Perceived challenges in genomic-based drug development

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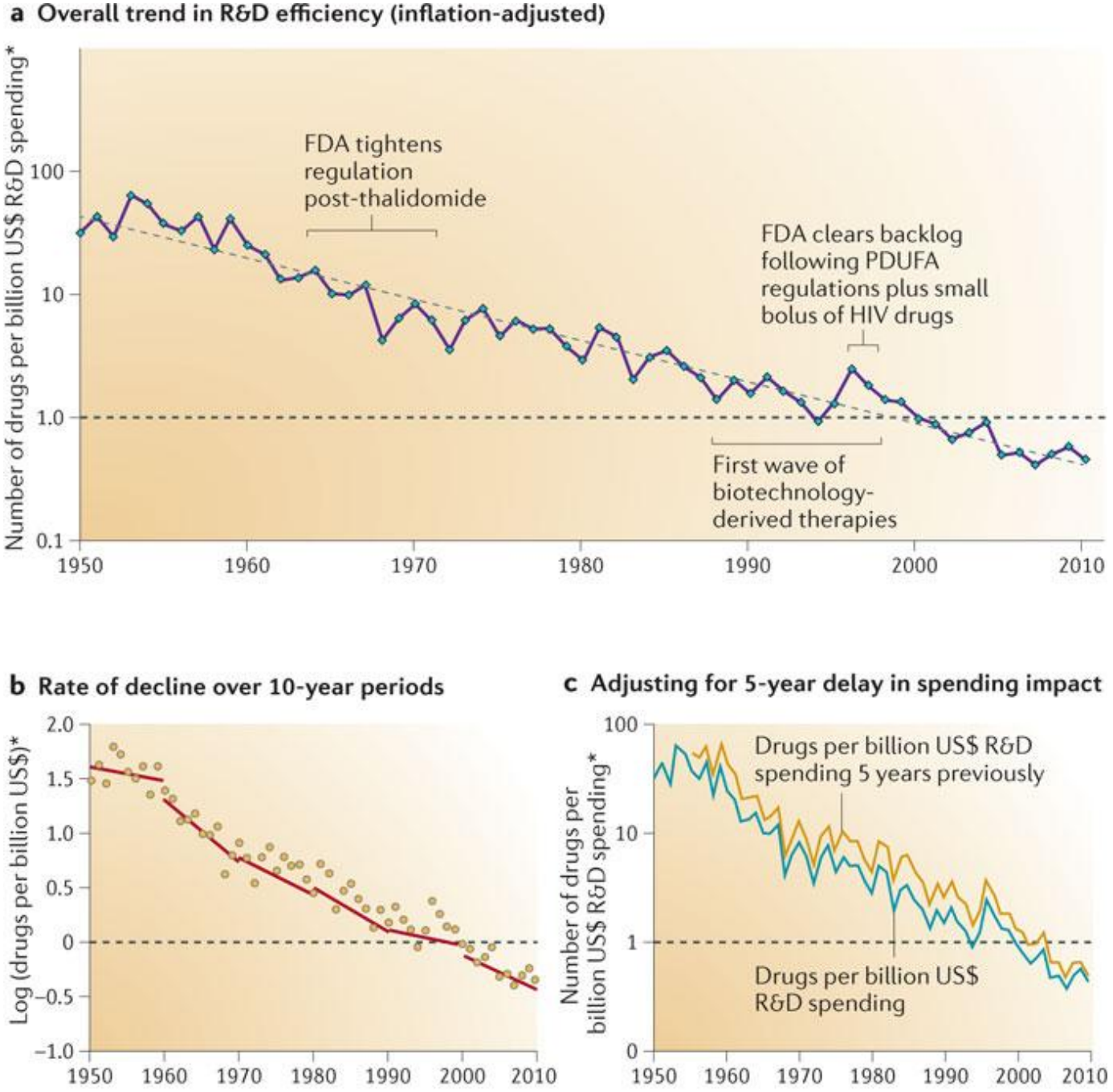
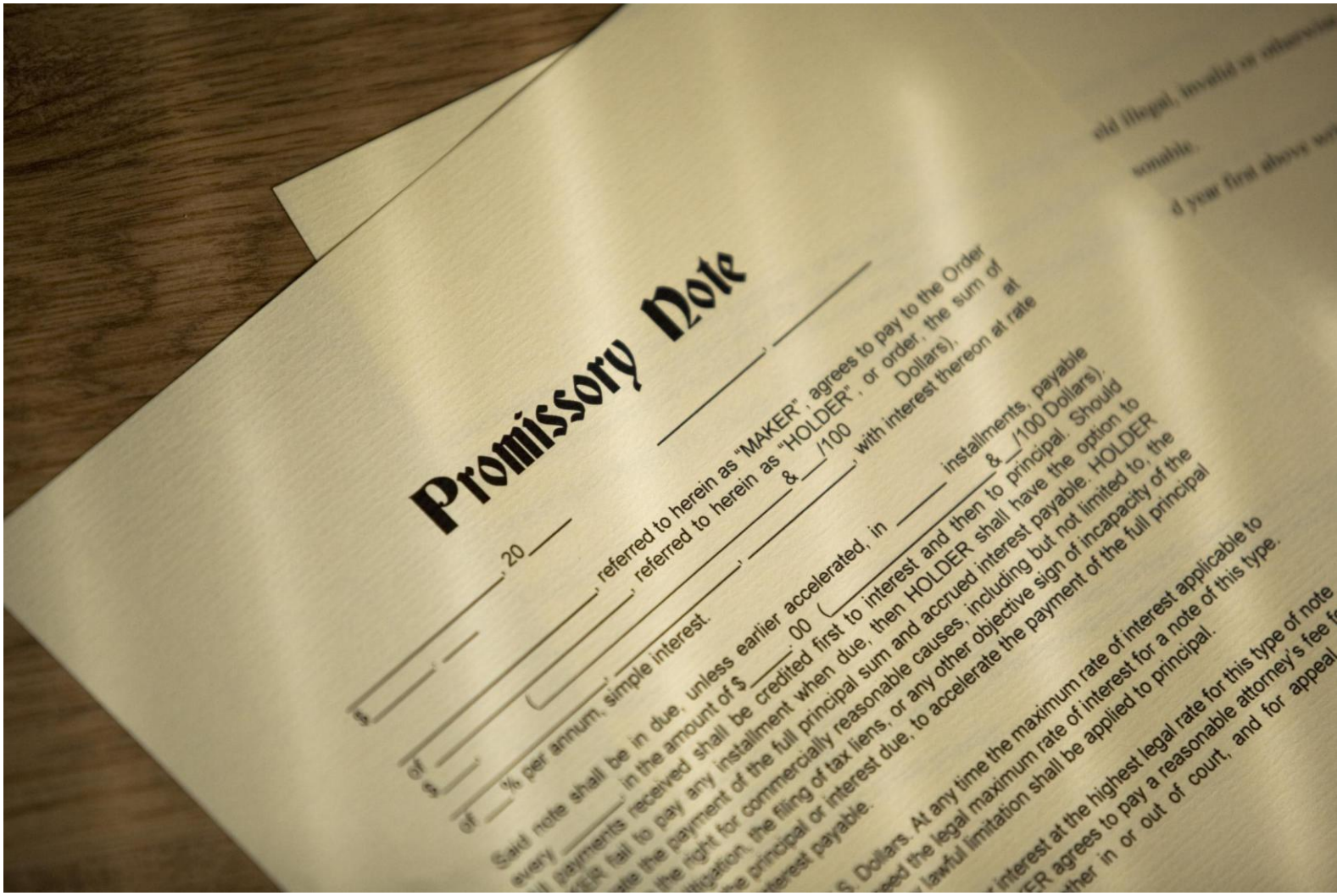
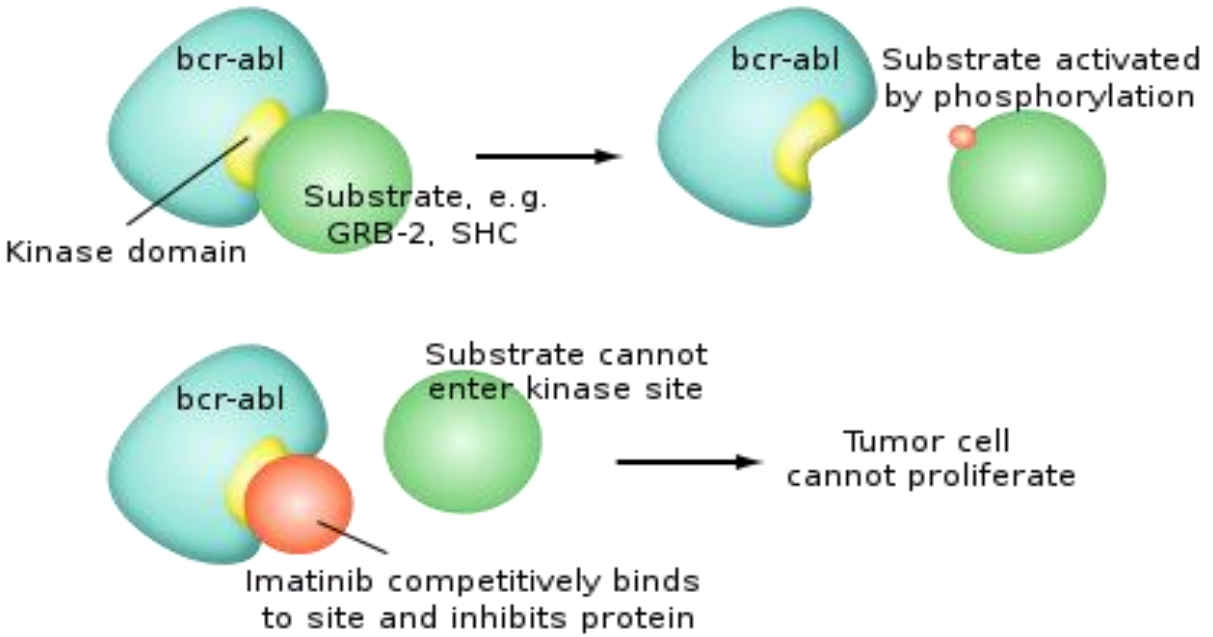

a Overall trend in R&D efficiency (inflation-adjusted)
Number of drugs per billion US$ R&D spending*
100
10
1.0
0.1
1950
1960
1970
1980
1990
2000
2010
FDA tightens regulation post-thalidomide
FDA clears backlog following PDUFA regulations plus small bolus of HIV drugs
First wave of biotechnology-derived therapies
b Rate of decline over 10-year periods
Log (drugs per billion US$)*
2.0
1.5
1.0
0.5
0
–0.5
–1.0
1950
1960
1970
1980
1990
2000
2010
c Adjusting for 5-year delay in spending impact
Number of drugs per billion US$ R&D spending*
100
10
1
0
1950
1960
1970
1980
1990
2000
2010
Drugs per billion US$ R&D spending 5 years previously
Drugs per billion US$ R&D spending

Genomics Based Personalization of Medicine



A Case in Point in Cancer



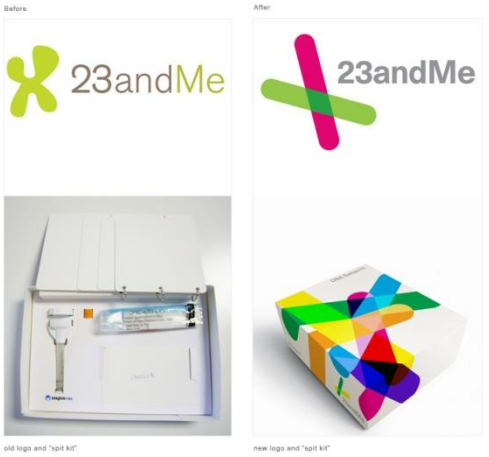
Aside from emerging resistance….

Some nice SNP examples…

- Variation in enzymes that activate drugs – warfarin and clopidogrel
- Variation in drug targets – warfarin
- Association with drug induced adverse effects – statin myopathy, abacavir hypersensitivity

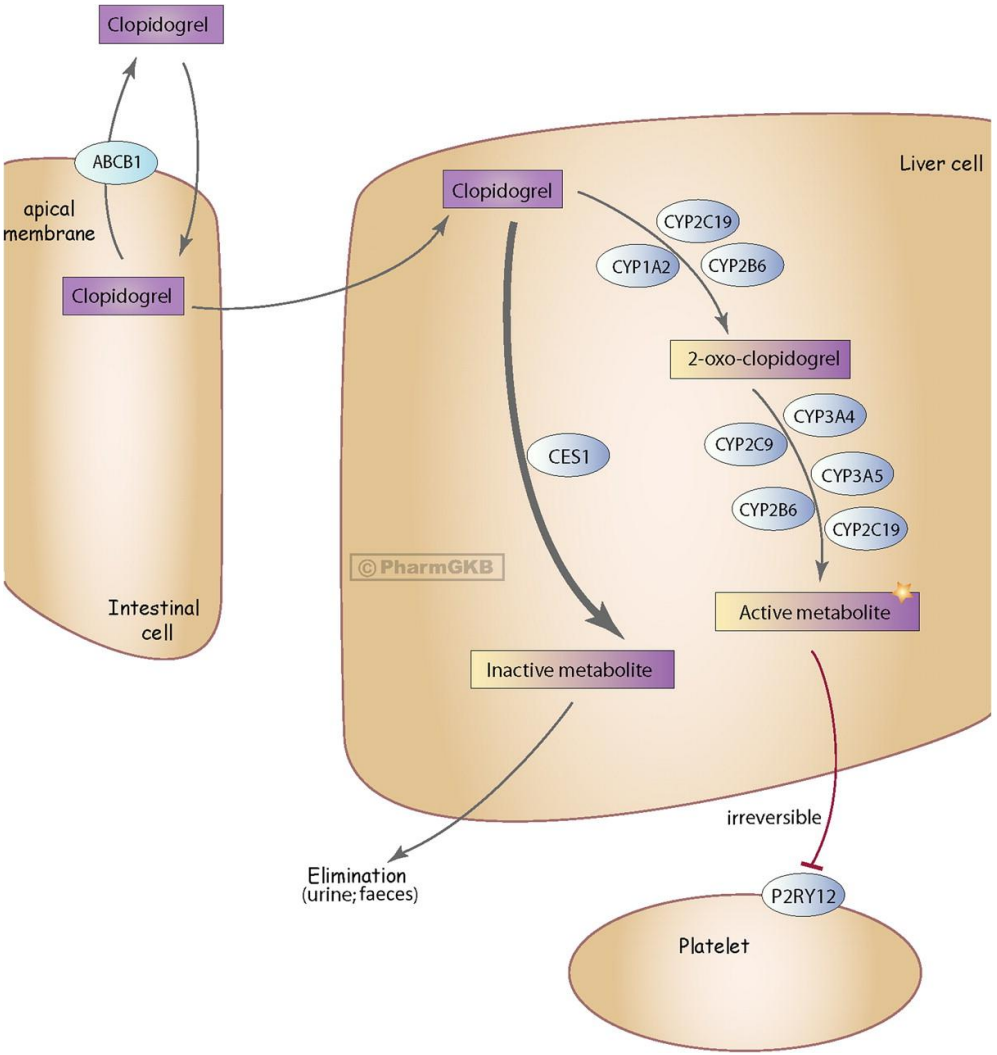
- Not to mention, Ivacaftor for CF

Pass the receptacle…

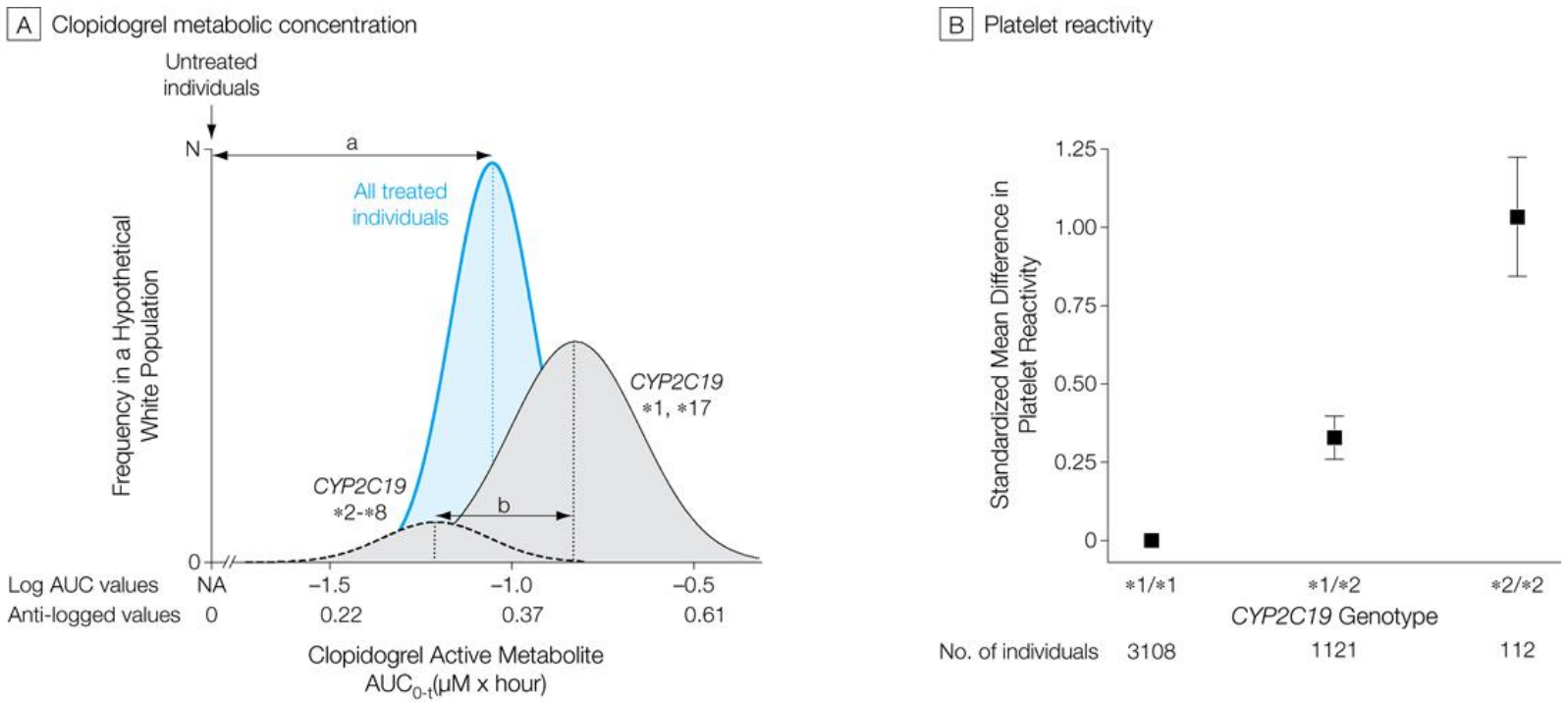


So, what's the problem

A nice example



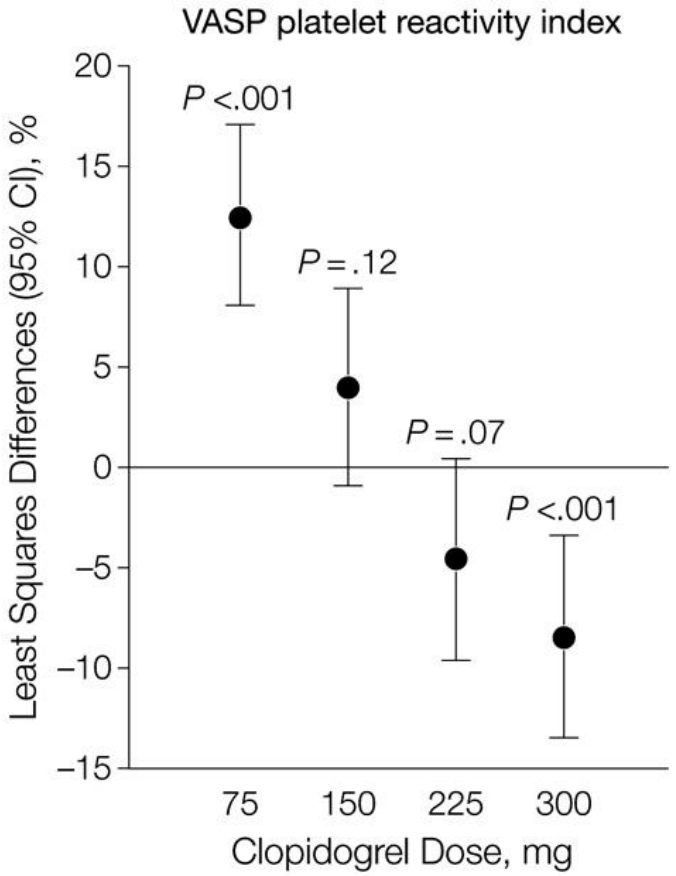
Relationship Between CYP2C19 Genotype, Active Drug Metabolite, and Platelet Reactivity

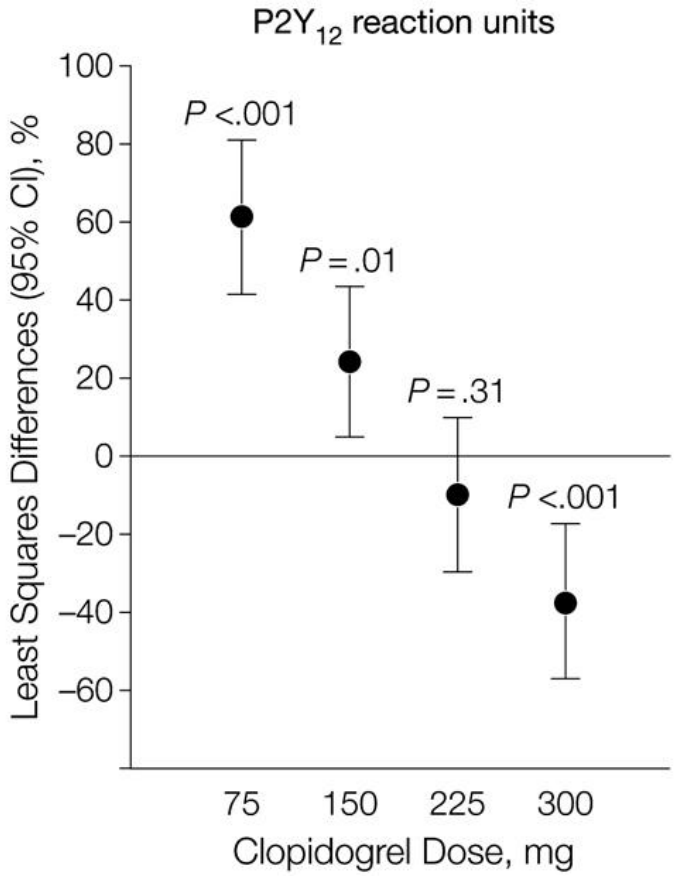


Holmes, M. V. et al. JAMA 2011;306:2704-2714

Copyright restrictions may apply.

Difference in Platelet Reactivity Between CYP2C19*2 Heterozygotes Treated With Increasing Doses of Clopidogrel vs Noncarriers Treated With 75 mg of Clopidogrel Daily



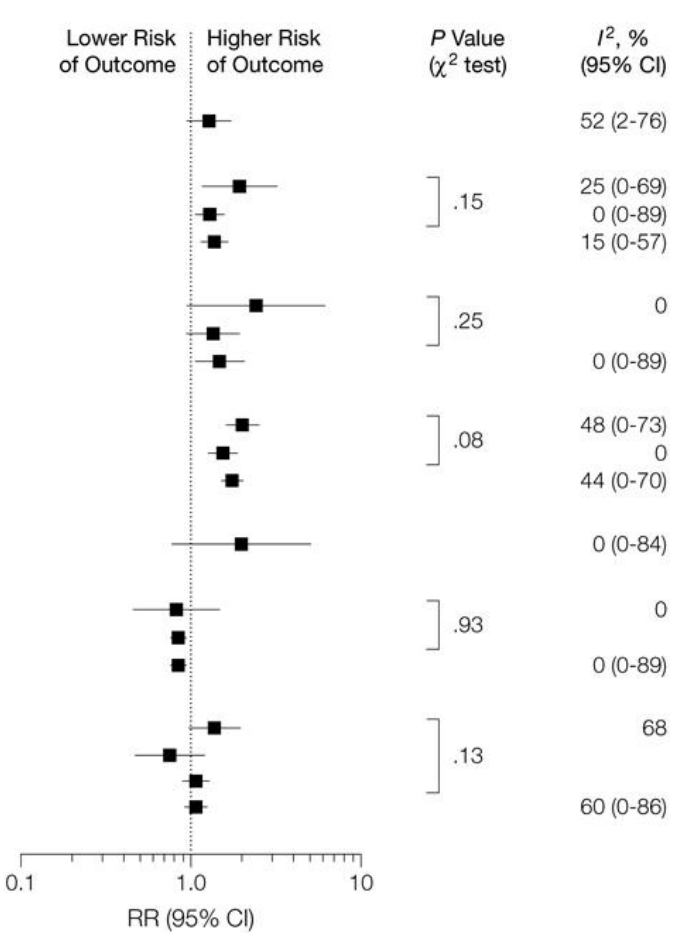


Mega, J. L. et al. JAMA 2011;306:2221-2228

Copyright restrictions may apply.

Association Between CYP2C19 Genotype (Any Copy of *2 Through *8 vs *1 or *17) and Risk of Individual Outcomes in the Treatment-Only Analysis in 32 studies

	Proportion of Total Participants, %	Studies, No.	Cases, No./Total No.		RR (95% CI)	P Value (χ^2 test)	I^2, % (95% CI)
			*2-*8	*1 or *17			
All-cause mortality							
<100 events	31	10	64/3123	128/6642	1.28 (0.95-1.73)		52 (2-76)
MI: fatal and nonfatal							
<100 events		6	31/1457	33/2179	1.92 (1.15-3.21)	.15	25 (0-69)
100-199 events		3	130/1425	266/3769	1.29 (1.06-1.58)		0 (0-89)
All studies	28	9	161/2882	299/5948	1.37 (1.13-1.65)		15 (0-57)
MI: nonfatal							
<100 events		2	13/1032	8/1219	2.42 (0.95-6.17)	.25	0
100-199 events		1	40/395	80/1064	1.35 (0.94-1.93)		
All studies	12	3	53/1427	88/2283	1.48 (1.05-2.07)		0 (0-89)
Stent thrombosis							
<100 events		12	135/4415	141/9431	2.01 (1.60-2.53)	.08	48 (0-73)
100-199 events		2	137/656	166/1506	1.54 (1.26-1.88)		0
All studies	51	14	272/5071	307/10937	1.75 (1.50-2.03)		44 (0-70)
Stroke: fatal and nonfatal							
<100 events	16	4	9/1385	11/3585	1.98 (0.77-5.09)		0 (0-84)
Bleeding: all							
<100 events		2	14/474	46/1280	0.82 (0.46-1.48)	.93	0
≥200 events		1	254/722	711/1706	0.84 (0.75-0.95)		
All studies	14	3	268/1196	757/2986	0.84 (0.75-0.94)		0 (0-89)
Bleeding: severe							
<100 events		2	45/861	82/2127	1.37 (0.97-1.96)	.13	68
100-199 events		1	21/650	81/1880	0.75 (0.47-1.20)		
≥200 events		1	143/1380	340/3506	1.07 (0.89-1.29)		
All studies	33	4	209/2891	503/7513	1.07 (0.92-1.25)		60 (0-86)



Holmes, M. V. et al. JAMA 2011;306:2704-2714

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Cautionary Tales

- Generic vs expensive alternative that doesn't much differ in efficacy at a population level
- Can overcome loss of function allele in hets with increased dosing
- Recovery of value based on theranostic …a once off test for a generic?
- Nice POC based on a biomarker from which is inferred clinical impact
- No proven impact on outcomes based on present evidence; no large prospective RCT

What about warfarin?

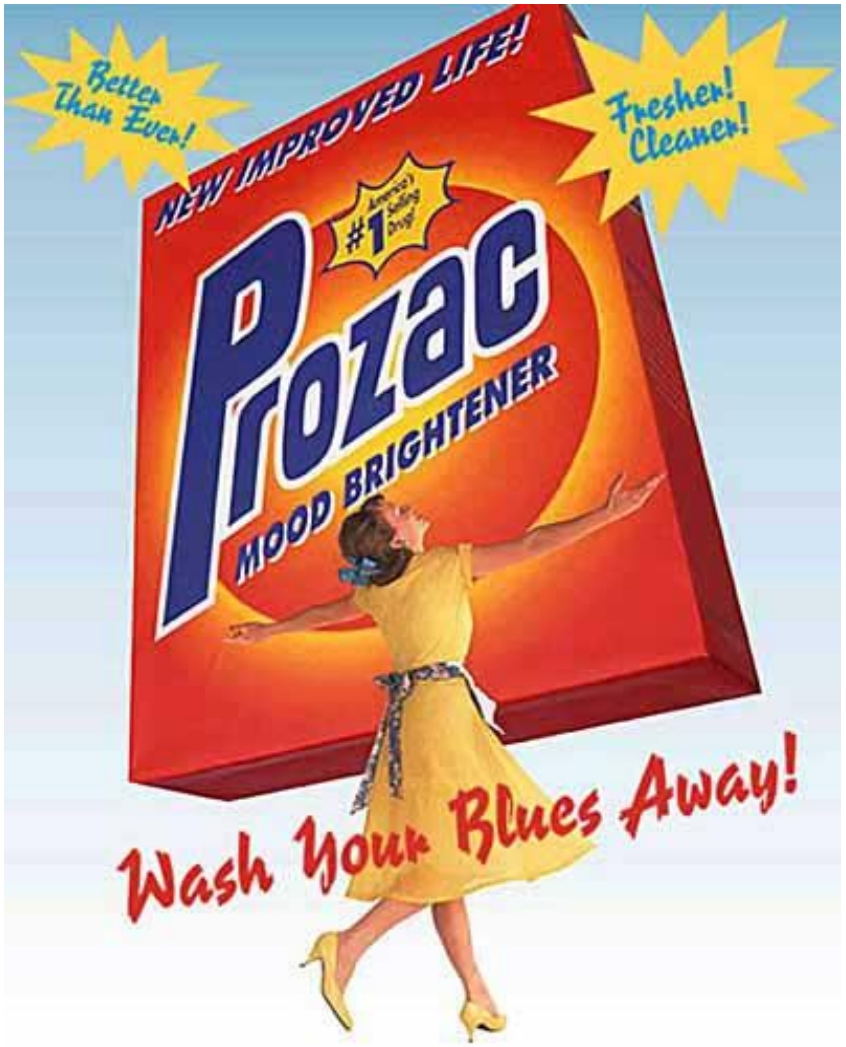
- CYP2C9 metabolizes it to active drug
- Variance in VKORC1 target conditions drug response
- Little impact on prescribing practice:

Physicians used to a pharmacodynamic test of drug action

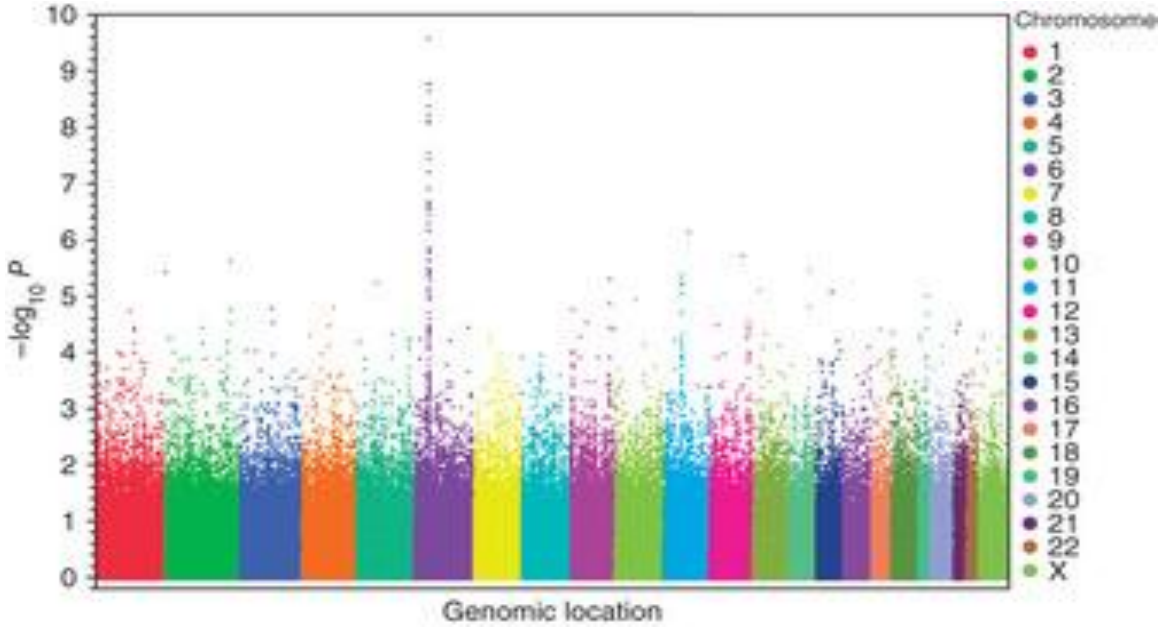
No clinical outcome studies

Who pays? Dalgatraban is the prasugrel problem

The Prescribing Physician's Primary Source of Drug Information….

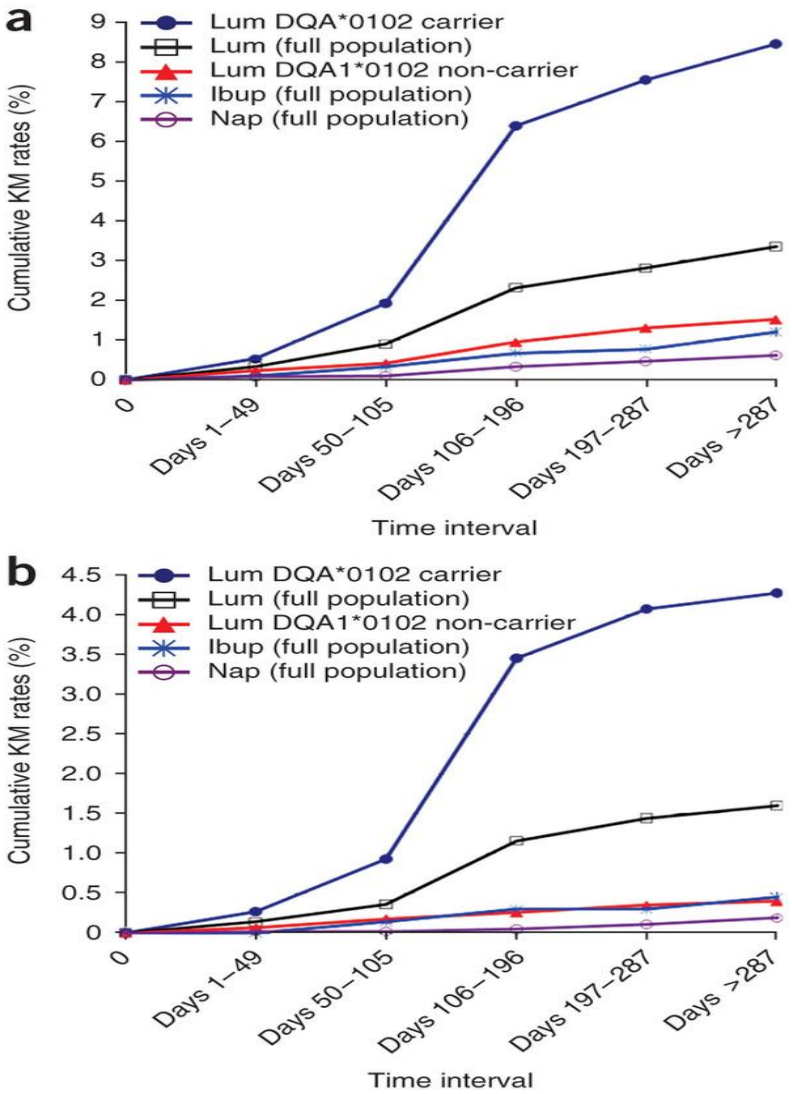


How about adverse effects?



Lumiracoxib, COX-2 inhibitor with hepatic AEs

Small GWAS study of Lumiracoxib

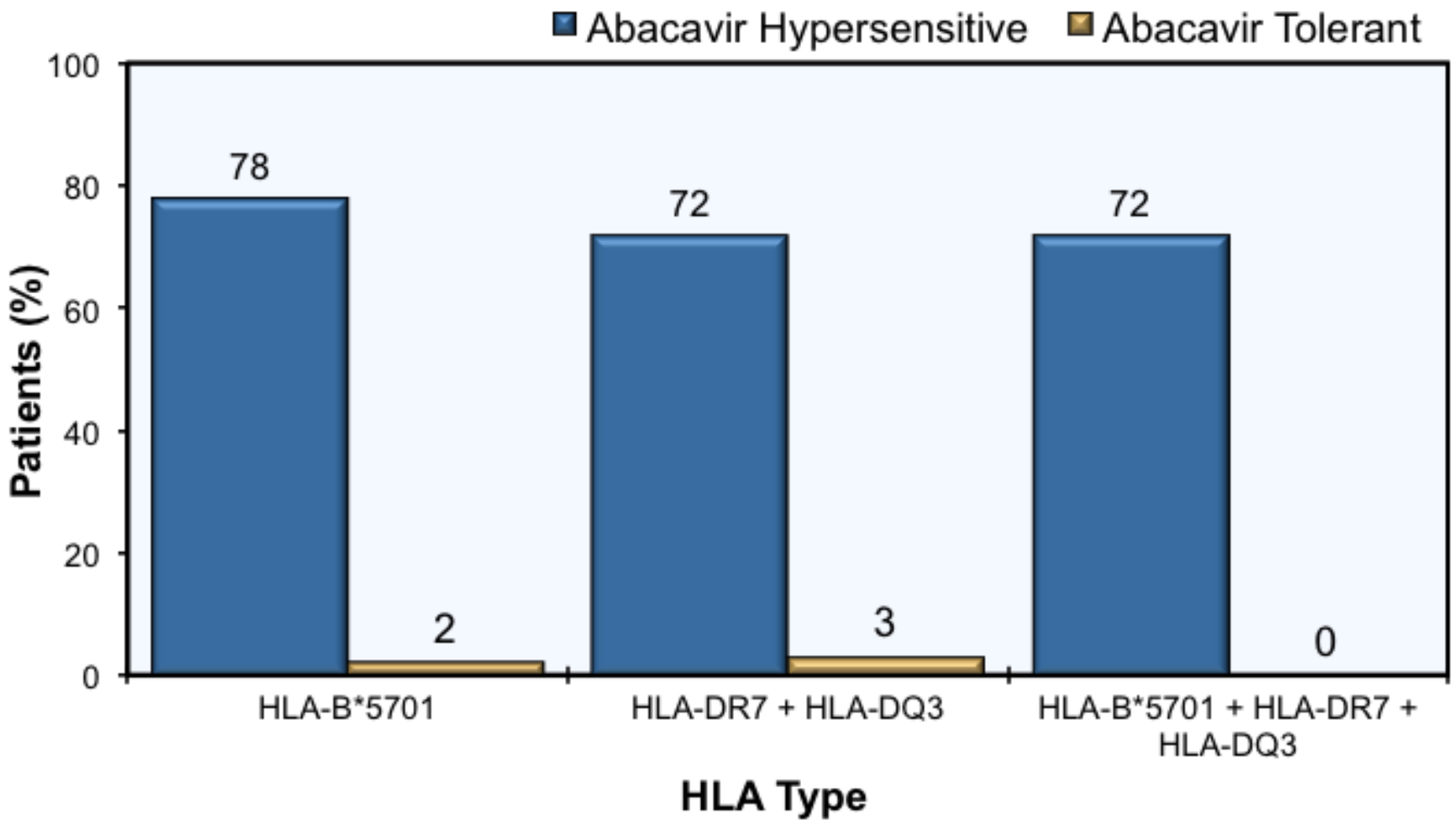


allelic odds ratio = 5.0, 95% CI 3.6-7.0

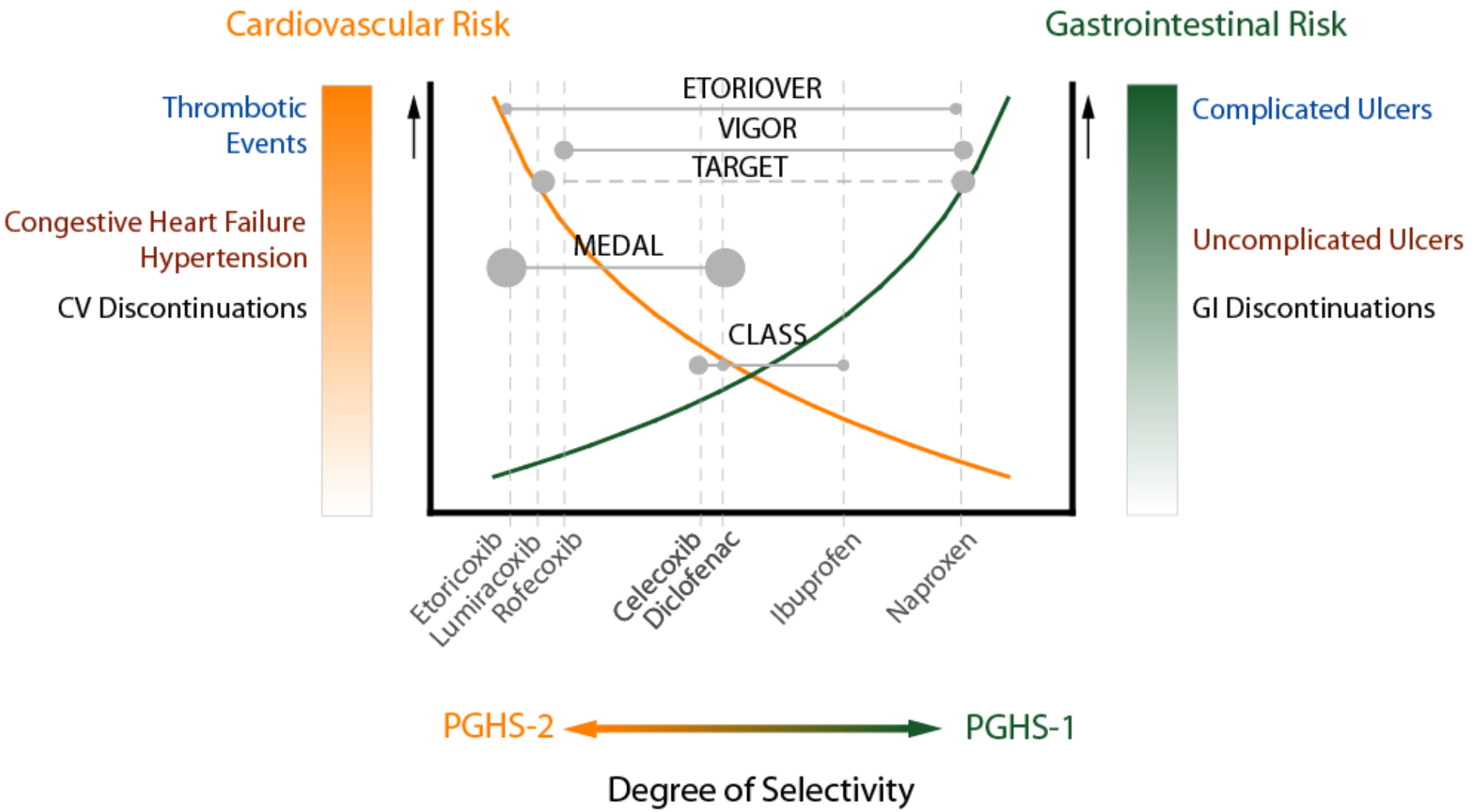
Nat Genet. 2010;42(8):711-4

41 vs 176

Prospective study leading to black box insert



Incidental collection of DNA leads to underpowered studies



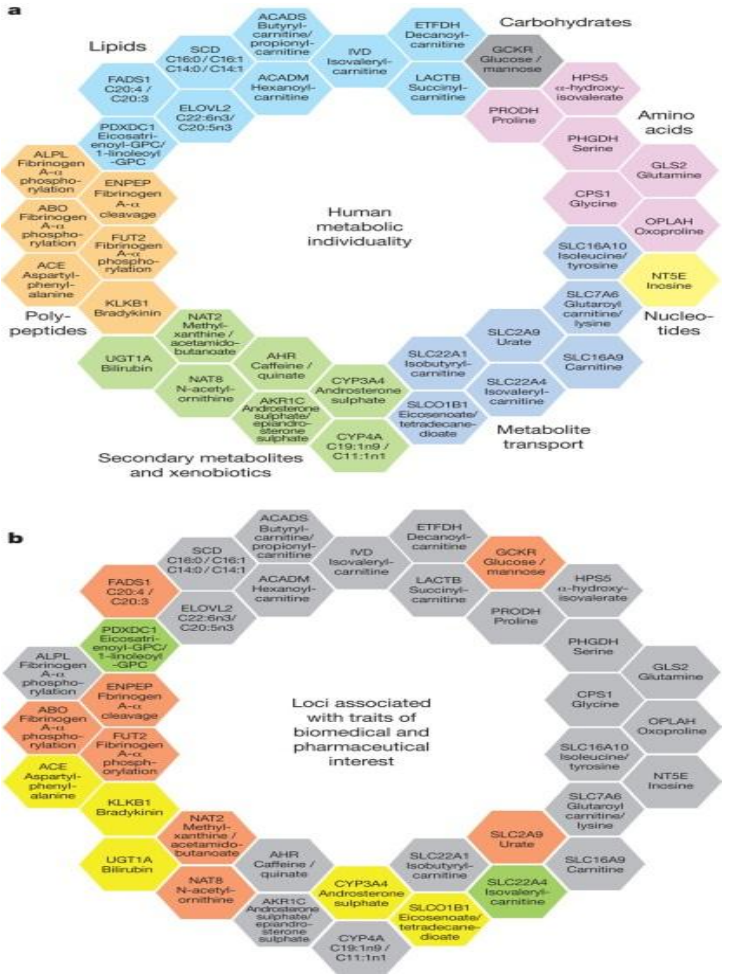
FitzGerald GA TiPS 2007.

PGN studies for drug AEs

- Need to be designed for this particular purpose
- AEs might not surface in EMRs …. All about the controls
- Inconstant information on drug labels …simvastatin
- Lower barriers to collaboration with sponsors
- FDA movement towards restricted use classifications – "behind the counter" and "on label" restriction.

One hand clapping

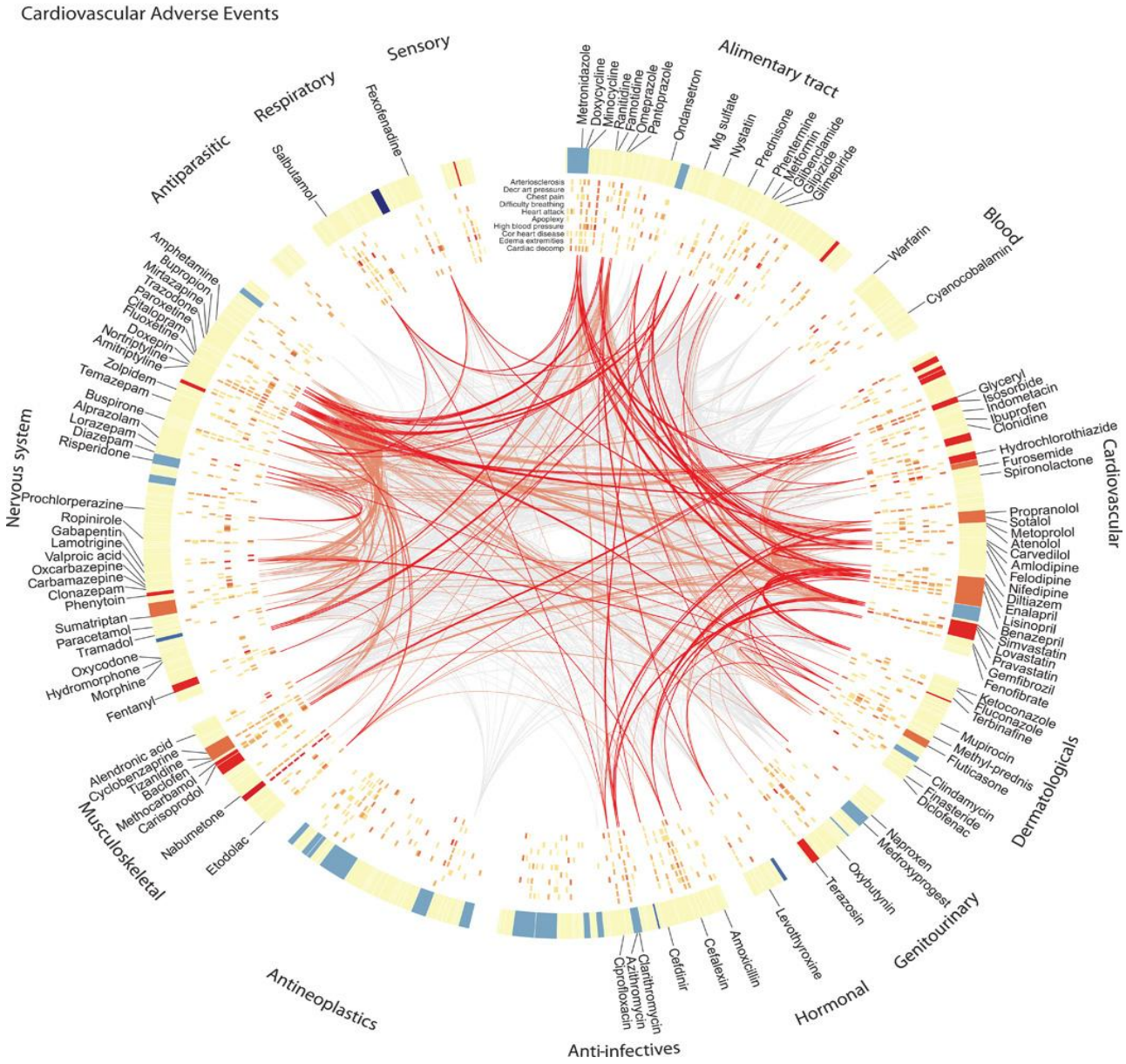
Genetic basis of human metabolic individuality and its overlap with loci of biomedical and pharmaceutical interest.



K Suhre *et al*. *Nature* **477**, 54-60 (2011) doi:10.1038/nature10354

nature

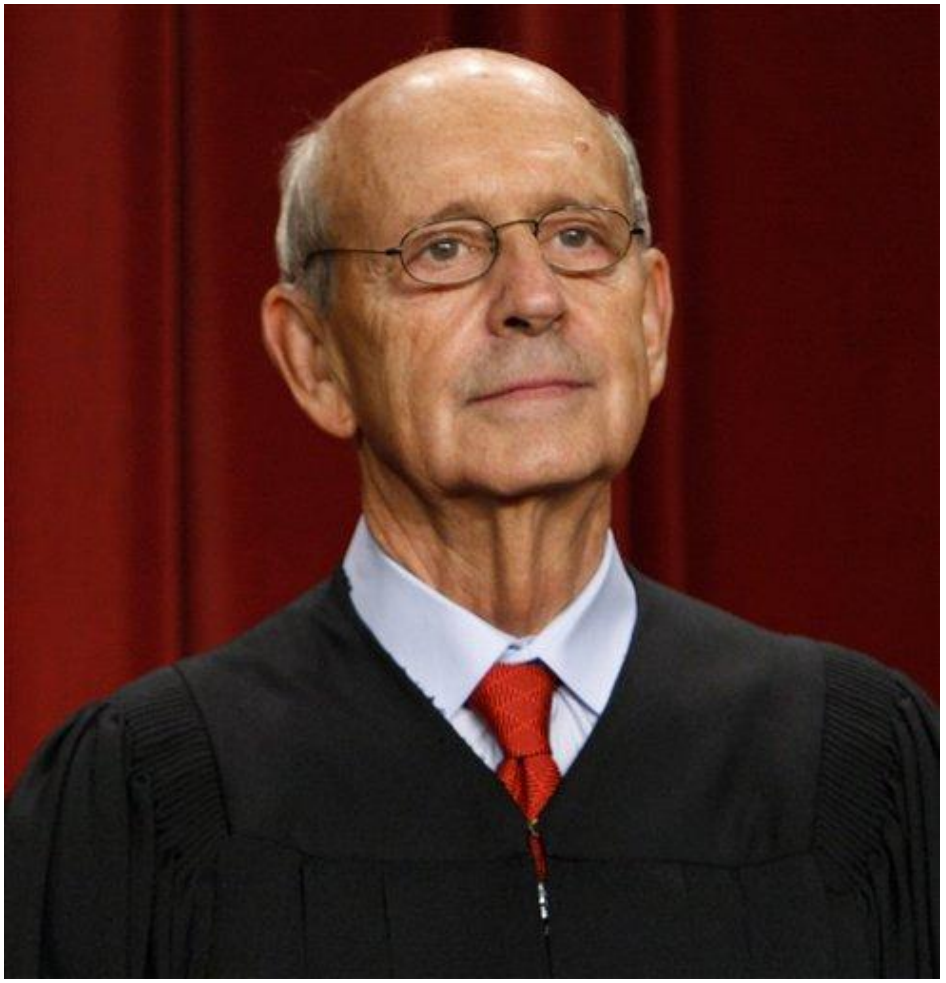
Interaction diagram depicting single-drug effects, drug-class effects, DDIs, and class-class interactions for cardiovascular adverse events.



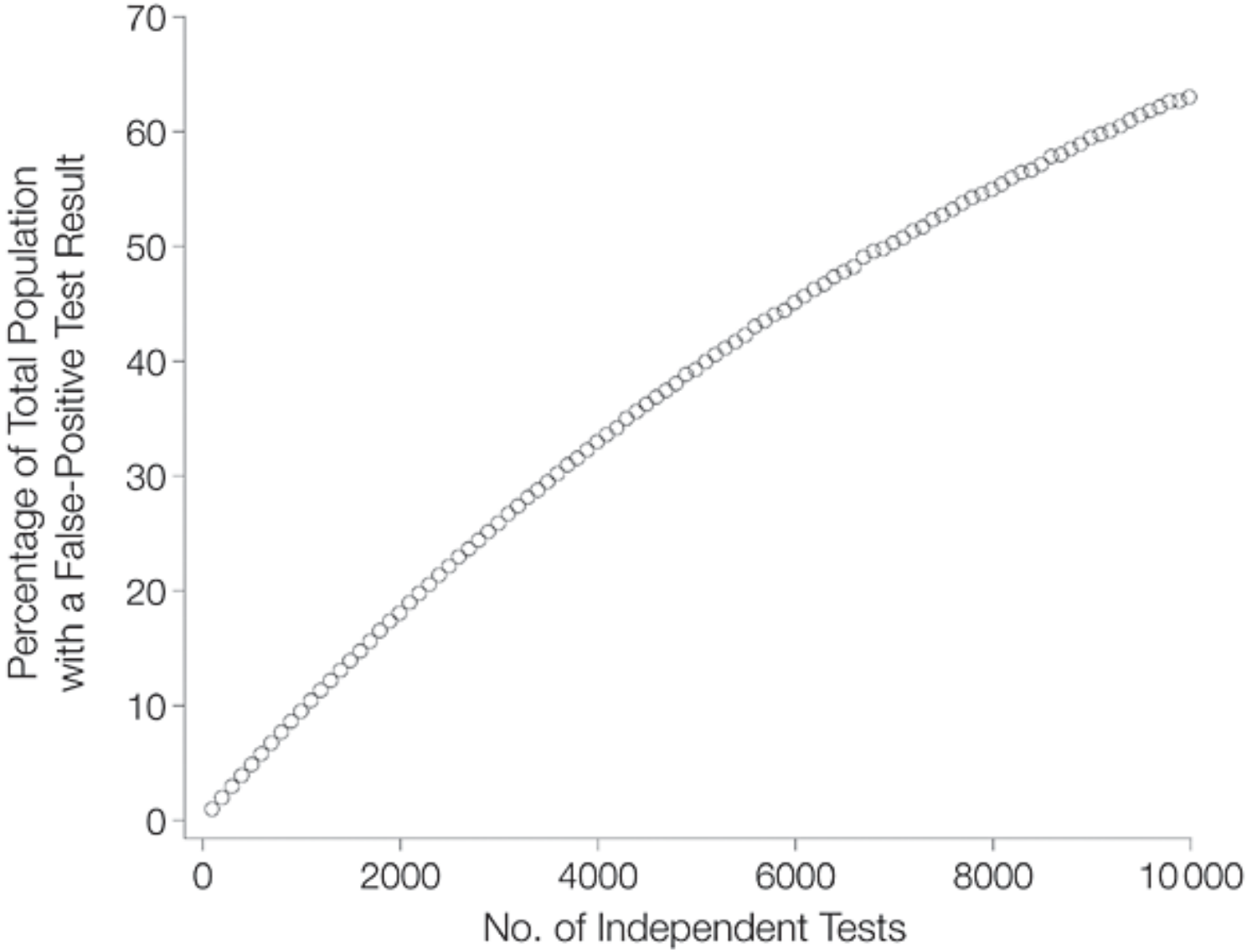
Tatonetti N P et al. Sci Transl Med 2012;4:125ra31-125ra31

Published by AAAS

Two wise men



Kohane's Incidentalome



Kohane, I. S. et al. JAMA 2006;296:212-215

JAMA

Copyright restrictions may apply.

The Breyer Legalome

- You can't patent a law of nature — "namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm."
- The company's instructions, he wrote, "simply tell doctors to gather data from which they may draw an inference in light of the correlations."
- Implications for pharmacogenetic testing that forecasts the levels of metabolites and implies efficacy or risk?

- Use of genomic testing must be shown to influence true clinical outcomes to influence practice and guarantee reimbursement

- Adoption still requires physician and patient education, financial incentive for test development, patent protection and reimbursement

- Particular opportunity for sponsor collaboration in small studies of NGS and drug evoked phenotyping of AEs

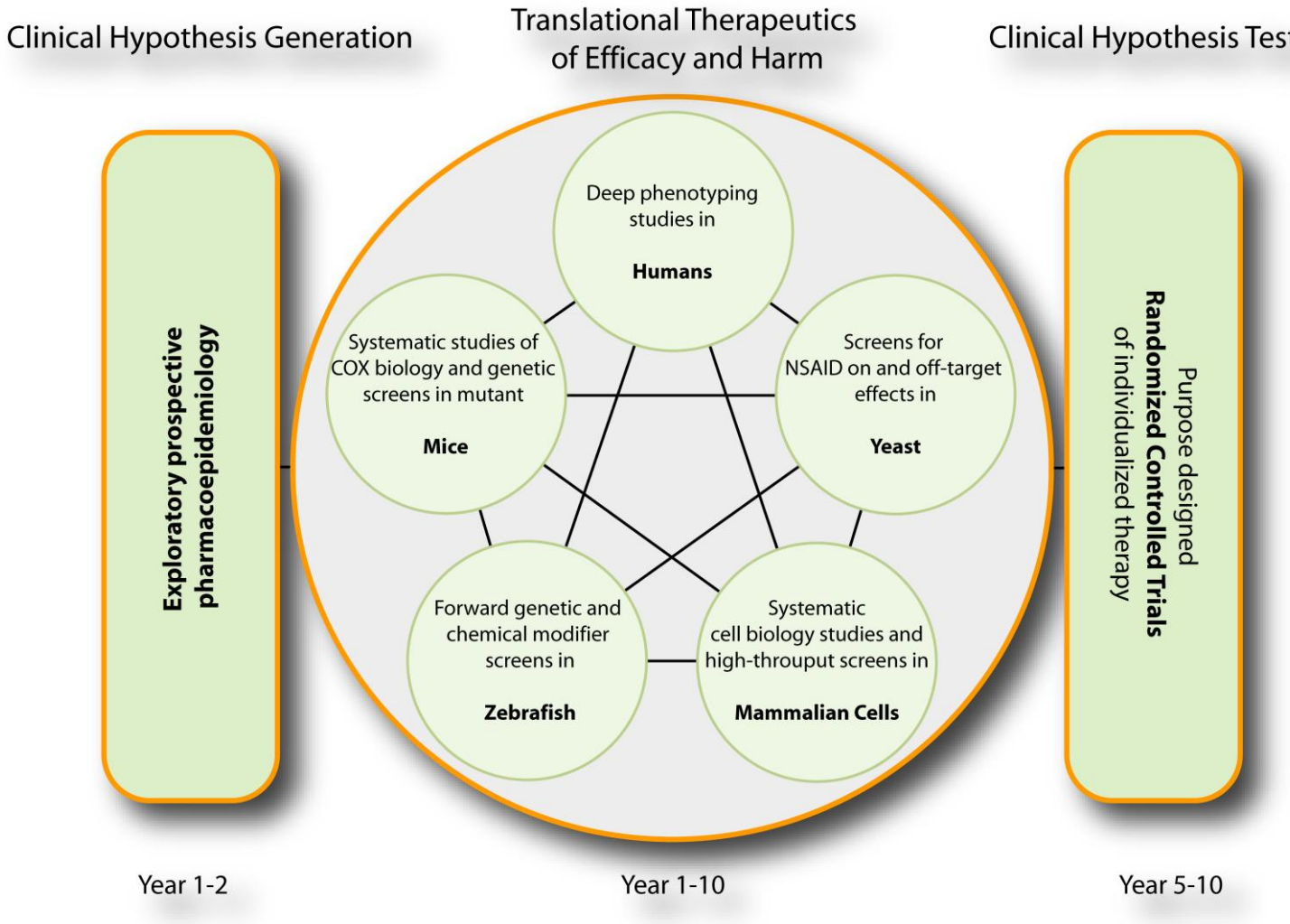
- NGS and informatics based clustering will raise new considerations of AE spectra – beware the incidentalome

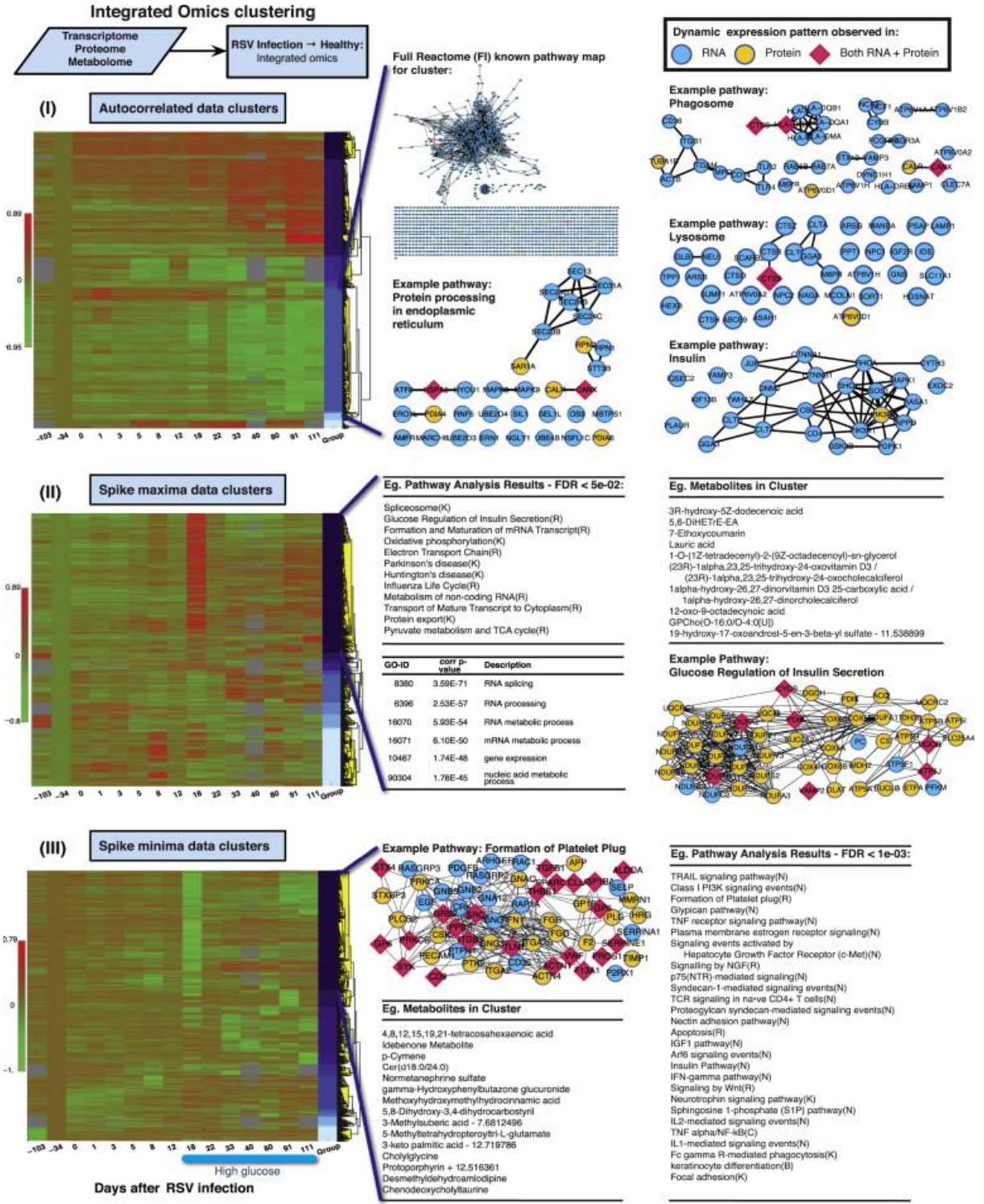
- Always remember the regulome and the legalome

That’s all for now, folks

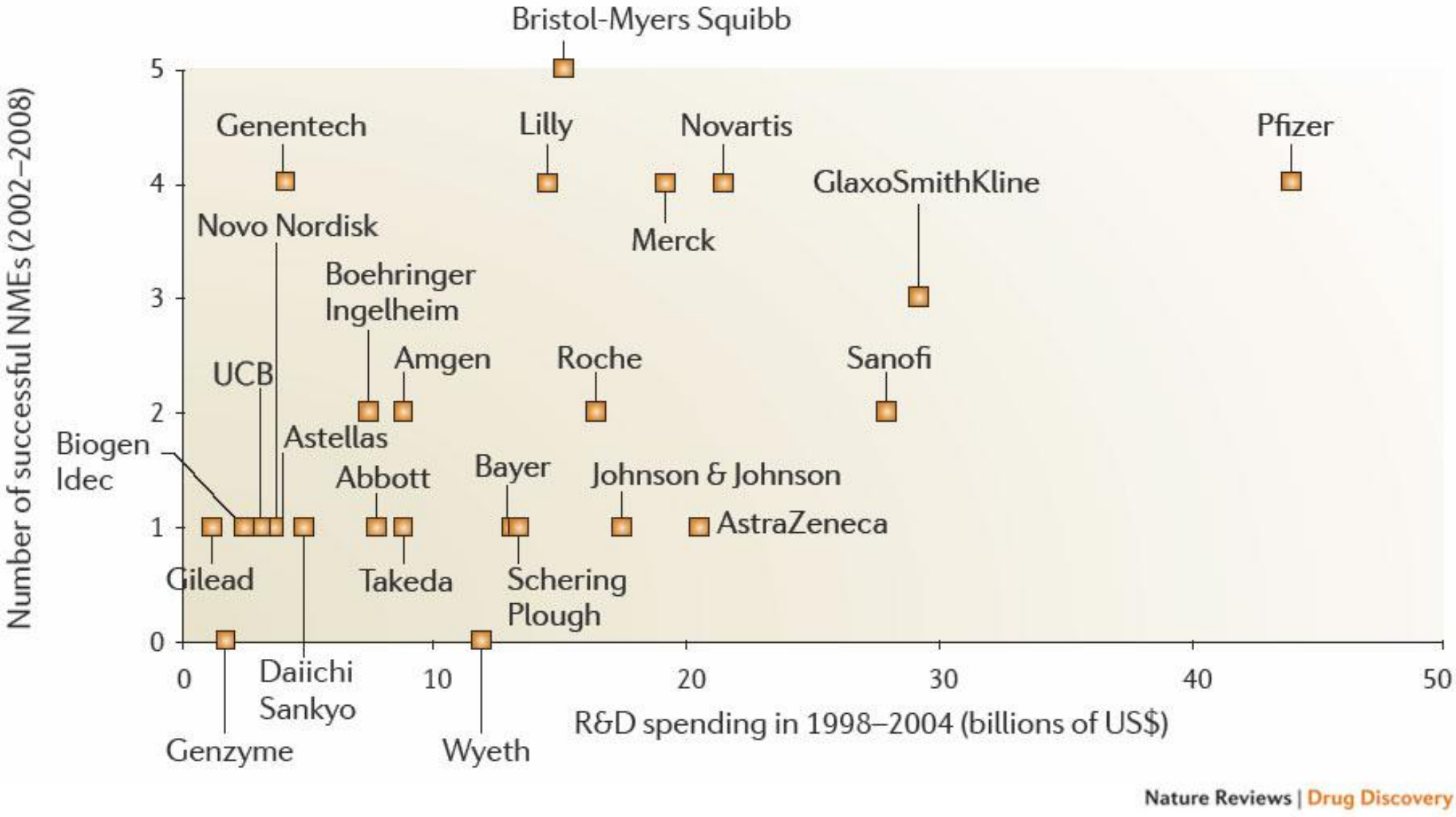
PENTACON

The Personalized NSAID Therapeutics Consortium



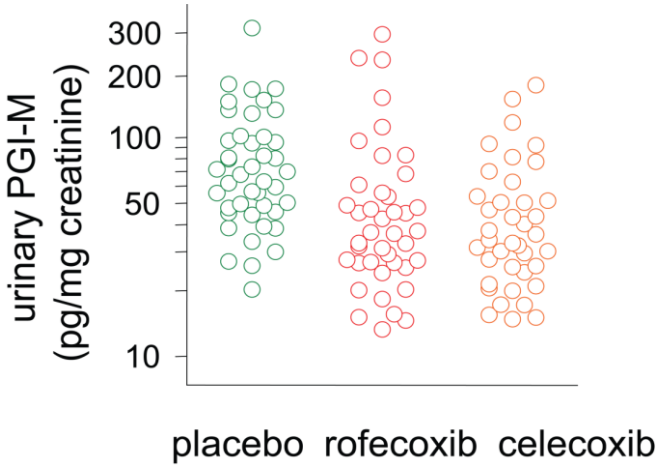

Integrated Omics clustering
Transcriptome
Proteome
Metabolome
RSV Infection → Healthy:
Integrated omics
(I)
Autocorrelated data clusters
Full Reactome (FI) known pathway map for cluster:
Example pathway:
Protein processing in endoplasmic reticulum
Dynamic expression pattern observed in:
RNA
Protein
Both RNA + Protein
Example pathway:
Phagosome
Example pathway:
Lysosome
Example pathway:
Insulin
(II)
Spike maxima data clusters
Eg. Pathway Analysis Results - FDR < 5e-02:
Spliceosome(K)
Glucose Regulation of Insulin Secretion(R)
Formation and Maturation of mRNA Transcript(R)
Oxidative phosphorylation(K)
Electron Transport Chain(R)
Parkinson's disease(K)
Huntington's disease(K)
Influenza Life Cycle(R)
Metabolism of non-coding RNA(R)
Transport of Mature Transcript to Cytoplasm(R)
Protein export(K)
Pyruvate metabolism and TCA cycle(R)
GO-ID
corr p-value
Description
8380
3.59E-71
RNA splicing
6396
2.53E-57
RNA processing
16070
5.93E-54
RNA metabolic process
16071
6.10E-50
mRNA metabolic process
10467
1.74E-48
gene expression
90304
1.78E-45
nucleic acid metabolic process
Eg. Metabolites in Cluster
3R-hydroxy-5Z-dodecenoic acid
5,6-DiHETrE-EA
7-Ethoxycoumarin
Lauric acid
1-O-(1Z-tetradecenyl)-2-(9Z-octadecenoyl)-sn-glycerol
(23R)-1alpha,23,25-trihydroxy-24-oxovitamin D3 / (23R)-1alpha,23,25-trihydroxy-24-oxocholecalciferol
1alpha-hydroxy-26,27-dinorvitamin D3 25-carboxylic acid / 1alpha-hydroxy-26,27-dinorcholecalciferol
12-oxo-9-octadecynoic acid
GPCho(O-16:0/O-4:0[U])
19-hydroxy-17-oxoandrost-5-en-3-beta-yl sulfate - 11.538899
Example Pathway:
Glucose Regulation of Insulin Secretion
(III)
Spike minima data clusters
Example Pathway: Formation of Platelet Plug
Eg. Metabolites in Cluster
4,8,12,15,19,21-tetracosahexaenoic acid
Idebenone Metabolite
p-Cymene
Cer(d18:0/24:0)
Normetanephrine sulfate
gamma-Hydroxyphenylbutazone glucuronide
Methoxyhydroxymethylhydrocinnamic acid
5,8-Dihydroxy-3,4-dihydrocarbostyril
3-Methylsuberic acid - 7.6812496
5-Methyltetrahydropteroyltri-L-glutamate
3-keto palmitic acid - 12.719786
Cholylglycine
Protoporphyrin + 12.516361
Desmethyldehydroamlodipine
Chenodeoxycholyltaurine
Eg. Pathway Analysis Results - FDR < 1e-03:
TRAIL signaling pathway(N)
Class I PI3K signaling events(N)
Formation of Platelet plug(R)
Glypican pathway(N)
TNF receptor signaling pathway(N)
Plasma membrane estrogen receptor signaling(N)
Signaling events activated by Hepatocyte Growth Factor Receptor (c-Met)(N)
Signalling by NGF(R)
p75(NTR)-mediated signaling(N)
Syndecan-1-mediated signaling events(N)
TCR signaling in na-ve CD4+ T cells(N)
Proteoglycan syndecan-mediated signaling events(N)
Nectin adhesion pathway(N)
Apoptosis(R)
IGF1 pathway(N)
Arf6 signaling events(N)
Insulin Pathway(N)
IFN-gamma pathway(N)
Signaling by Wnt(R)
Neurotrophin signaling pathway(K)
Sphingosine 1-phosphate (S1P) pathway(N)
IL2-mediated signaling events(N)
TNF alpha/NF-kB(C)
IL1-mediated signaling events(N)
Fc gamma R-mediated phagocytosis(K)
keratinocyte differentiation(B)
Focal adhesion(K)
High glucose
Days after RSV infection

You get what you pay for….

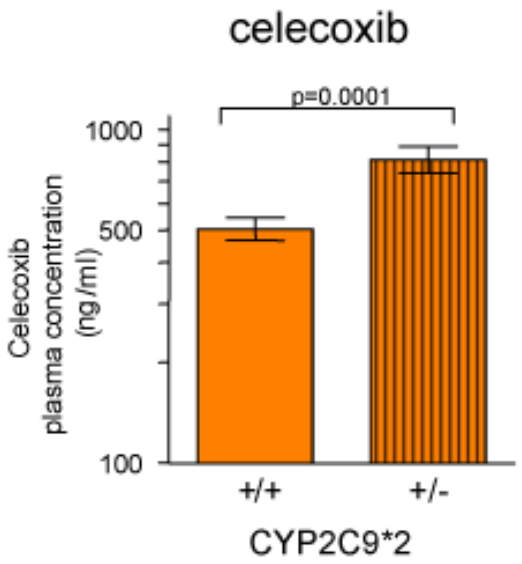


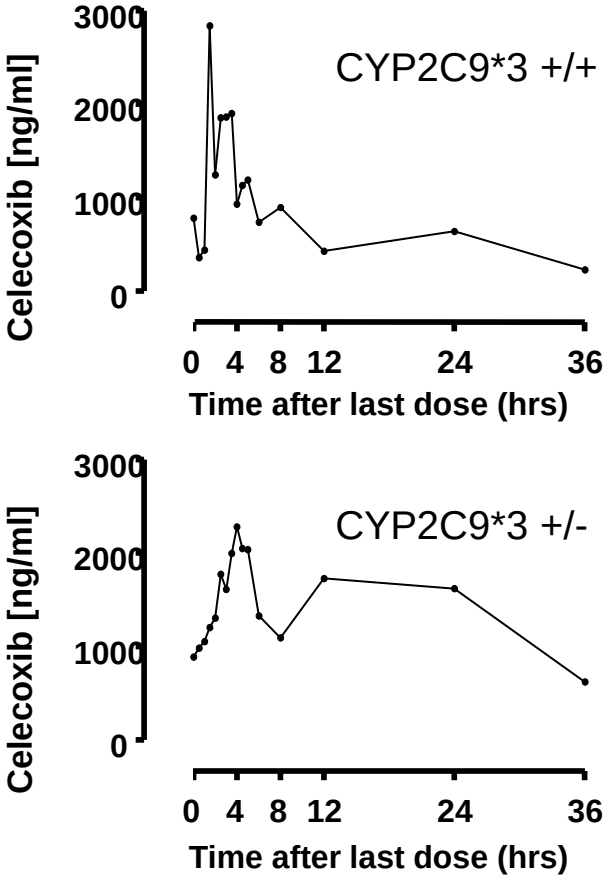
…..sort of

Variability in the response to COX-2 inhibition



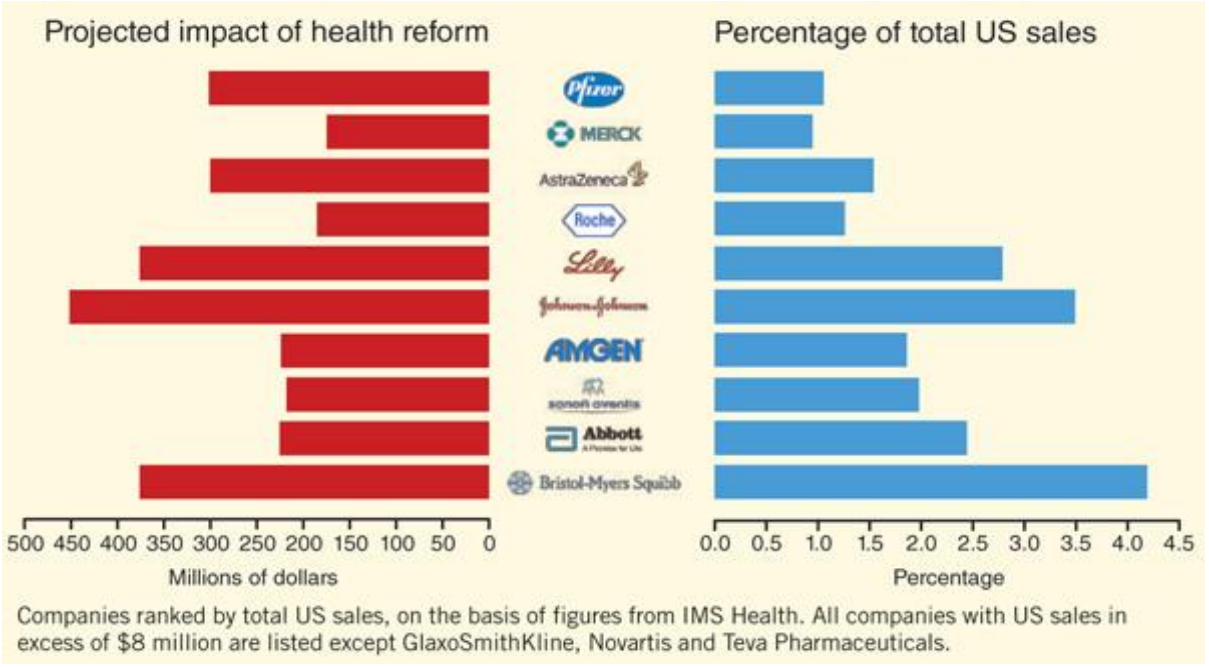
- 30% of the total variability may be from inter-individual variability.





Fries et al., *Gastroenterology*,

US Health Reform



Companies ranked by total US sales, on the basis of figures from IMS Health. All companies with US sales in excess of $8 million are listed except GlaxoSmithKline, Novartis and Teva Pharmaceuticals.