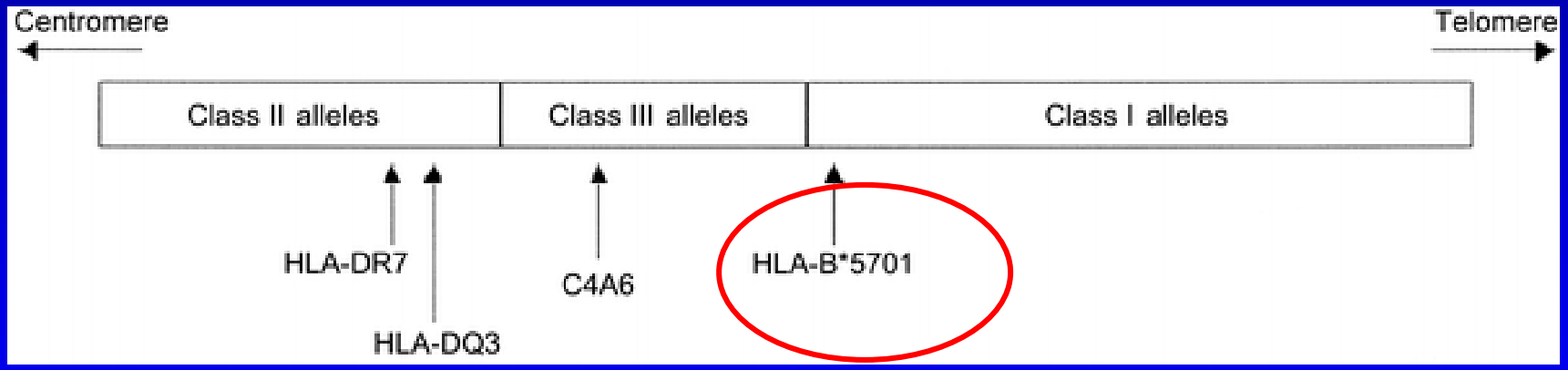
Abacavir

Abacavir hypersensitivity : Clinical presentation



Hetherington S, et al. Poster 60, 7th CROI, 2000

HLA genes located on chromosome 6 is associated with abacavir hypersensitivity



Quirk E. et al. CID 2004;39:98-106

PREDICT-1 - Results –

	Prospective Screening (N = 803)	Control (N = 847)
Clinically diagnosed hypersensity reaction to abacavir, %	3.4	7.8
Immunologically confirmed reaction,%	0	2.7

- Clinical utility (Immunologically confirmed reaction):
  - Sensitivity: 100% (85.2–100) (all positives)
  - Specificity: 96.9% (95.5–98.0)
  - Positive predictive value: 47.9% (33.3–62.8)
  - Negative predictive value: 100% (99.5–100)

Mallal S, et al. N Engl J Med. 2008;358:568-79.

Abacavir

- US prescribing information

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of

- Clinical guidelines

HLA-B*5701 SCREENING (Updated December 1, 2007)

Panel's Recommendations:

- *The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) (AI).*
- *HLA-B*5701-positive patients should not be prescribed ABC (AI).*
- *The positive status should be recorded as an ABC allergy in the patient's medical record (AII).*
- *When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR (CIII).*

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Panel on Antiretroviral Guidelines for Adults and Adolescents. January 10, 2011; 1–166. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed July 15th 2011.**

Panitumumab

KRAS mutations

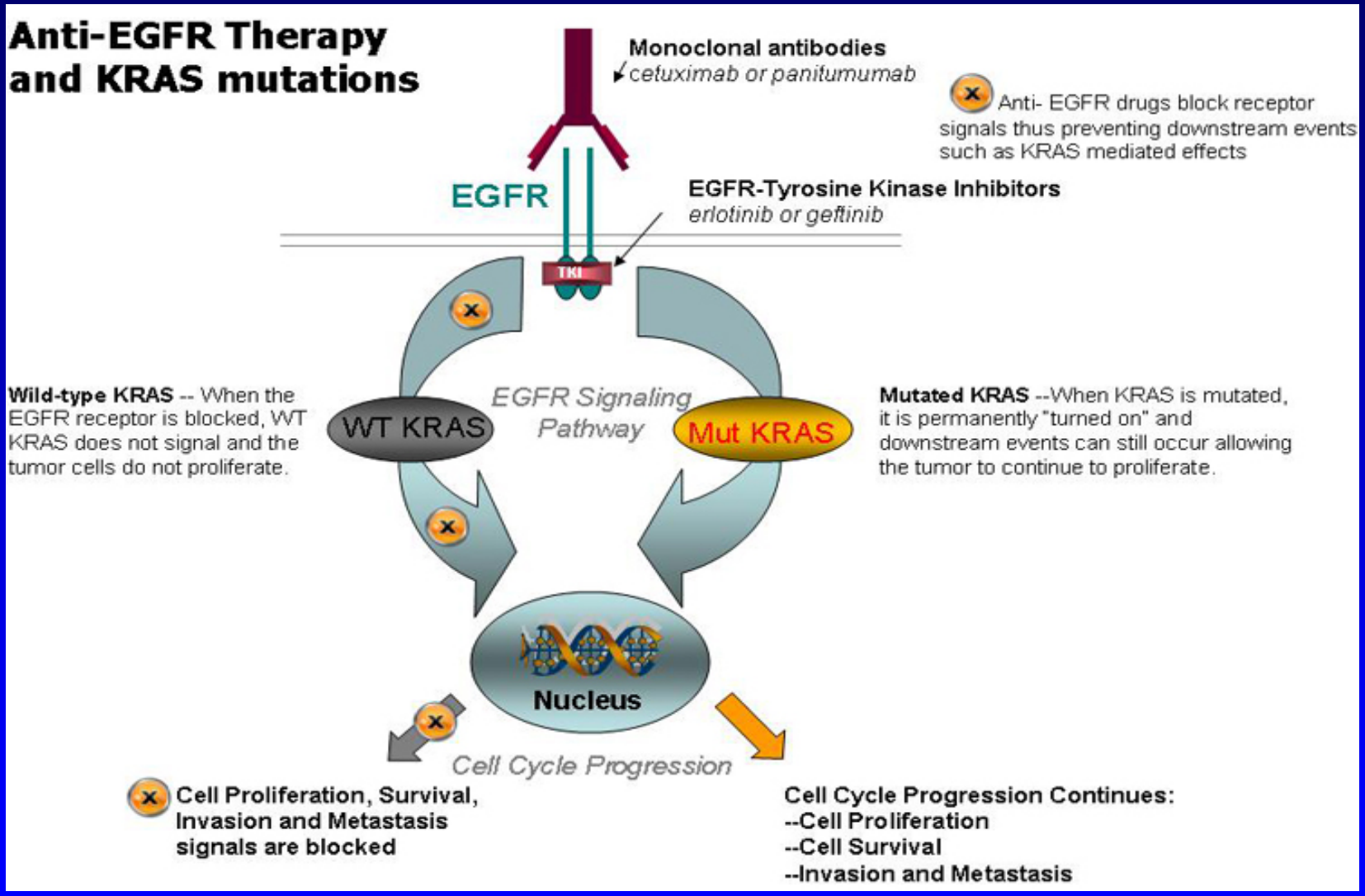
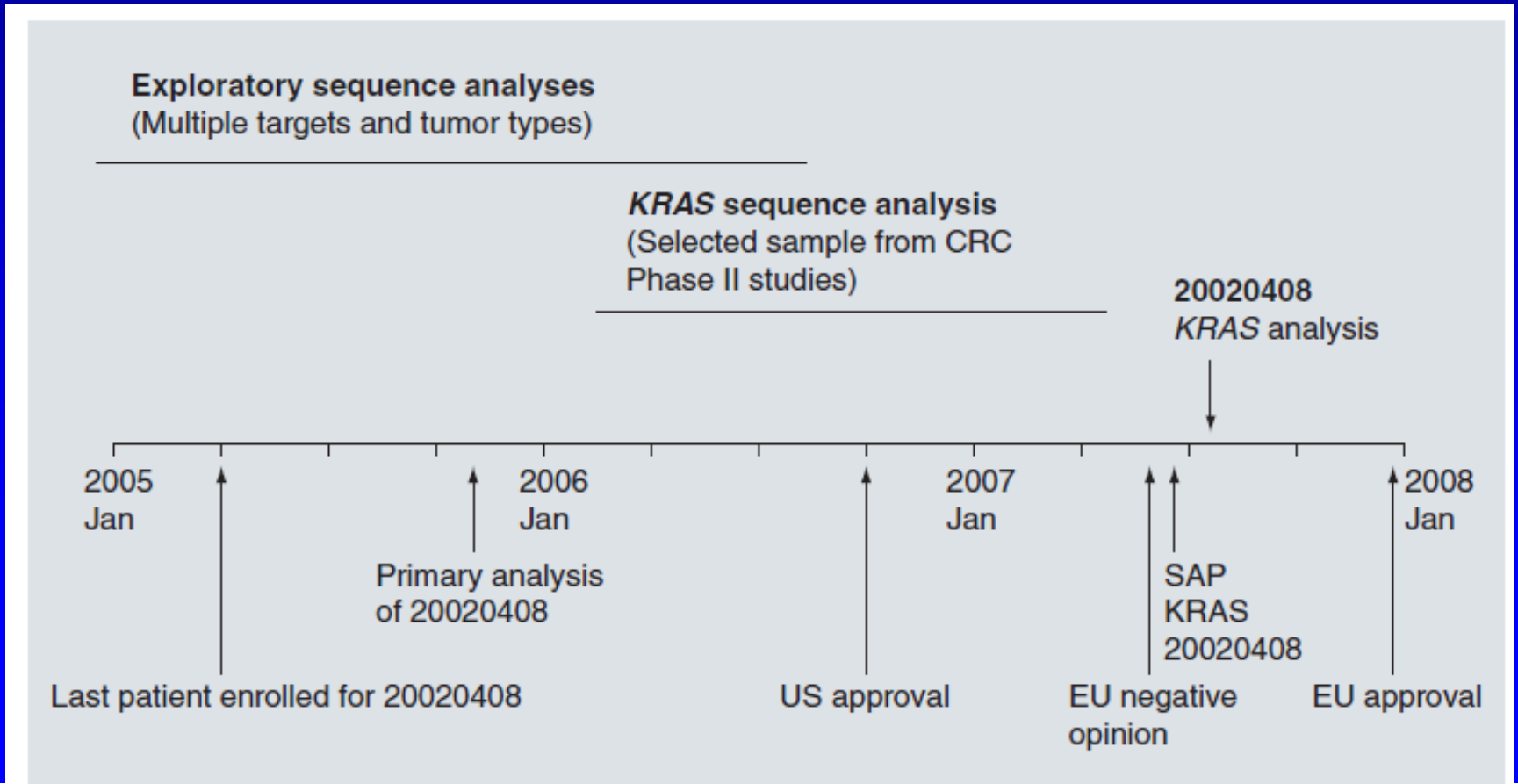


Image: http://www.exiqon.com/dxps/PublishingImages/BRAF%20mutation%20analysis/EGFR%20BRAF%20Pathway%20ver2b.jpg

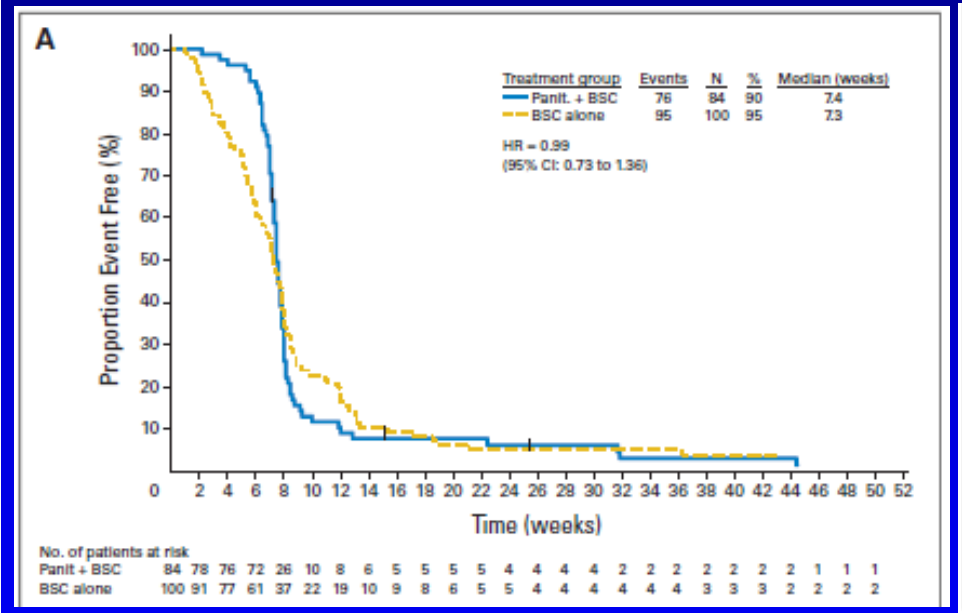
Panitumumab

- Conflicting data from phase II and epidemiological studies suggested that patients with mutations in the *KRAS* gene did not respond to panitumumab.
- Incidence:

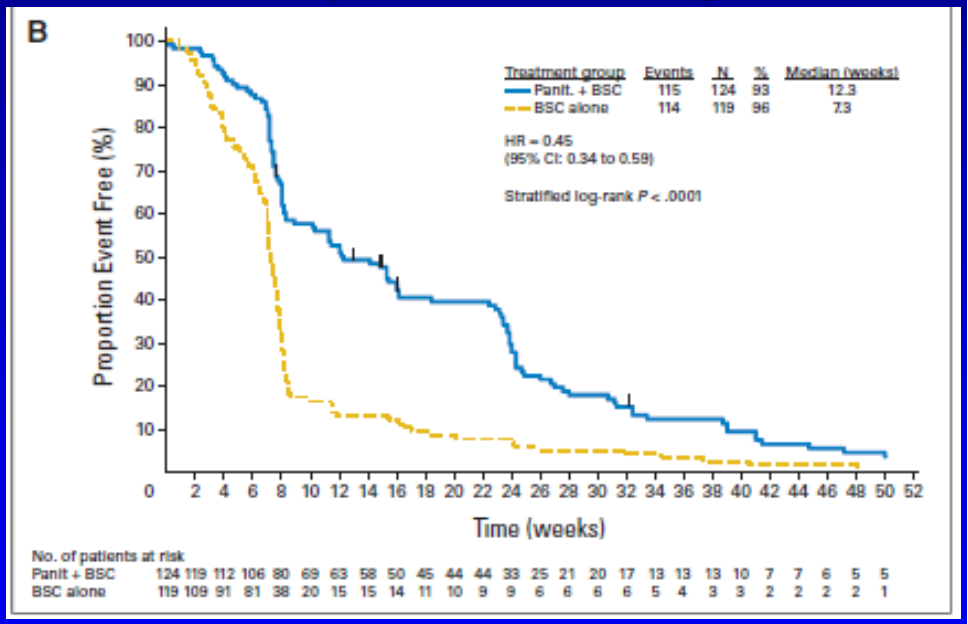


Panitumumab

Mutant *KRAS* group



Wild-type *KRAS* group



Jamado RG, et al. Clin Oncol. 2008;26:1626-34.

Panitumumab

- Retrospective Pgx analyses lead to the approval of panitumumab in Europe.
- US prescribing information updated to limit the use KRAS wild-type carriers only.
- Integrated in clinical practice guidelines.

1 INDICATIONS AND USAGE

Vectibix is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy

The effectiveness of Vectibix as a single
carcinoma is based on progression-free su
improvement in disease-related symptom

Retrospective subset analyses of metastat
in patients whose tumors had *KRAS* muta
treatment of colorectal cancer with these

VOLUME 27 · NUMBER 12 · APRIL 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

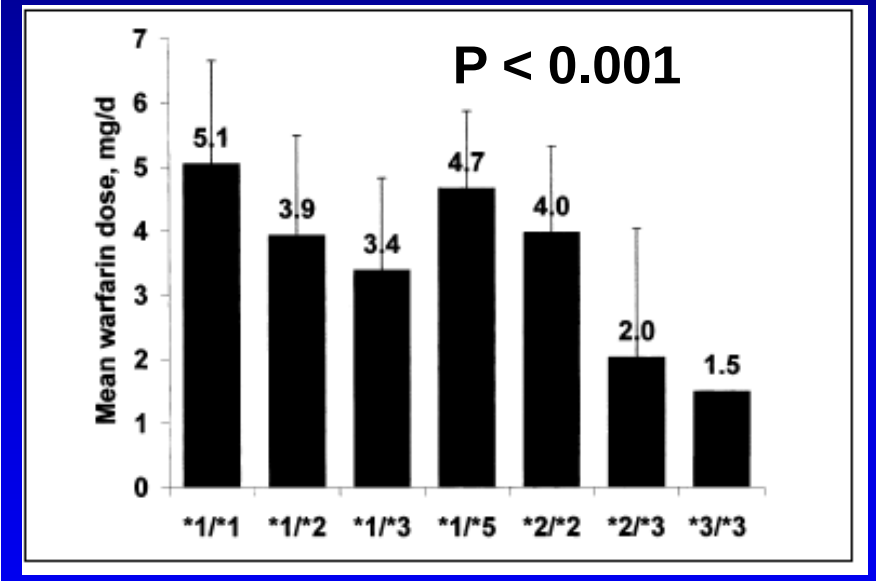
American Society of Clinical Oncology Provisional Clinical Opinion: Testing for *KRAS* Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy

Carmen J. Allegra, J. Milburn Jessup, Mark R. Somerfield, Stanley R. Hamilton, Elizabeth H. Hammond, Daniel F. Hayes, Pamela K. McAllister, Roscoe F. Morton, and Richard L. Schilsky

Warfarin

Association of *CYP2C9 and VKORC1* and warfarin dosing

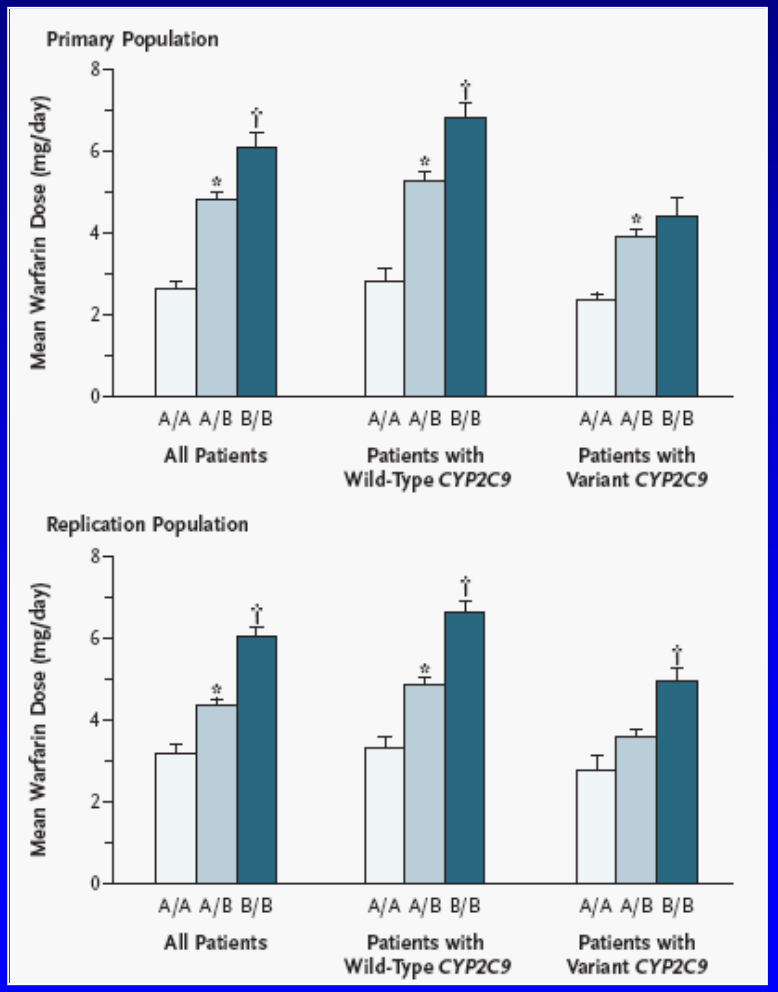
N = 369



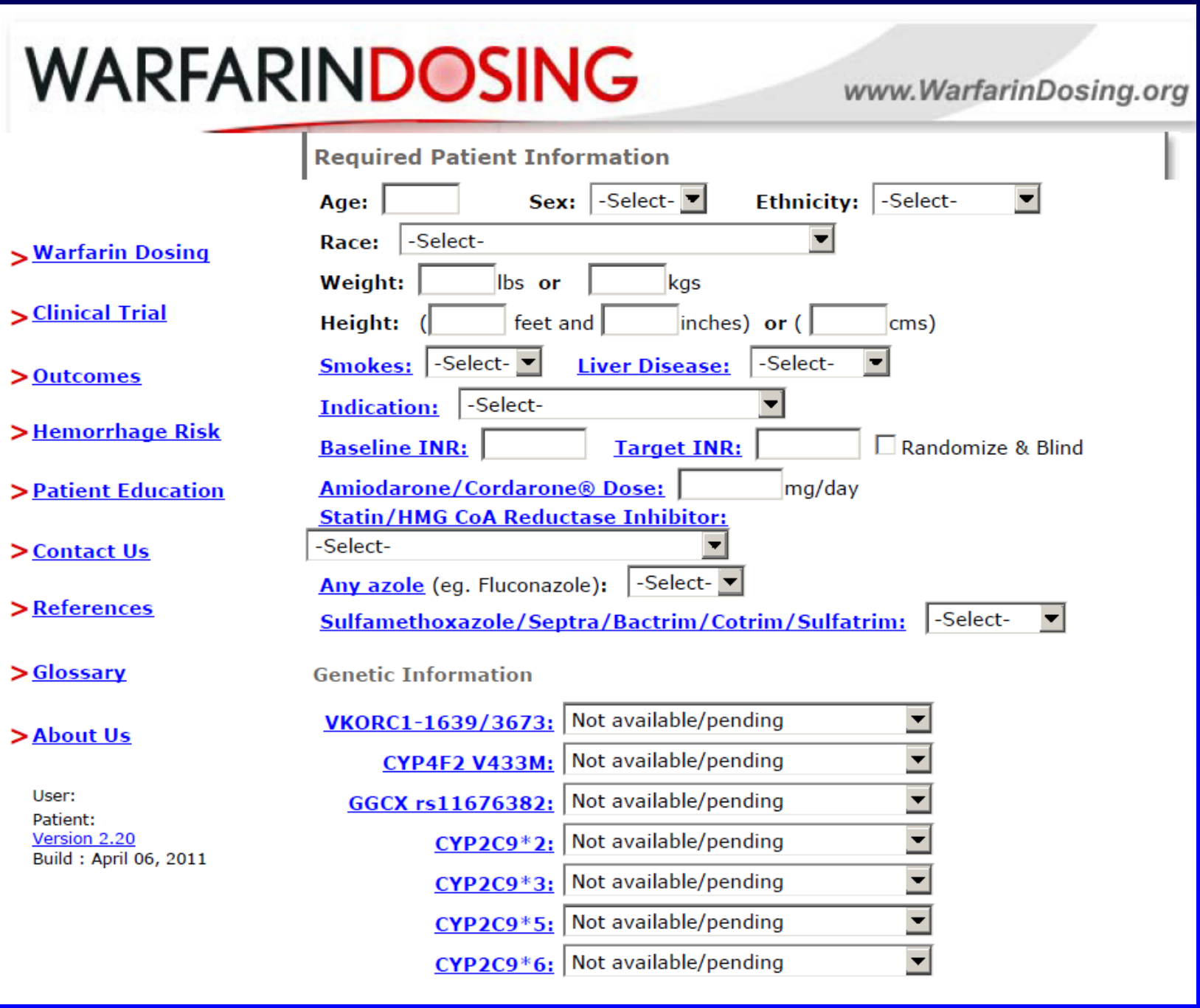
CYP2C9

Thromb Haemost 2004; 91: 87–94

VKORC1



Rieder, MG, et al. N Engl J Med 2005;352:2285-93


WARFARINDOSING
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Warfarin Dosing
Clinical Trial
Outcomes
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References
Glossary
About Us
User:
Patient:
Version 2.20
Build : April 06, 2011
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

The COUMAGEN studies

COUMAGEN I

- Randomized trial (N = 206)
  - PGx-guided warfarin vs conventional treatment
  - Primary objective not met (reduction of the number of INR outside the target range)…
  - … but, better dose prediction ($p<0.001$), fewer dosing changes ($p=0.03$) and INRs ($p=0.06$)

Anderson JL, et al. Circulation. 2007;116:2563-70.

COUMAGEN II

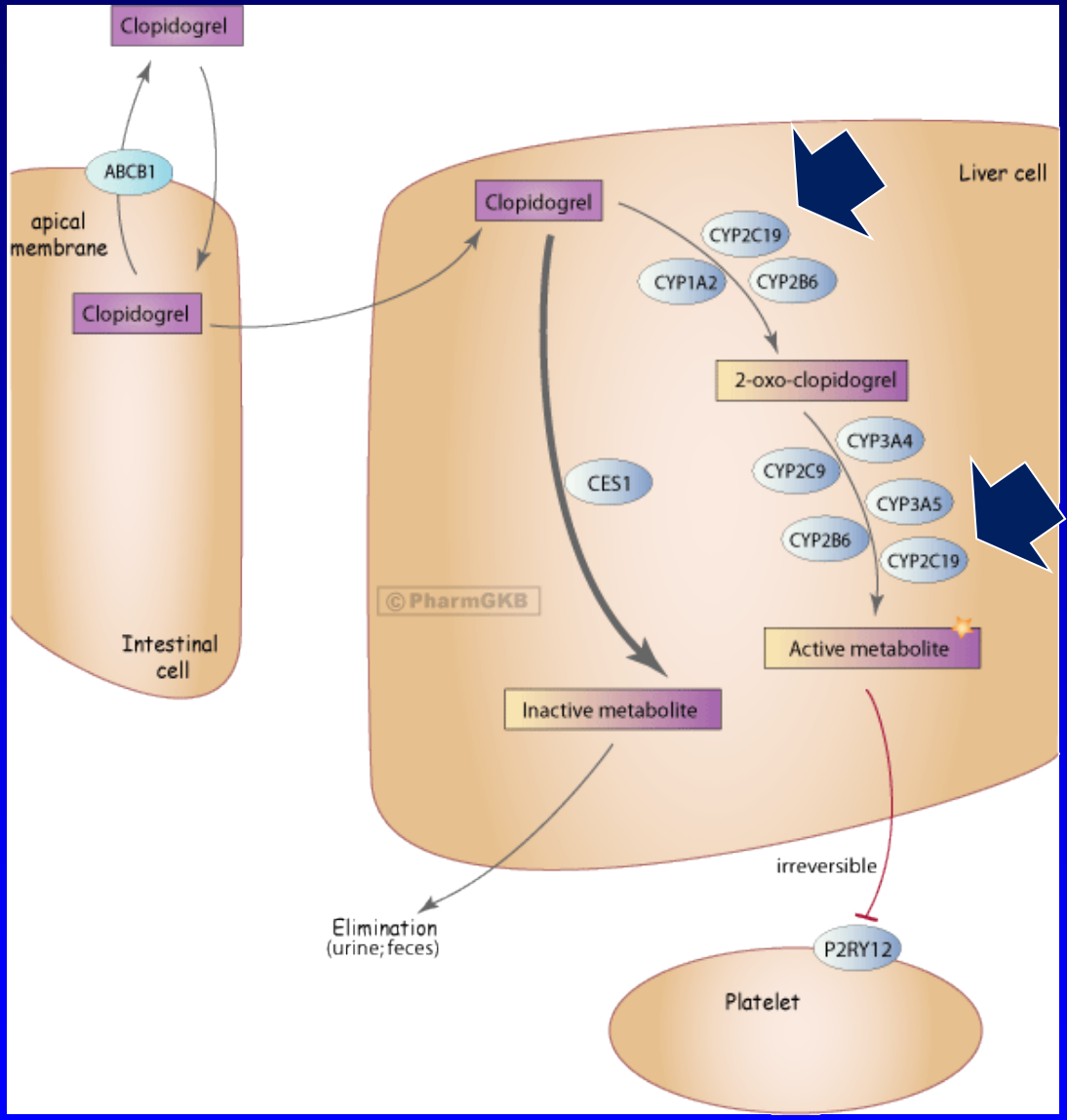
- Randomized trial (N = 504)
  - compared 2 PGx algorithms + parallel control group(n = 1911)
  - No difference between PGx algorithms
  - Better anticoagulation control in the two PGx arms that in the control group…

Anderson JL, et al. Circulation. 2012;125:1997-2005.

…but the study design greatly limits the conclusions that can be drawn

Clopidogrel

Clopidogrel pharmacokinetics



http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway

The NEW ENGLAND JOURNAL of MEDICINE

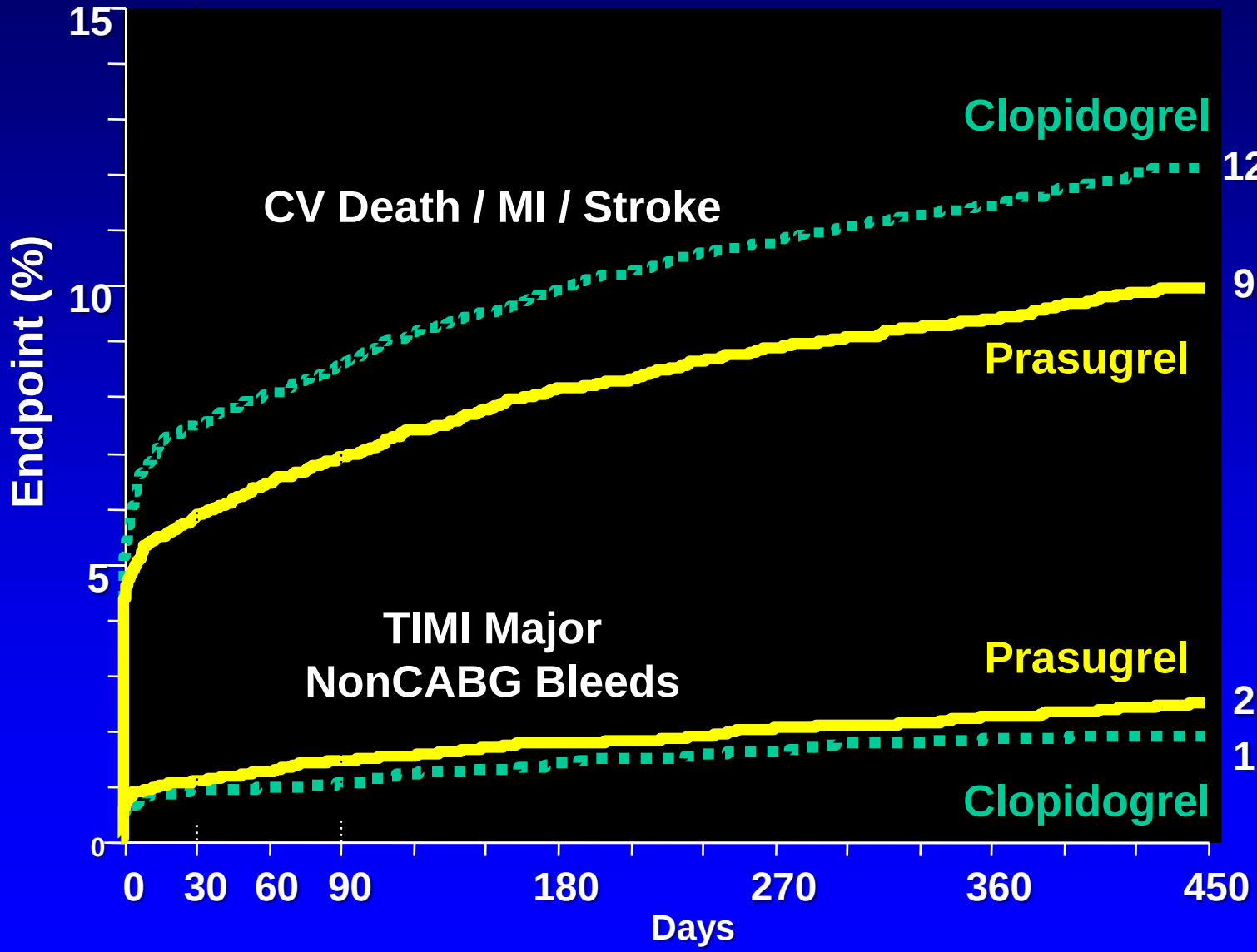
ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.

Mega JL, et al. N Engl J Med. 2009;360:354-62.

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

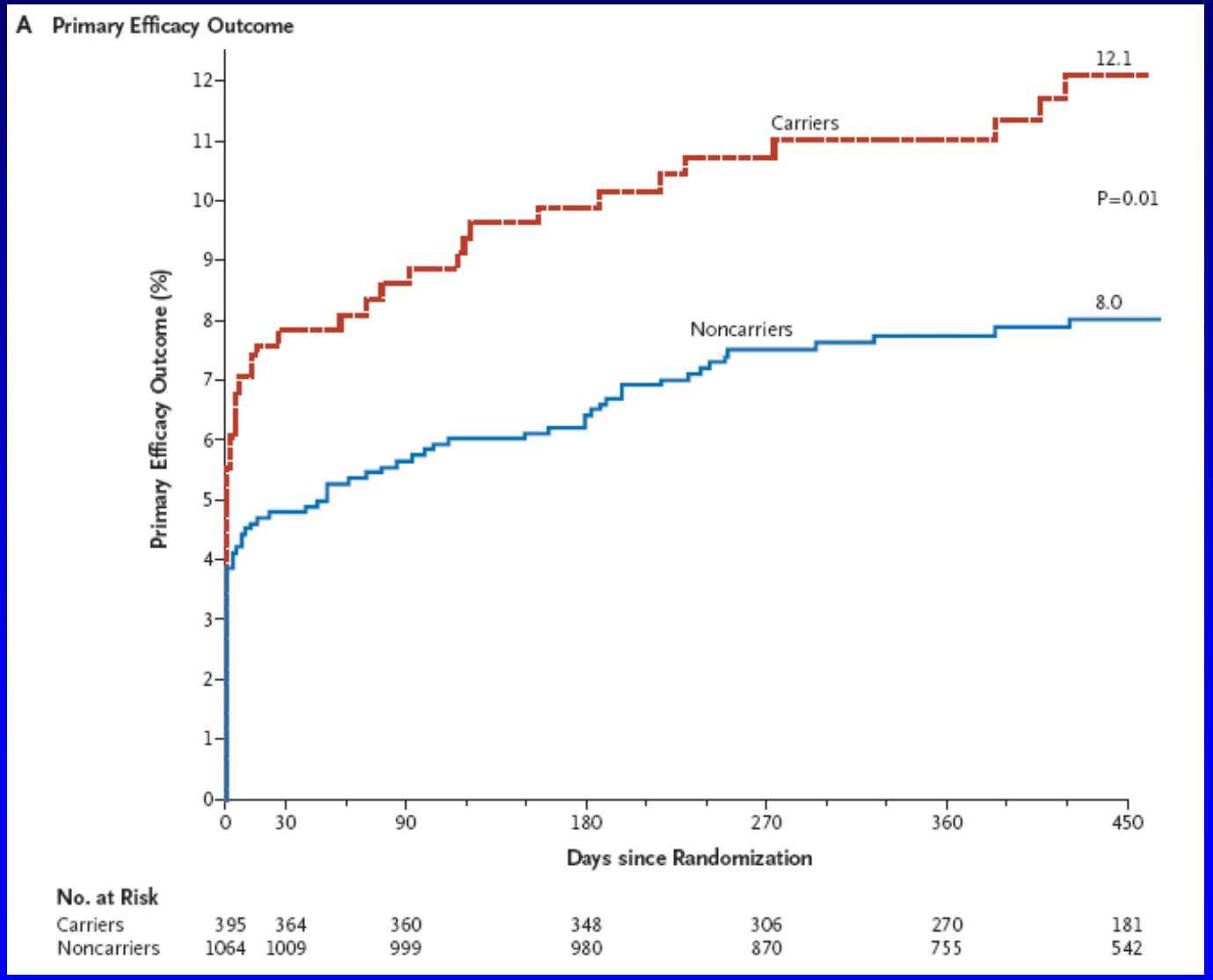
↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

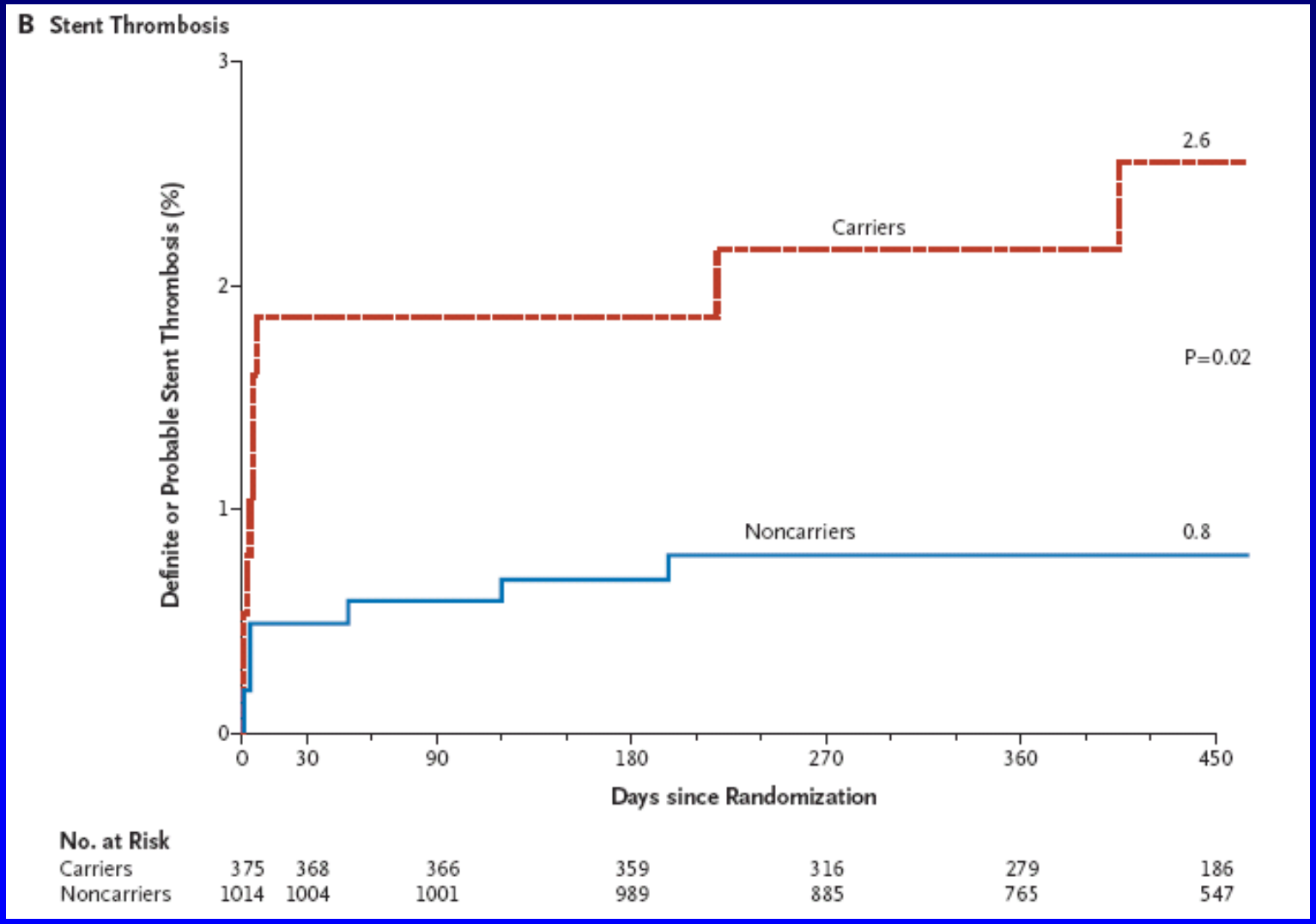
Wiviott SD, et al. N Engl J Med. 2007;357:2001-15.

Primary end point according to *CYP2C19* genotype in patients receiving clopidogrel



Mega JL, et al. N Engl J Med. 2009;360:354-62.

Risk of stent thrombosis according to *CYP2C19* genotype in patients receiving clopidogrel



Mega JL, et al. N Engl J Med. 2009;360:354-62.

Replication???

Replication!!!

Journal of the American College of Cardiology
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Vol. 51, No. 20, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.12.056

REVIEW

Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI

A Meta-analysis

JAMA. 2010;304(16):1821-1830

Dir
Kat
Nic
Mehilli,
and

ABSTRACT

Department of Cardiology, Deutsches Herzzentrum and 1. Medizinische Klinik rechts der Isar, Technische Universität München, Munich, Germany

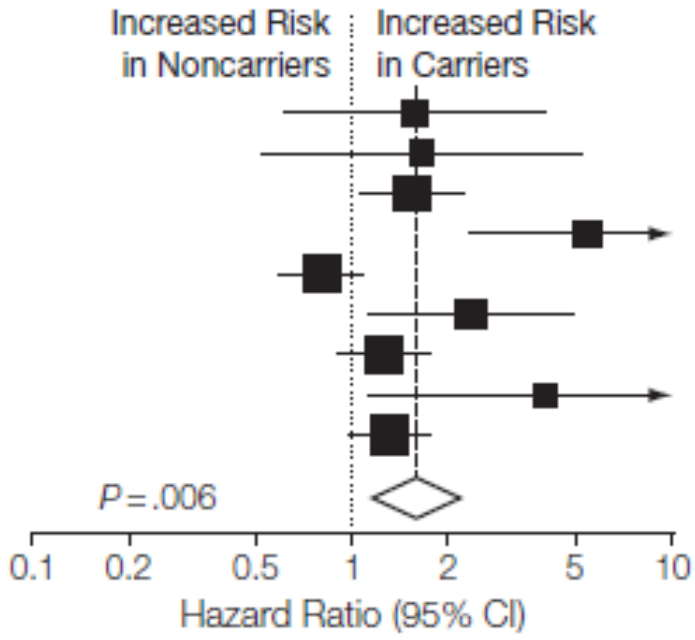
Received 3 October 2008; revised 16 December 2008; accepted 12 January 2009; online publish-ahead-of-print 4 February 2009

Results

Figure 2. Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke by *CYP2C19* Genotype

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	
CLARITY-TIMI 28	8/77	10/150	1.56 (0.61-3.94)
EXCELSIOR	5/243	7/554	1.63 (0.52-5.14)
TRITON-TIMI 38	46/395	83/1064	1.53 (1.07-2.19)
AFIJI	15/73	11/186	5.38 (2.32-12.47)
FAST-MI	63/635	193/1573	0.79 (0.59-1.06)
RECLOSE	15/247	14/525	2.32 (1.12-4.81)
ISAR	55/680	119/1805	1.23 (0.89-1.70)
CLEAR-PLATELETS	6/68	4/160	3.95 (1.11-14.02)
Intermountain	68/344	141/906	1.29 (0.97-1.72)
Overall	281/2762	582/6923	1.57 (1.13-2.16)
	10.2%	8.5%	



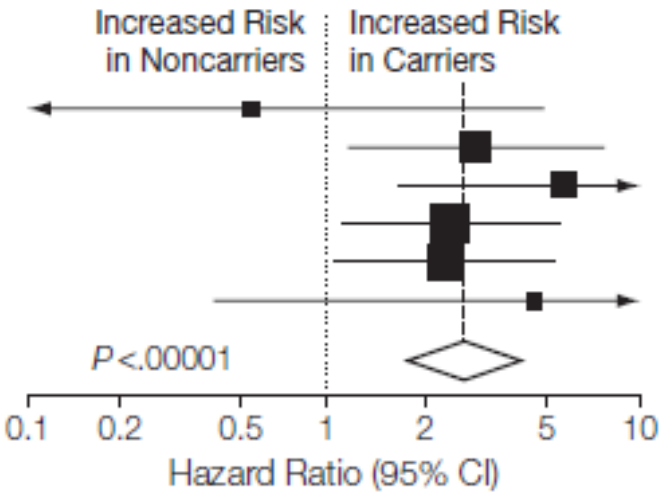
Mega JL, et al. JAMA. 2010;304:1821-1830

Results

Figure 3. Stent Thrombosis by *CYP2C19* Genotype

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)



2.6% 0.9%

Mega JL, et al. JAMA. 2010;304:1821-1830

Can we do anything about this?

- Use of high-dose clopidogrel?
  - In stable CAD patients (n = 333), clopidogrel 225-300 mg/day produced similar levels of platelet reactivity in *CYP2C19*2* heterozygotes than 75 mg in non carriers.
    - But not in homozygotes!
  - No robust clinical data to support the use of such doses
- Alternatives?
  - The effects of prasugrel and ticagrelor are independent of *CYP2C19*.
    - Genotype-guided use vs unselected use of these new agents ?

Price AJ, et al. JAMA. 2011;305(11):1097-1105. CURRENT-OASIS 7 Investigators. N Engl J Med. 2010 ;363:930-42. Mehta SR, et al. Lancet 2010; 376: 1233–43. Wallentin L, et al. Lancet 2010; 376: 1320–28. Mega JL, et al. Circulation 2009;119:2553-60. Mega JL, et al. JAMA 2011;306:2221-8.

Pgx of clopidogrel and warfarin, ready for prime time?

- It all depends on the evidence!
- … and your definition of “evidence”

Will personalized medicine impact our notion of evidence-based practice?

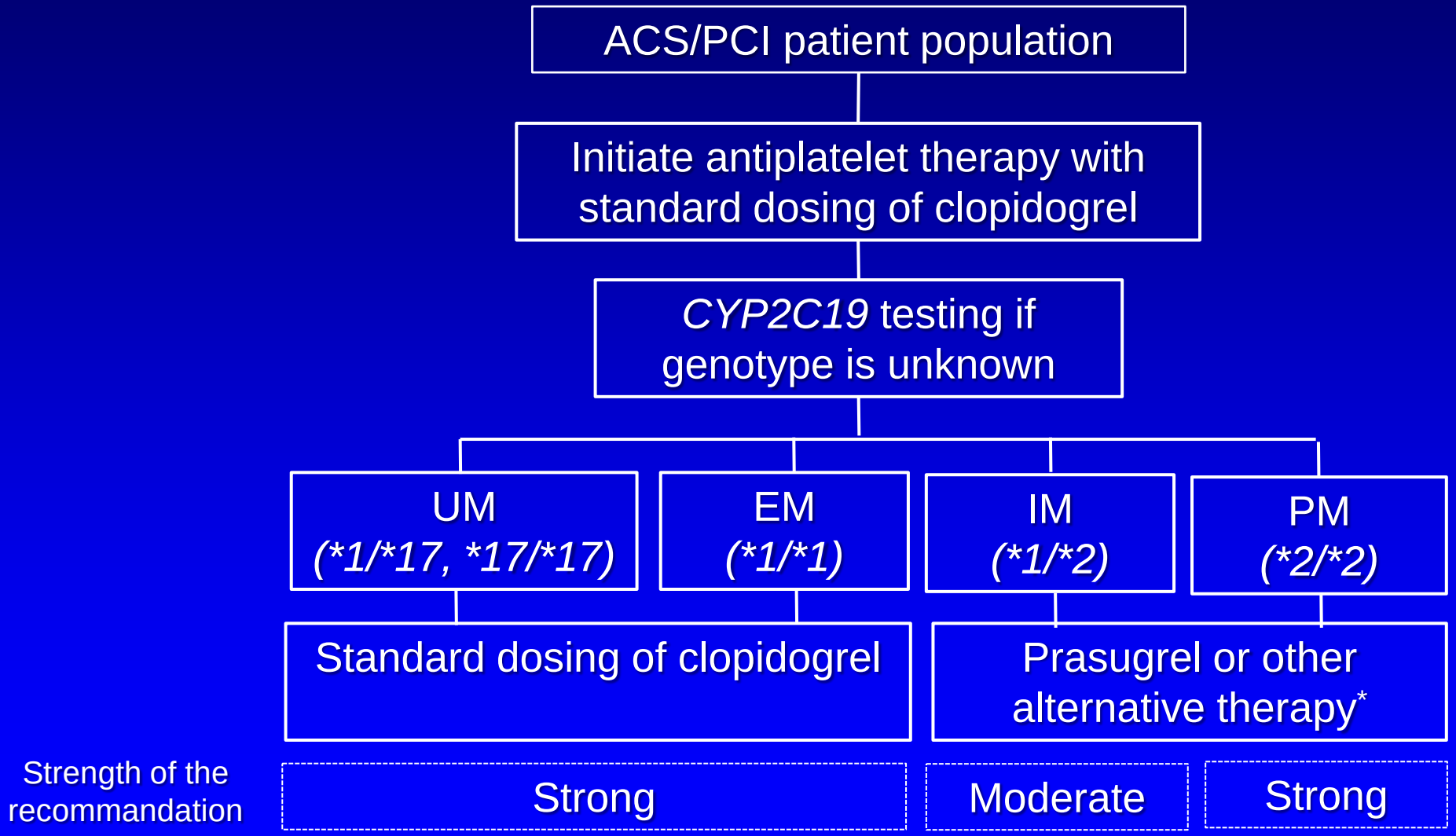
« Evidence » - based pharmacogenomics

- Marked differences in the evaluation of the "evidence"
  - American Heart Association, American College of Chest Physician
    - RCTs are at the center of the evaluation process.
  - Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
    - One (Level 2) or two (level 1) RCTs are required to provide convincing evidence of clinical utility
  - Clinical Pharmacogenetics Implementation Consortium (CPIC) of the NIH's PGX Research Network:
    - Level 1 evidence: the evidence includes consistent results from well-designed, well-conducted studies.

CYP2C19 and AHA/ACC

- *"Genotyping for CYP2C19 for a loss of function variant in patients with UA/NSTEMI (or after ACS with PCI) on clopidogrel therapy might be considered if results of testing may alter management (IIB recommendation; LOI:C)"*

The Clinical Pharmacogenetics Implementation Consortium of the NIH Pharmacogenomics Research Network - Clopidogrel



Adapted from Scott SA, et al. Clin Pharmacol Ther. 2011;90:328-32.

* If not contraindicated

Warfarin pharmacogenomics and ACCP

- « ***For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA*** *(Grade 1B).”*

Guyatt GH et al. Chest 2012 141:2 suppl 7S-47S.

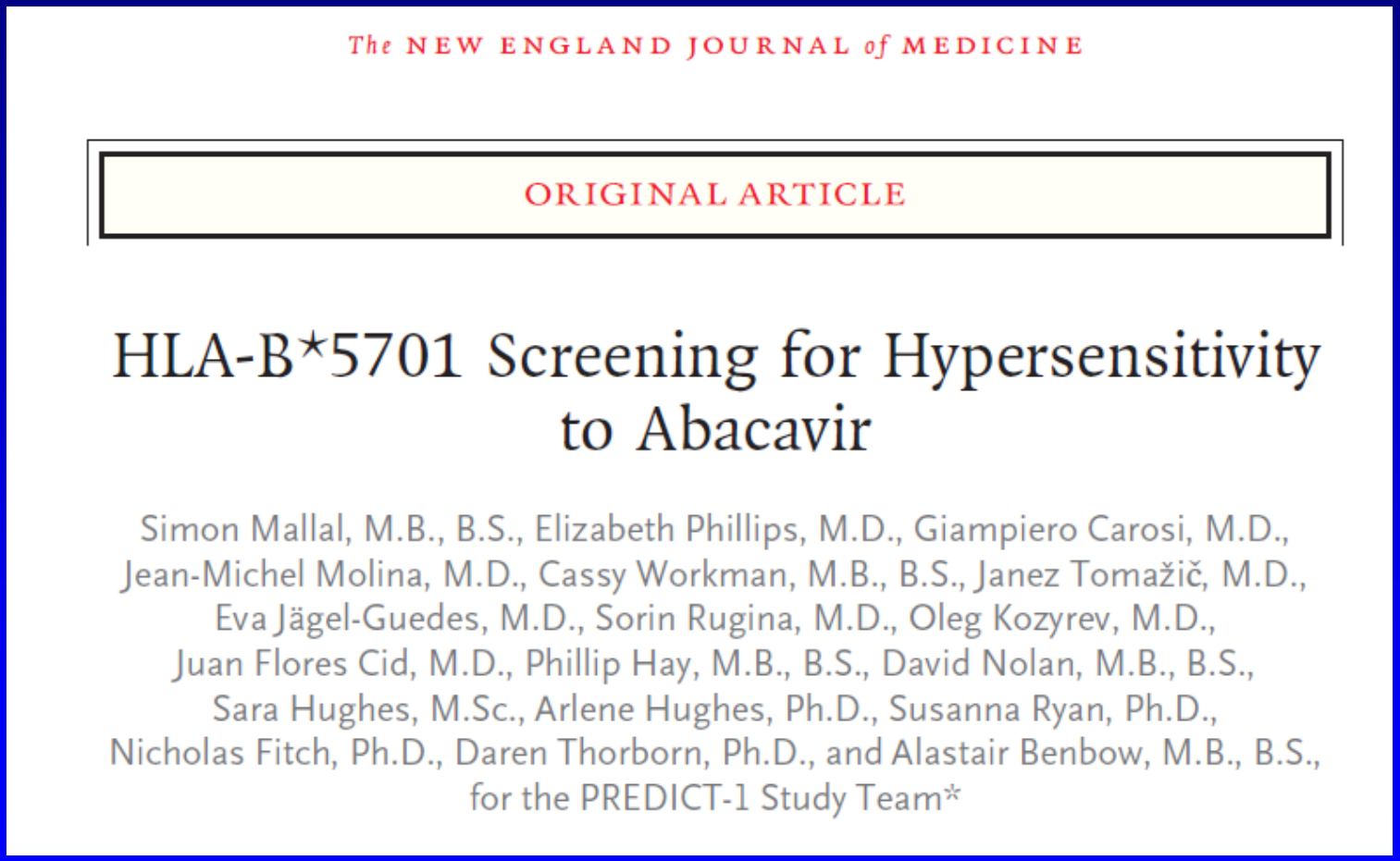
The Clinical Pharmacogenetics Implementation Consortium of the NIH Pharmacogenomics Research Network - Warfarin

- « *The recommendations for dosing based on genotype contained herein are rated as level A, or strong, (...) However, (...) the impact on clinical outcomes is unknown.* »

Johnson JA, et al. Clin Pharmacol Ther. 2011;90:625-9.

Can RCTs of Pgx markers be performed?

- Yes!



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

Mallal S, et al. N Engl J Med. 2008;358:568-79.

Are they always necessary?

- No, not always.
- We use « markers » to personalize our selection of drugs, in the absence of RCTs:
  - Choice of an antibiotic in a patient treated with digoxin or warfarin (clarithromycin vs cefuroxime)
  - Choice of a beta-blocker in a patient with severe renal dysfunction (atenolol vs metoprolol)

Are they always necessary?

- Clopidogrel
  - RCTs not necessary when alternatives exist for a specific indication (prasugrel or ticagrelor in non-ST elevation ACS undergoing a PCI)
  - Becomes a question of the cost-effectiveness of the Pgx tests
    - Would not be an issue if the information was readily available
      - Do we have RCTs of all drugs for which we adjust dosage based on renal function?

Are they always necessary?

- Different paradigms:
  - The Pgx test leads to withholding treatment (or providing a less effective treatment):
    - Beta-blockers appear ineffective in heart failure patients who are *ADRB1* Gly389 carriers

<u>3 major ongoing randomized trials</u>:

COAG (Clarification of Optimal Anticoagulation Through Genetics)

GIFT (Genetics Informatics Trial of Warfarin Therapy)

EU-PACT (European Pharmacogenetic Approach to Coumarin Anticoagulant Therapy)

Will personalized medicine change pharmacy education?

In the United States…

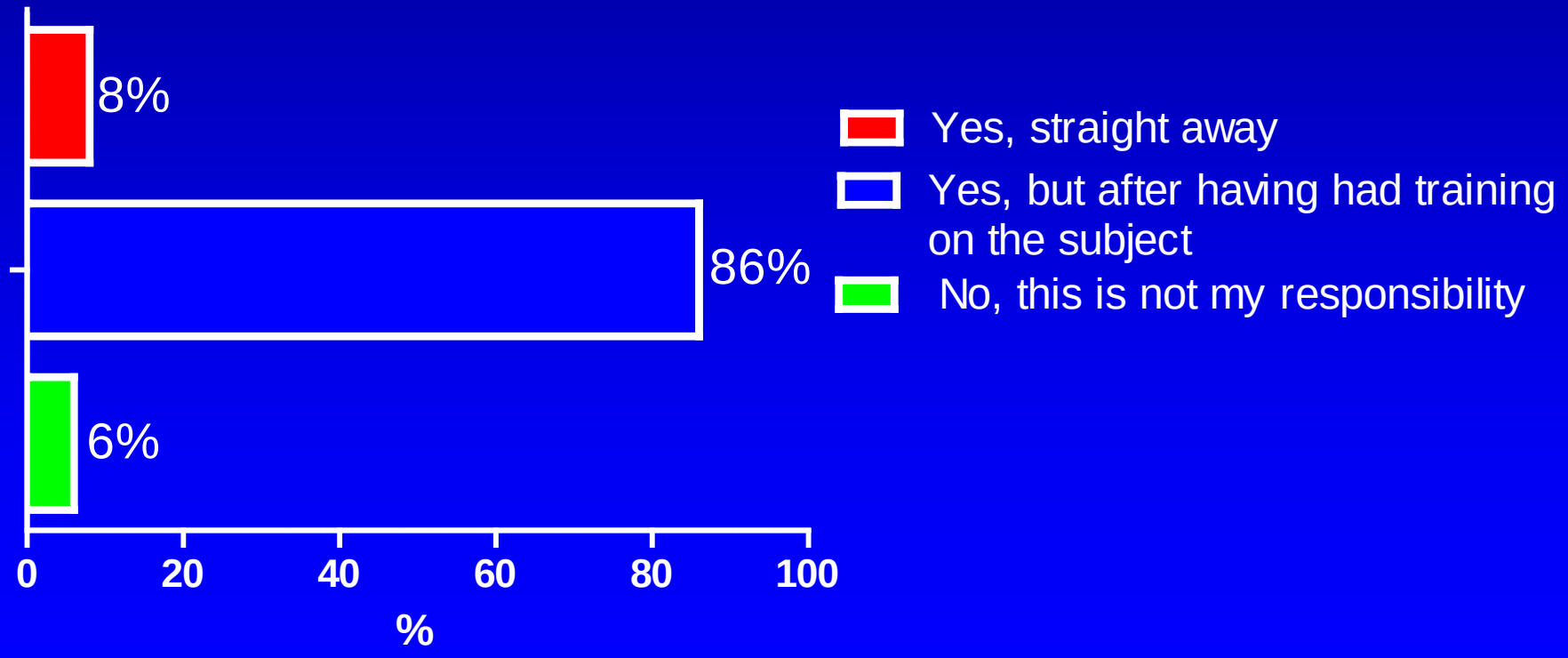
- Survey by Murphy et al.
  - PGx taught in 92% of Pharmacy schools
    - 97.1% at PharmD entry-level
    - Estimated didactic hours:
      - <10 hours: 40.6%
      - 11 to 30 hours: 42.0%
      - 31 to 60 hours: 14.5%
- Practicing pharmacists
  - Survey by Roederer et al (n = 737).
    - Ninety percent want to receive Pgx training

Murphy JE, et al. Am J Pharm Educ. 2010 Feb 10;74(1):7.
Roederer MW, et al Personalized medecine 2012;9:19-27.

In Canada…

- Survey of 284 pharmacists

Would you agree to receive your patient's pharmacogenomic testing results, interpret them and advise your patient on a treatment choice?

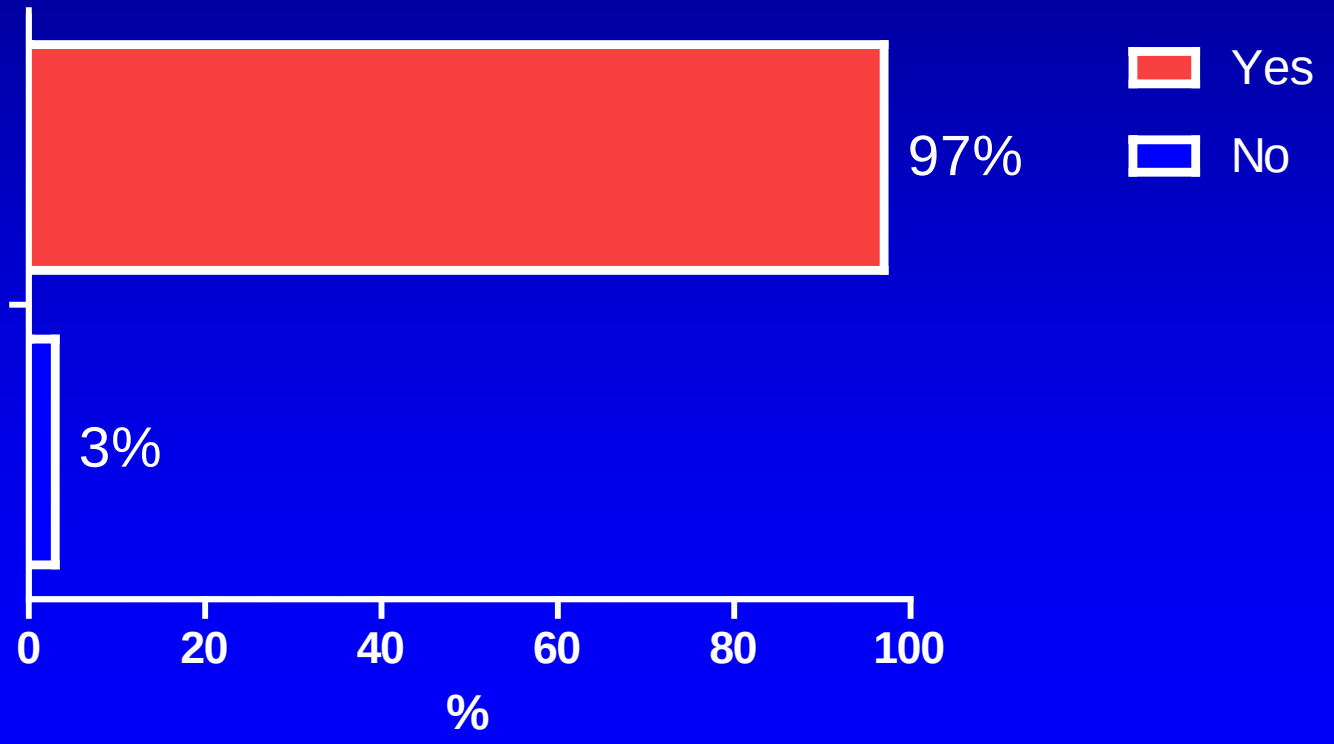


de Denus S, et al. (unpublished data)

In Canada…

- Survey of 284 pharmacists

Would you like to participate in training on pharmacogenomics?



de Denus S, et al. (unpublished data)

Conclusions

- Personalized medicine is entering clinical practice
- Because of their expertise of pharmacotherapy, pharmacists are well-positioned to face the arrival of this new field.
  - Additional training is required for most
    - Educational programs must be developed
- Pharmacists **must** play a leading role in **developing** and **implementing** personalized medicine in clinical practice.

Acknowledgements:

- **Université de Montréal Beaulieu-Saucier Chair in Pharmacogenomics**
- Montreal Heart Institute Foundation
- Funding :
  - AstraZeneca
  - Pfizer
  - Hoffman-Laroche

Faculté de pharmacie

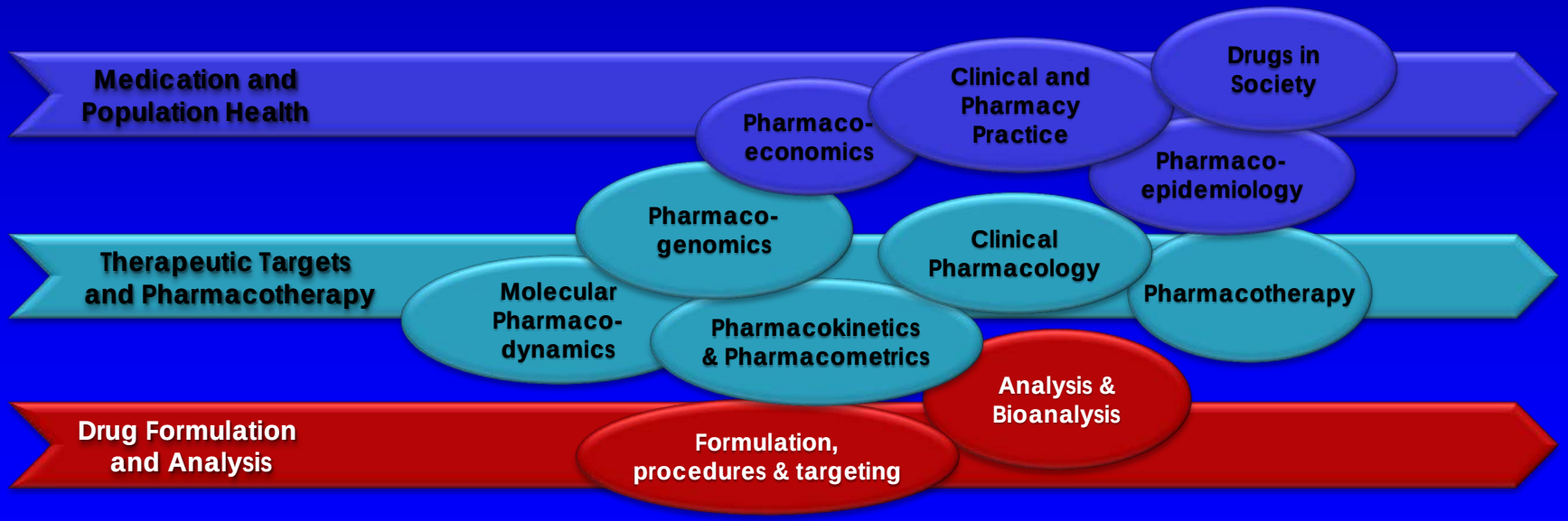
Université de Montréal

Because drugs are complex

Mission

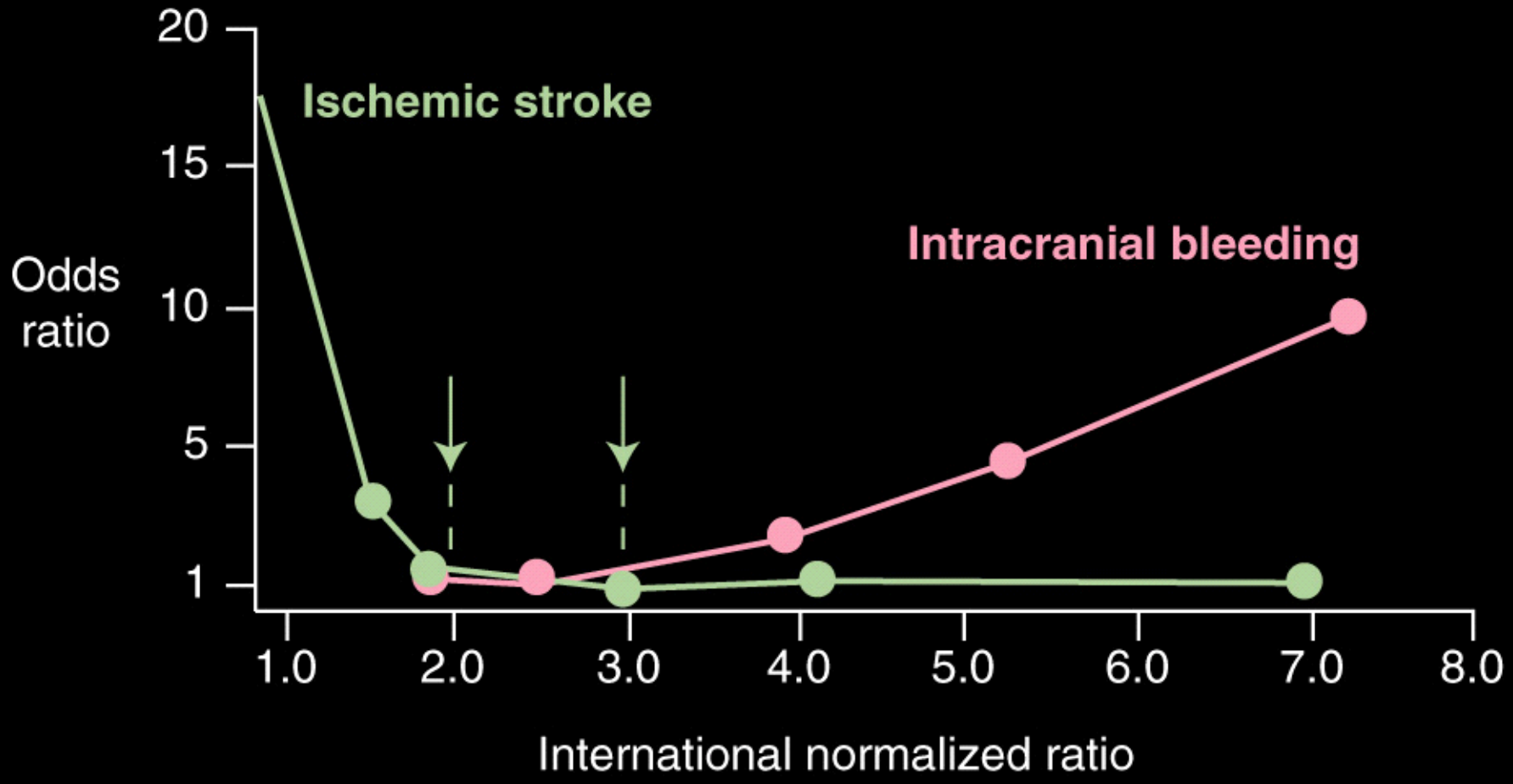
- To train devoted, creative and open-minded professionals and specialists;
- To perform basic and applied research;
- To share knowledge and expertise;
- To contribute to the development of pharmacy practice and pharmaceutical sciences.

Research Themes



www.pharm.umontreal.ca

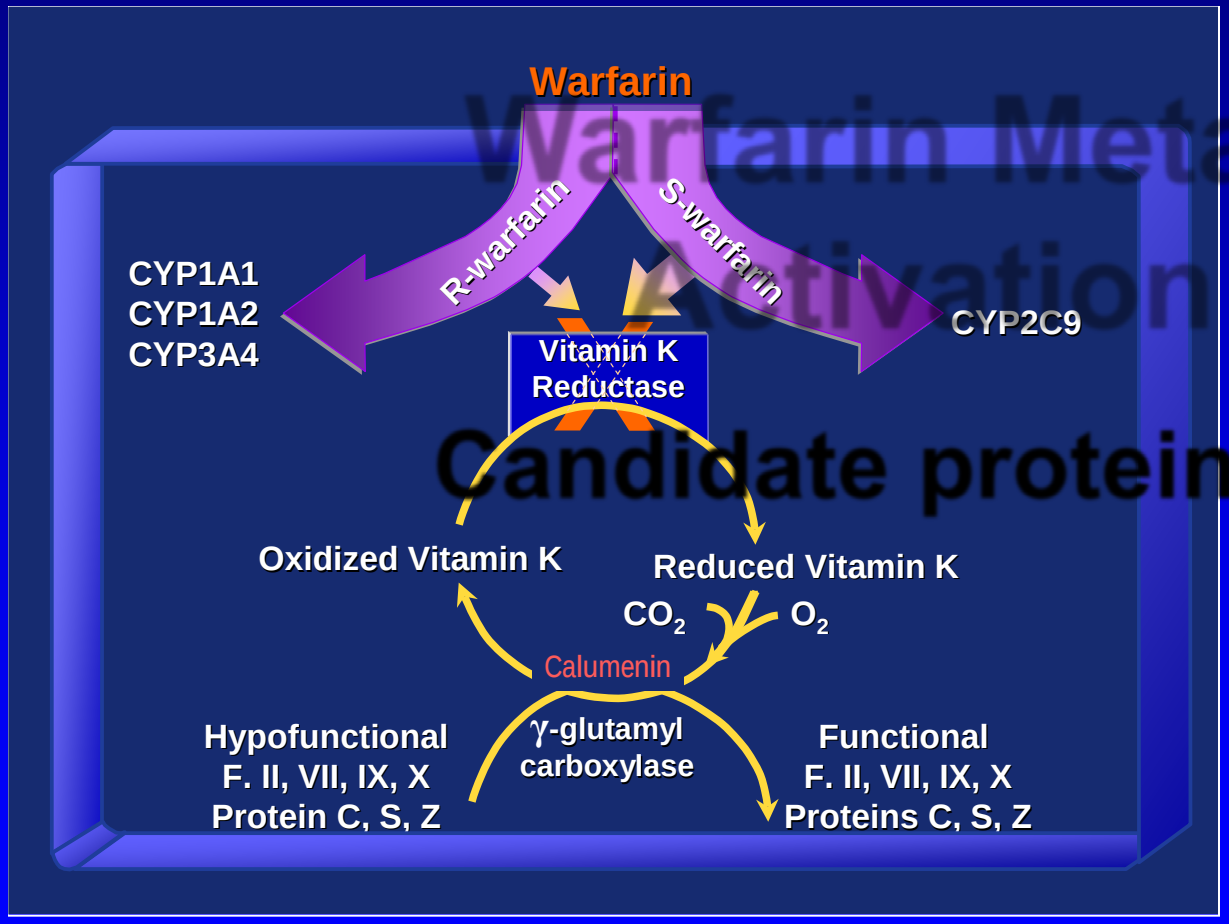
Warfarin: Narrow therapeutic window



Fuster V, et al. *J Am Coll Cardiol*. 2001;38:1231-1265.

Warfarin Metabolism and Activation Pathway

Candidate proteins in the pathway



Gage et al. 2005

Are they always necessary?

- Nevertheless, the clinical utility of PGX tests must be established before their implementation in practice.
- We need to move from analytic and clinical validity, towards clinical utility.
- Clinical validity vs utility?
  - Clinical validity: a test's ability to accurately and reliably diagnose a disorder, assess susceptibility or risk, or provide information on prognosis or variation in drug response
  - Clinical utility: evidence that test results can change patient management decisions and improve net health outcomes (balance of benefits and harms)

EGAPP Working Group; Genet Med 2009;11:3-14.
Thanassoulis G, et al Circulation 2010;122:2323-34.

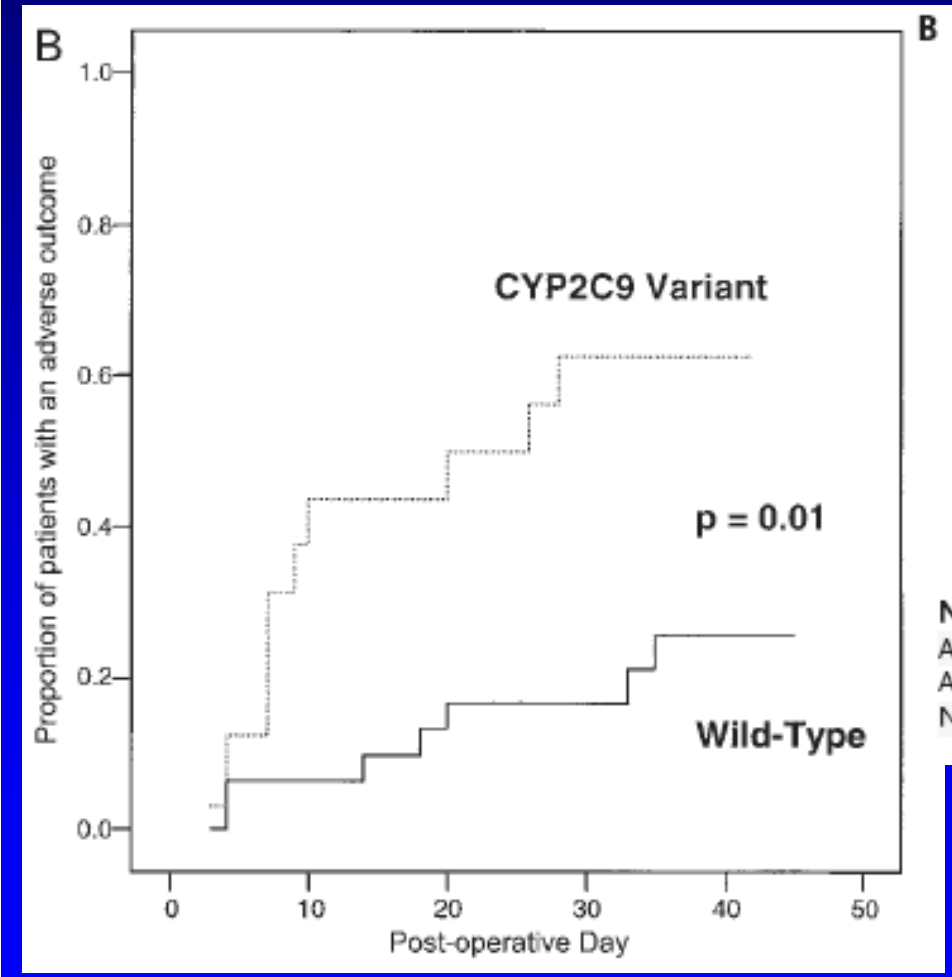
SNP* (pronounced snip!), *is…

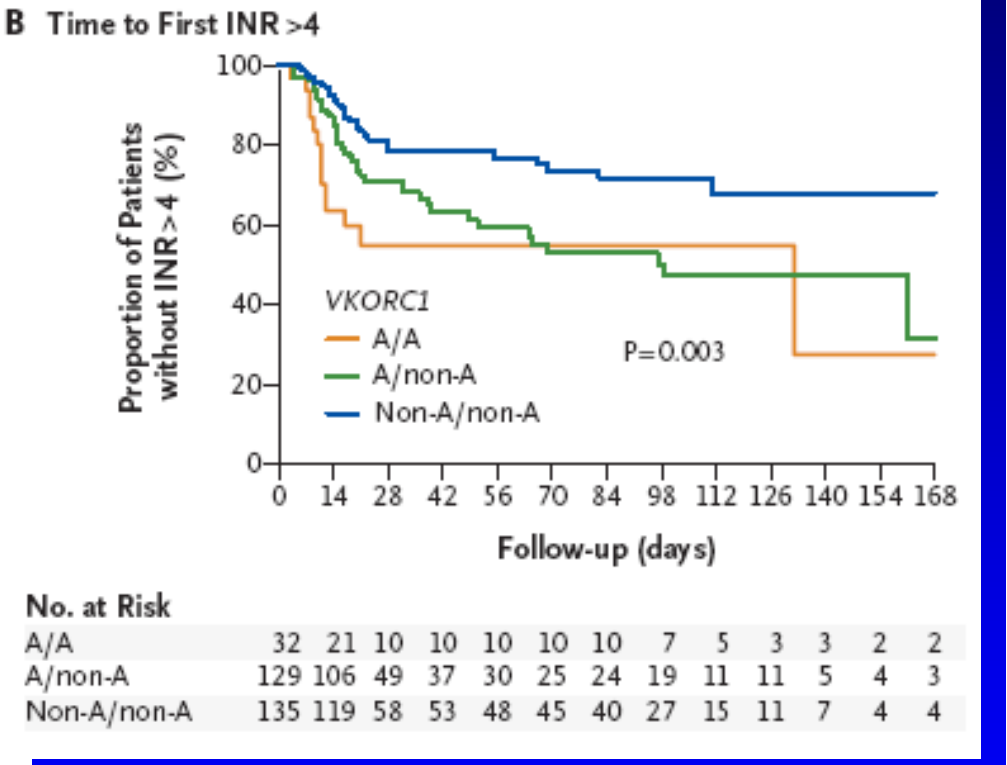
A) One of the three Rice Krispies® caracters(SNP, Crackle et Pop!)

B) A new hybrid car (The SNP!)

C) The abbreviation de *Single Nucleotide Polymorphisms*

Coumarin derivatives and excessive anticoagulation





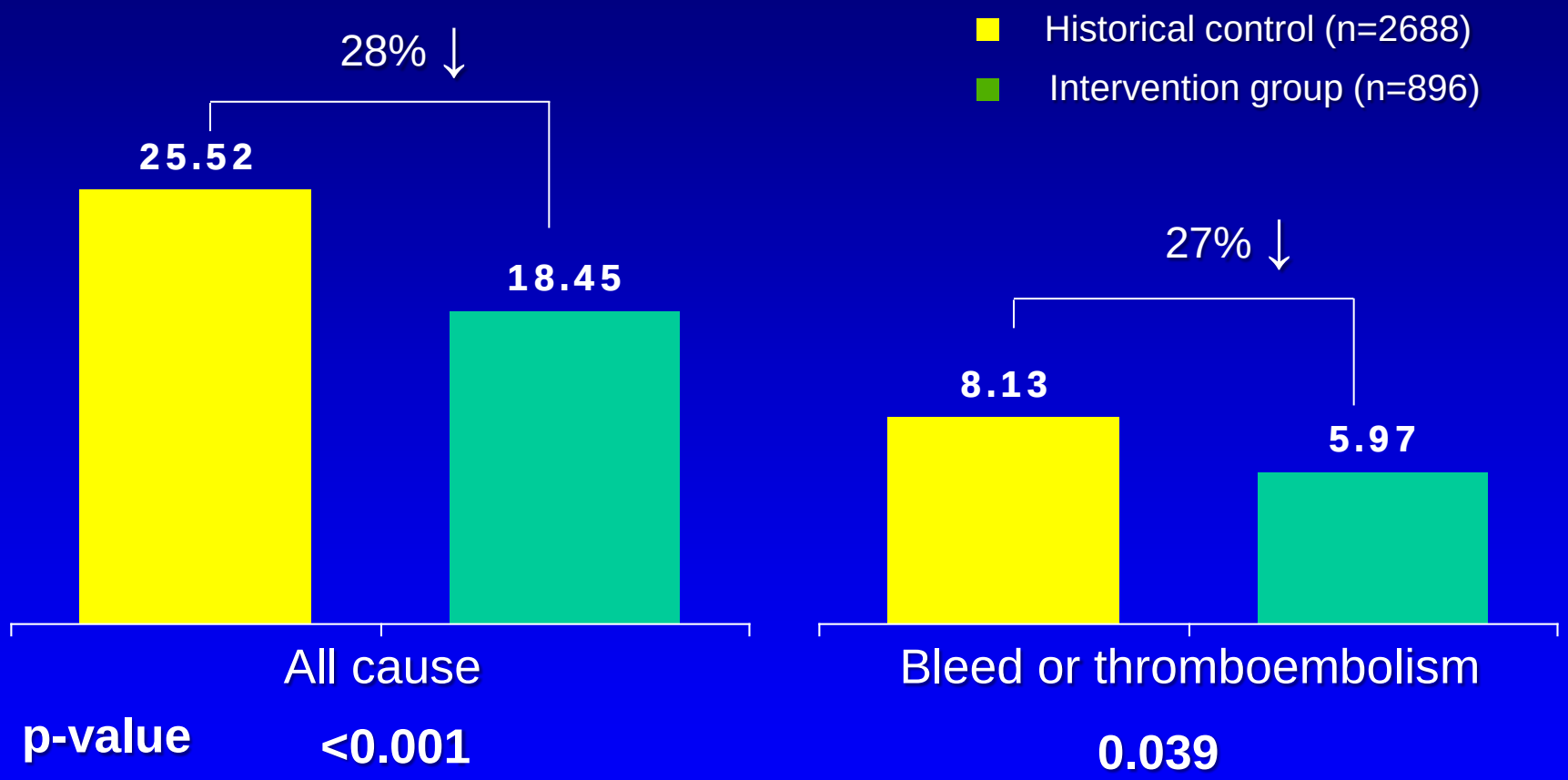
No. at Risk

A/A	32	21	10	10	10	10	10	7	5	3	3	2	2
A/non-A	129	106	49	37	30	25	24	19	11	11	5	4	3
Non-A/non-A	135	119	58	53	48	45	40	27	15	11	7	4	4

Voora L, et al. Thromb Haemost 2005; 93: 700-5

Schwarz UI, et al. N Engl J Med 2008;358:999-1008.

Results: Unadjusted 6 mo. hospitalization rates >=1 hospitalization per 100 patients/6months



Intention to treat (ITT)

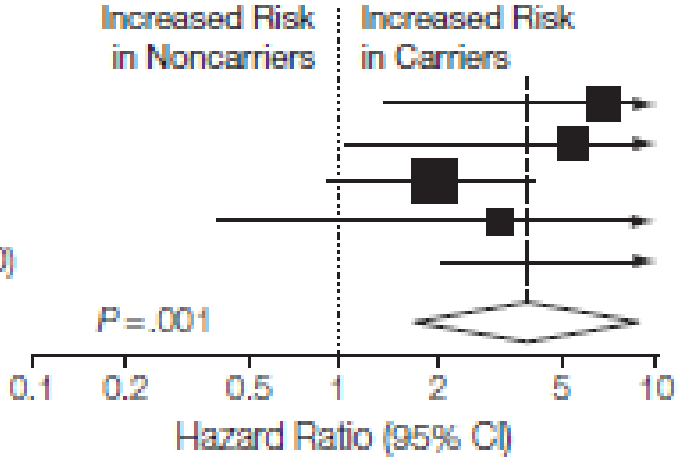
Epstein RS, et al. J Am Coll Cardiol 2010:2804-12.

Results

C Carriers of 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	2	None	
TRITON-TIMI 38	2/36	8/1014	6.79 (1.42-32.53)
AFIJI	1/8	4/162	5.46 (1.05-28.38)
RECLOSE	2/26	11/525	1.95 (0.92-4.13)
ISAR	1/47	12/1805	3.21 (0.42-24.60)
CLEAR-PLATELETS	1/5	1/160	34.41 (2.15-551.50)
Overall	7/122	36/3666	3.97 (1.75-9.02)

5.7% 1.0%



Mega JL, et al. JAMA. 2010;304:1821-1830

"Oh, I forgot,….
here are my latest CBC, creatinine clearance, electrolytes, biomarkers and, of course… my genome …"

US monograph of warfarin

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.

Simple!

But much less precise than the algorithm available at http://www.warfarindosing.org

Finkelman BS, et al. J Am Coll Cardiol 2011;57:612–8.