Pharmacogenetics

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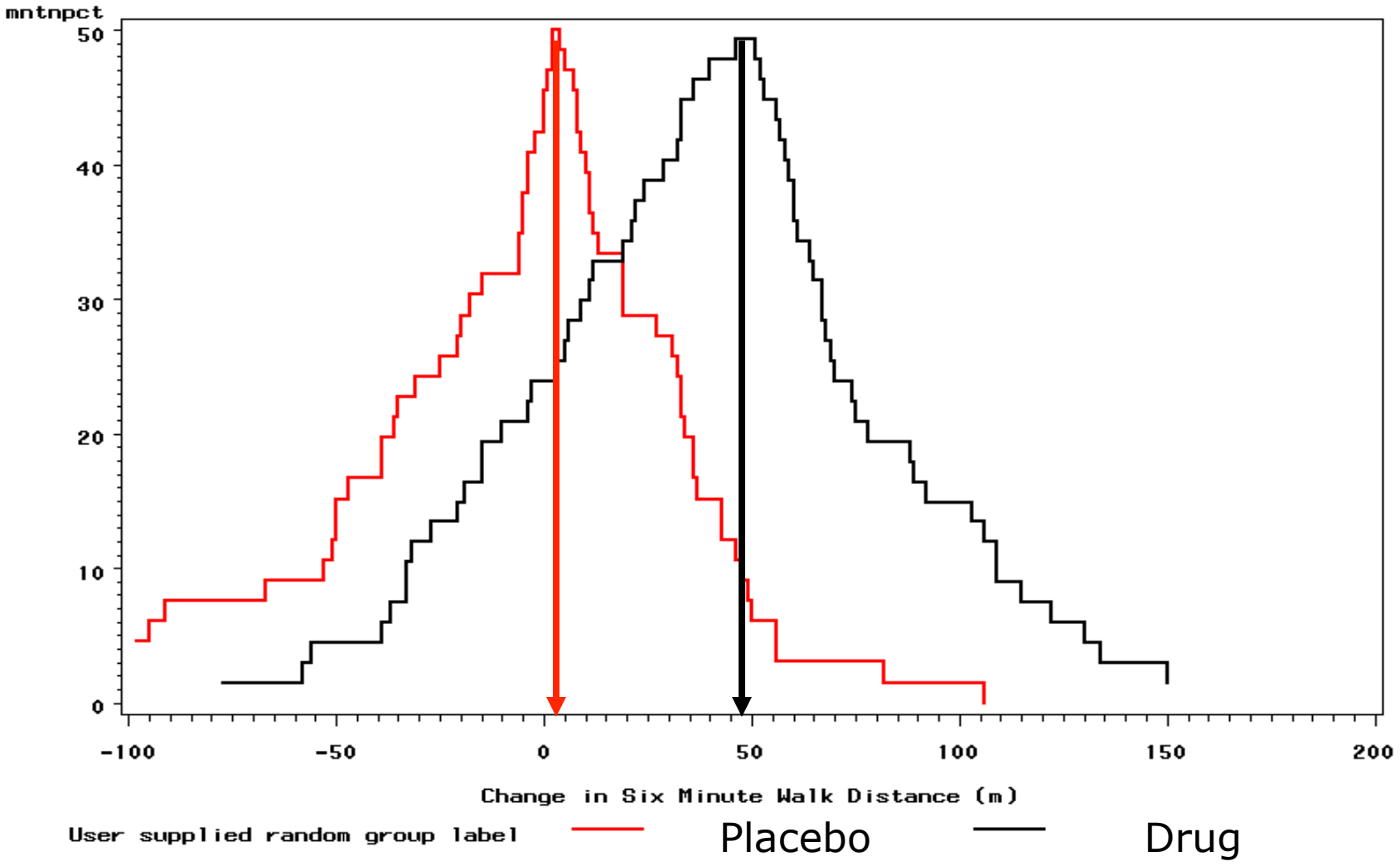
Nomenclature

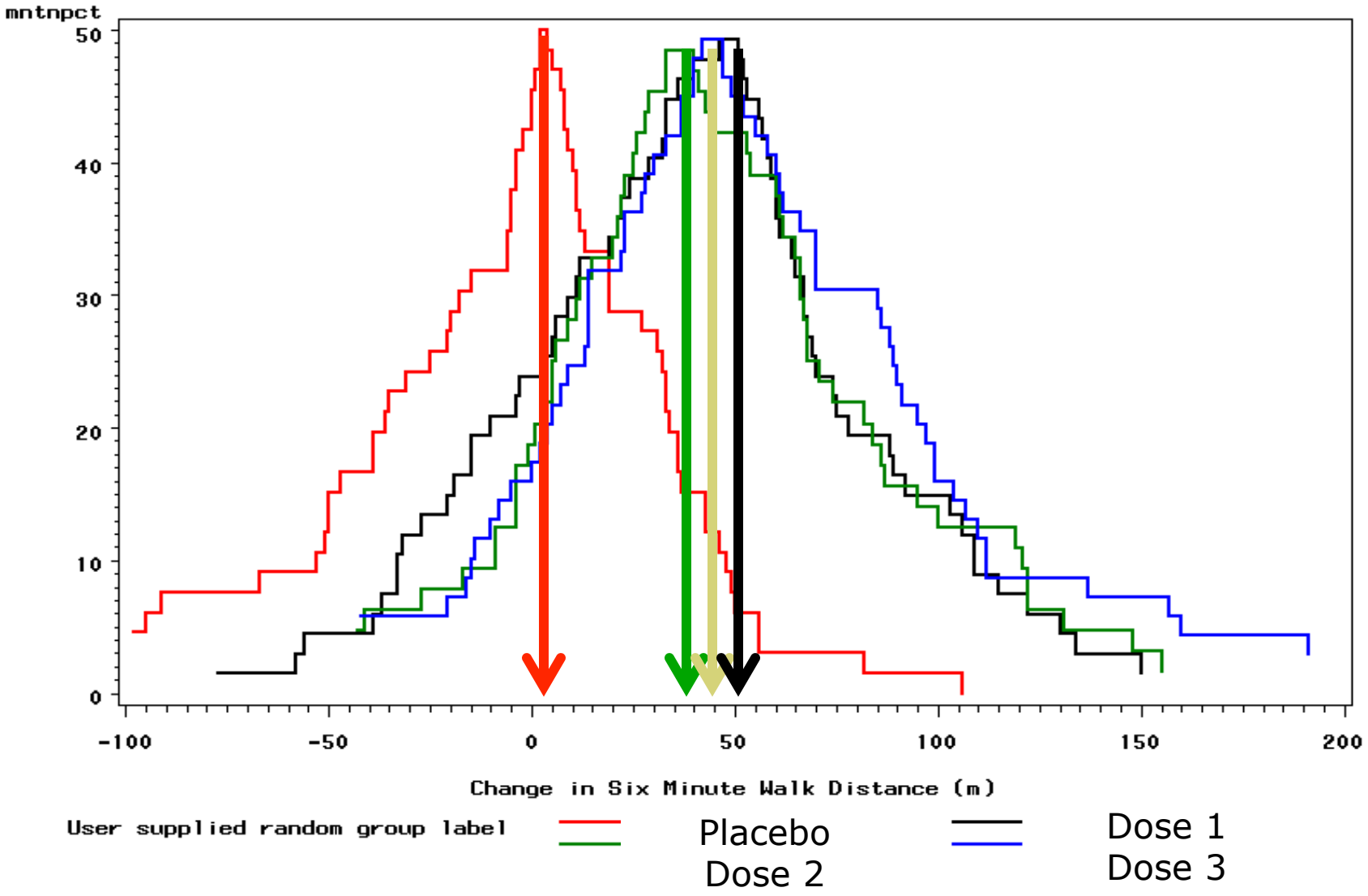
P h a r m a c o g e n o m i c s is
P h a r m a c o g e n e t i c s

..with two single nucleotide polymorphisms

Variablility in response to a PAH drug



Variablility in response to a PAH drug



Response rate to drugs for different diseases

Anti-depressant drugs	38%
Asthma drugs	40%
Diabetes drugs	43%
Arthritis drugs	50%
Alzheimer's drugs	73%
Cancer drugs	75%

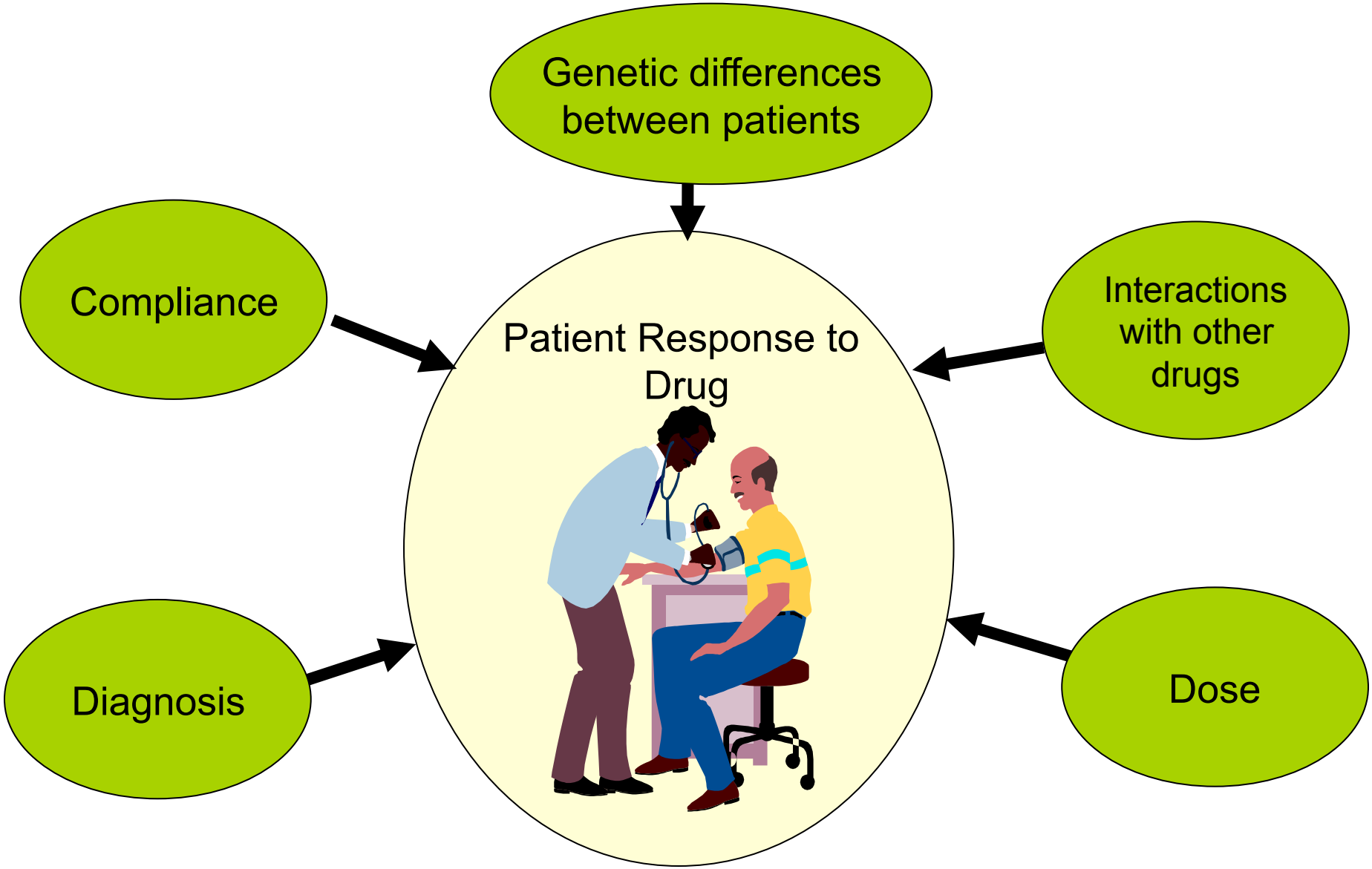
Spear et al Clinical Trends in Mol Med 2001

Glaxo Chief: Our Drugs Do Not Work on Most Patients
by Steve Connor

A senior executive with Britain's biggest drugs company has admitted that most prescription medicines do not work on most people who take them.

Published on Monday, December 8, 2003 by the Independent/UK

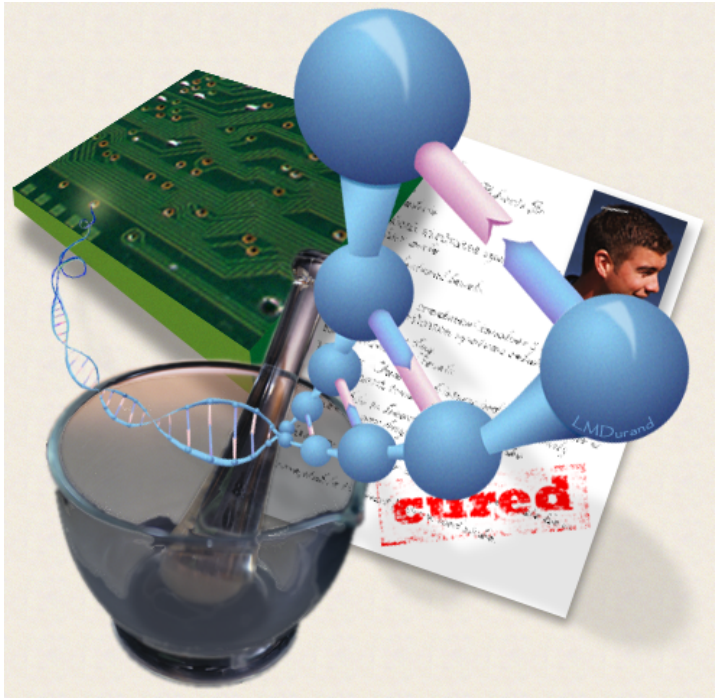
Factors That Influence Medicine Response



Pharmacogenomics
"Drugs by Design?"

"In the very near future, primary care physicians will routinely perform genetic tests before writing a prescription because (they will) want to identify the poor responders."

F. Collins
(AAFP Annual Meeting, 1998)



Objectives

1. To understand the principles underlying the use of genetic information to inform prescribing

2. To appreciate the present state-of-the-art and be aware of the hurdles to implementing pharmacogenetics/genomics in clinical practice

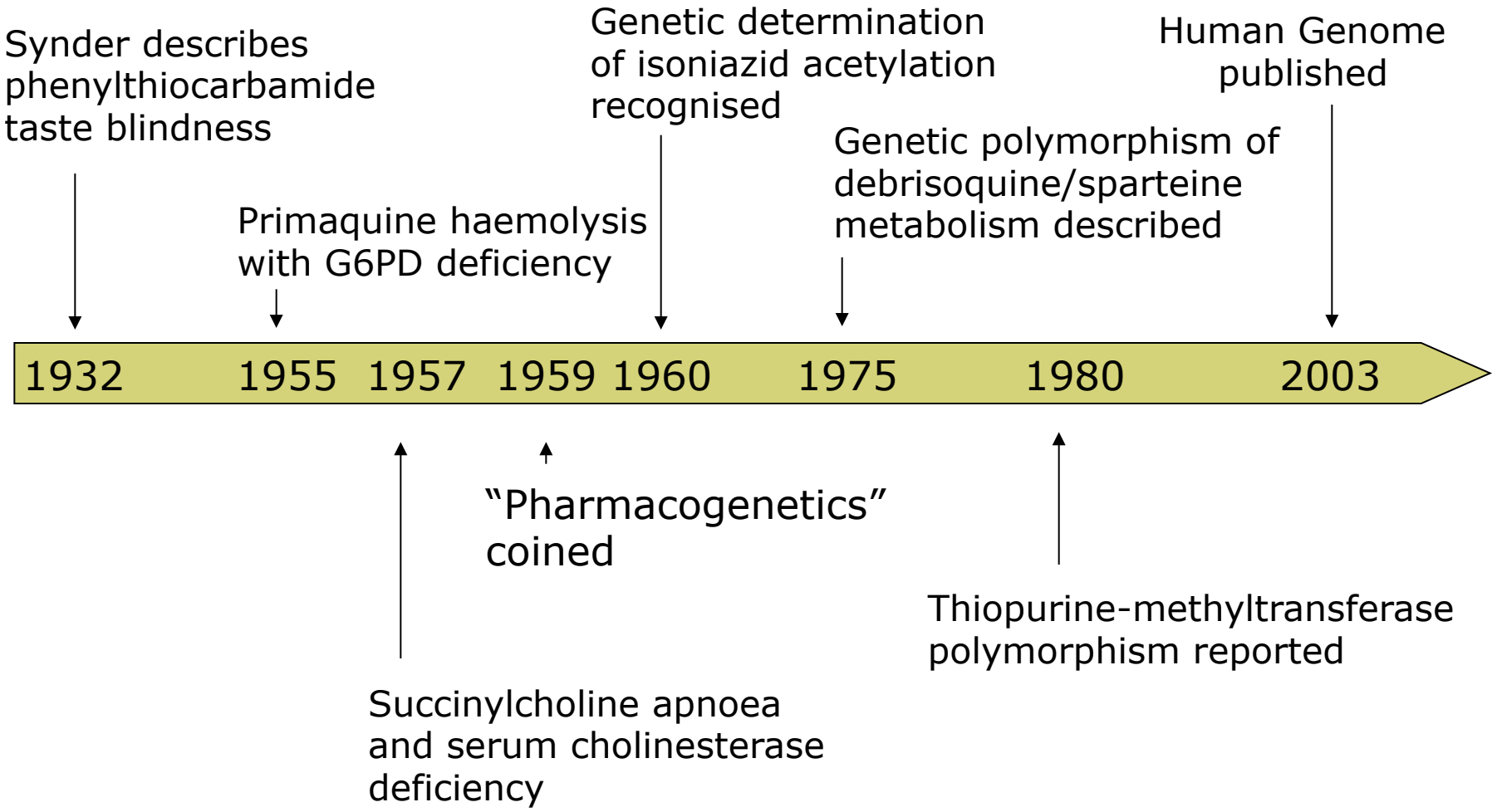
Historical Background

Sir Archibald Garrod 1858-1936

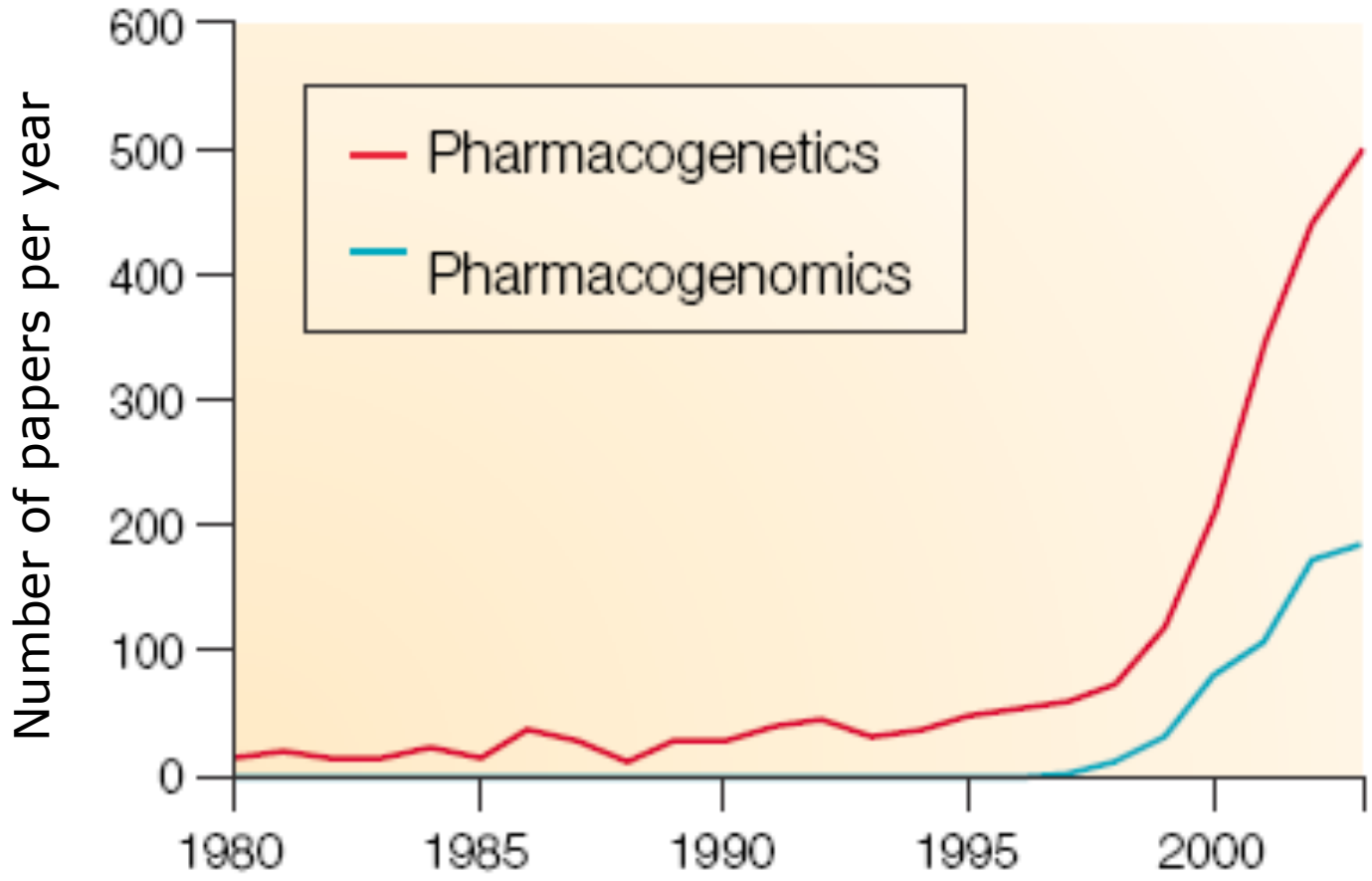
In his 1908 Croonian Lecture he coined the phrase

"Chemical Individuality"

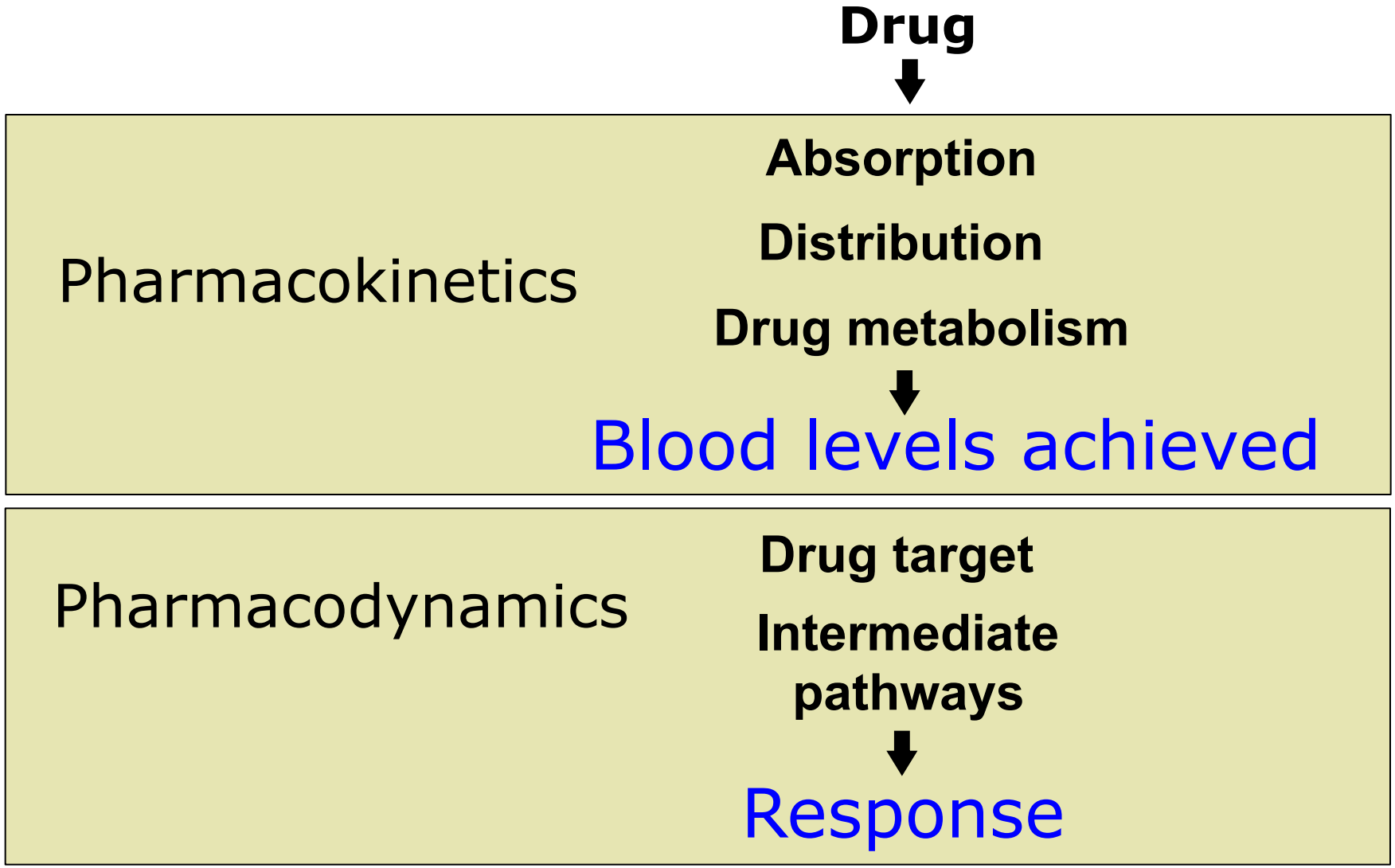
Historical Background



Increasing interest in genetics and medicines



Genetic variation can influence patient response at two levels



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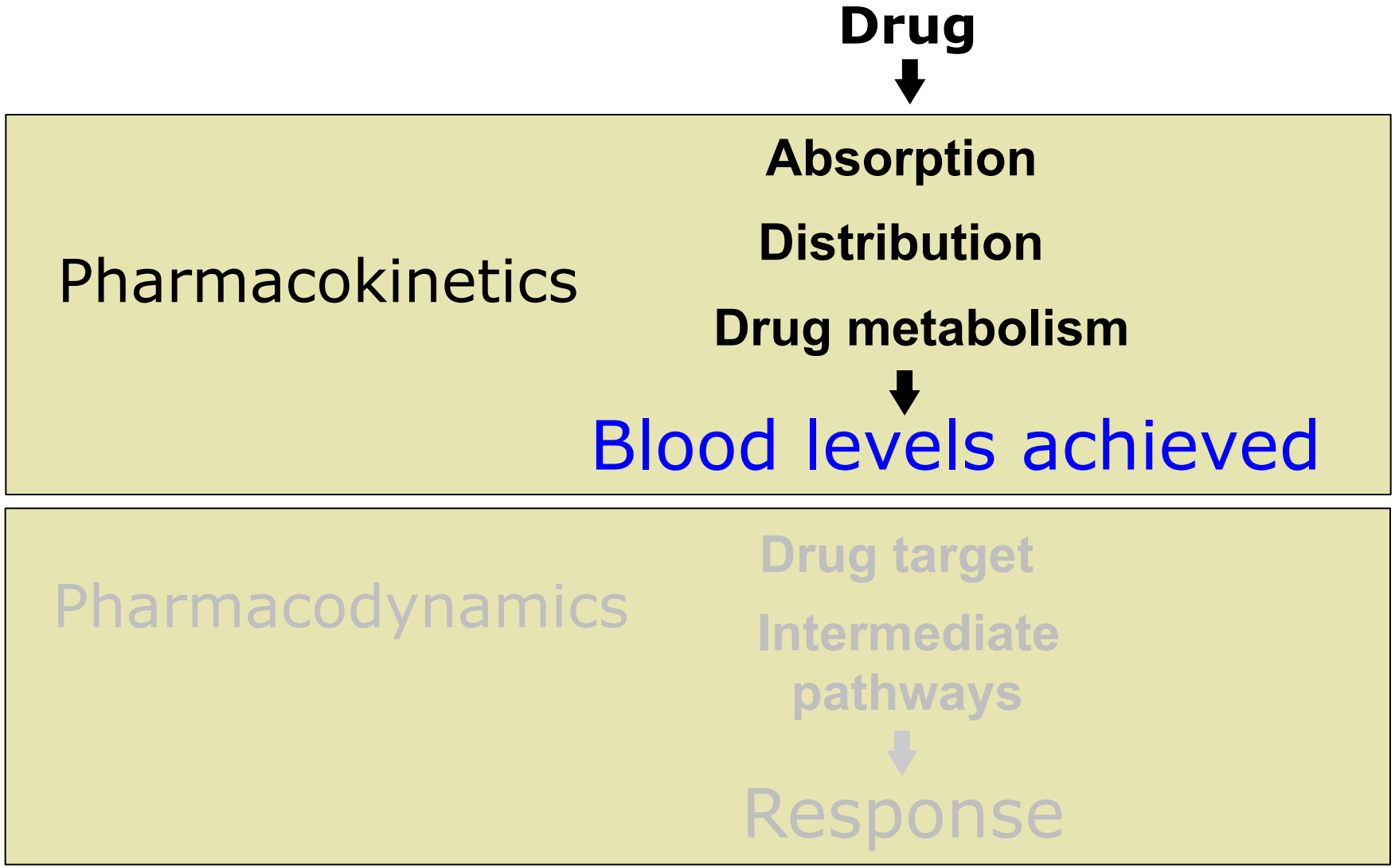
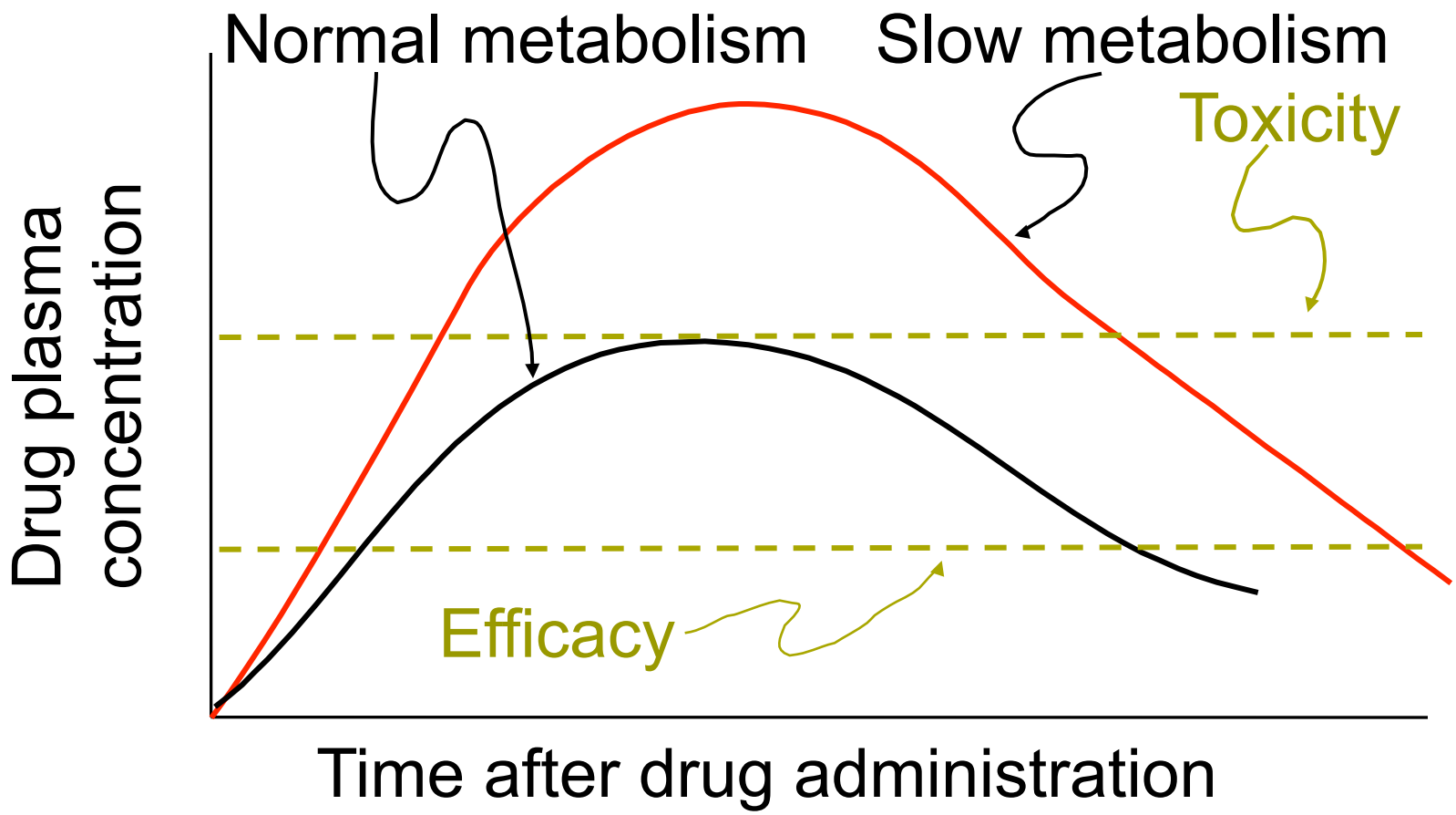


Genetic variation can influence drug metabolism

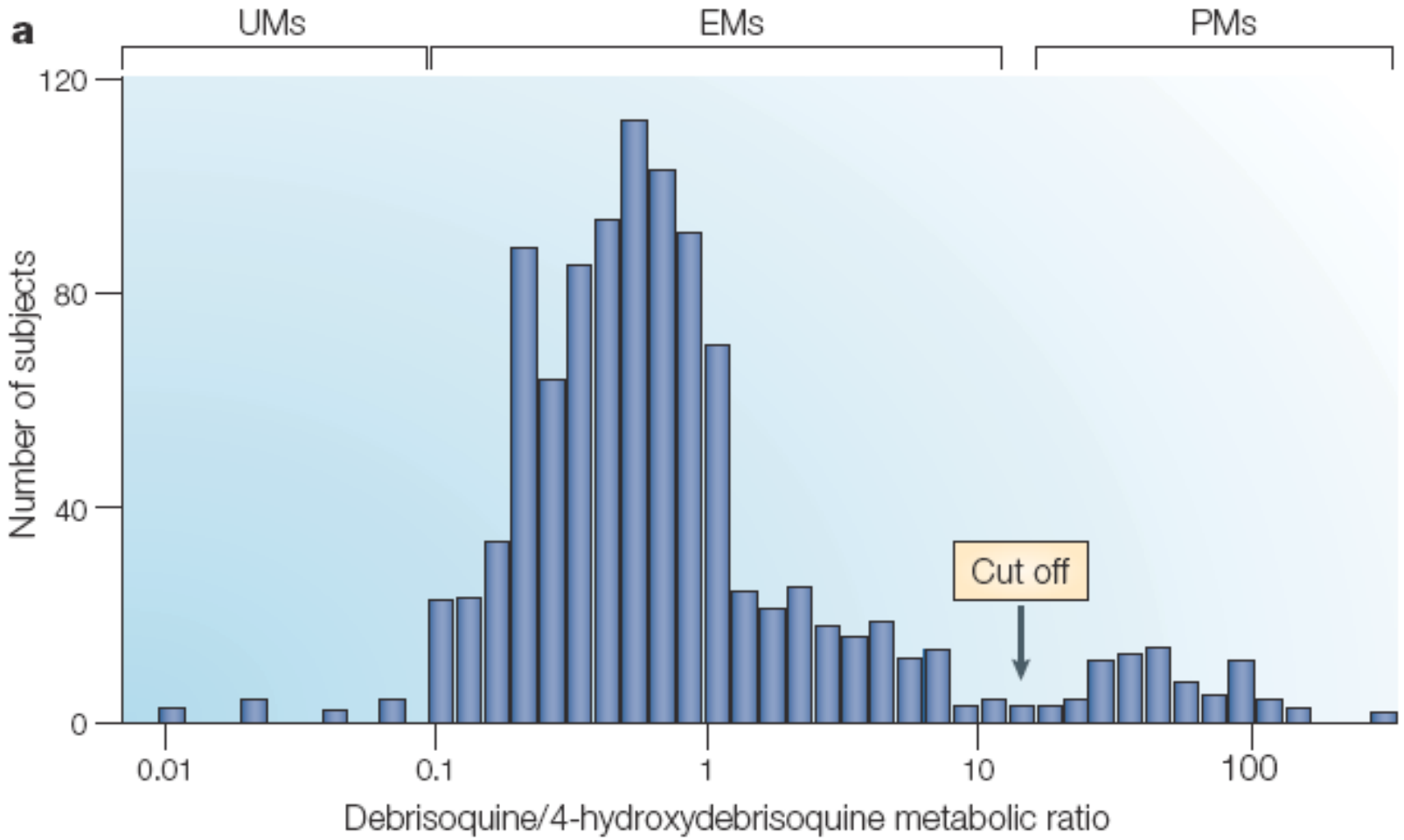
Poor drug metabolisers can be exposed to increased blood levels



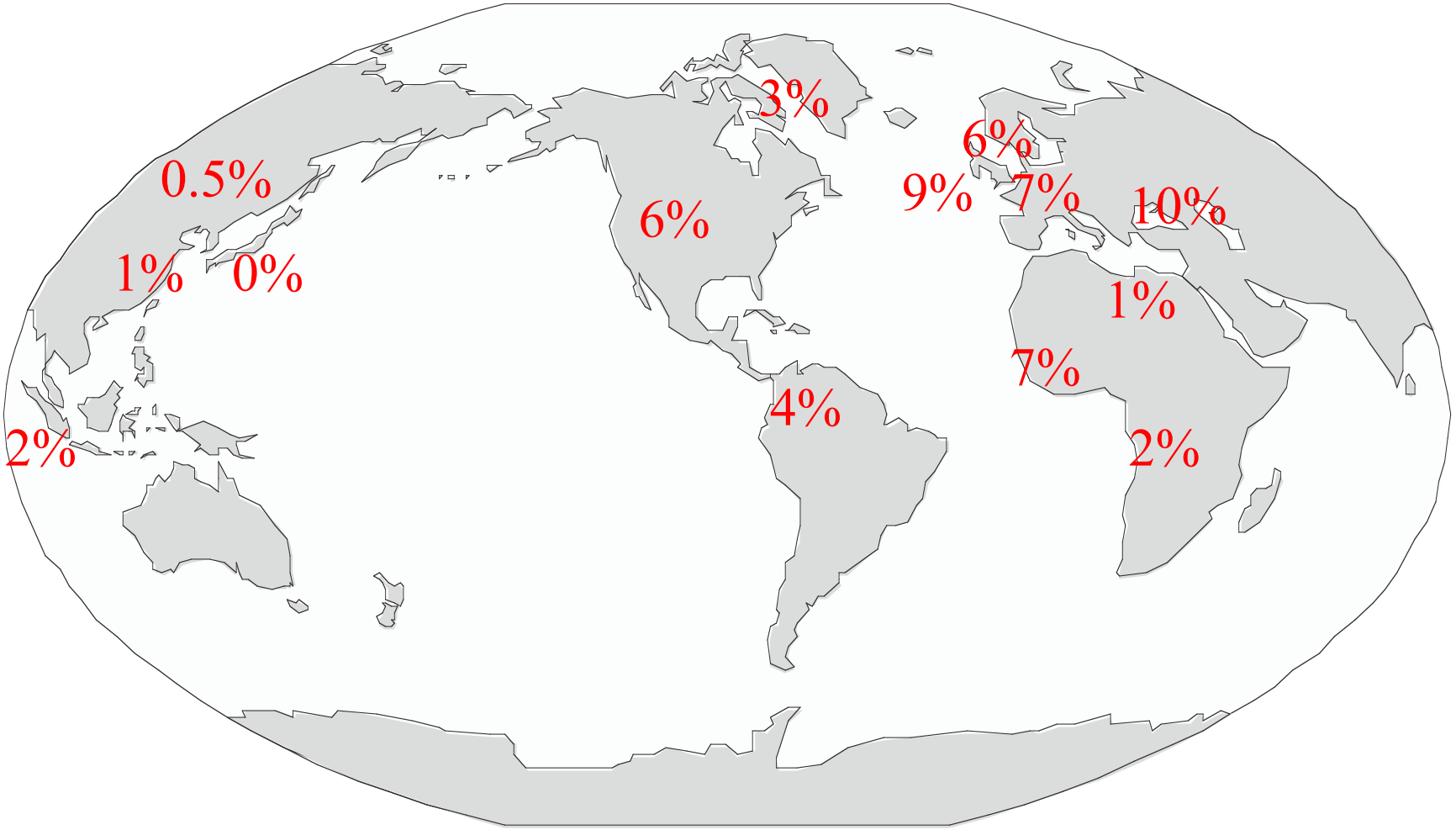
When is genetic variation in drug metabolism important?

- When the drug has a steep dose-response curve
- When the therapeutic window is narrow
- When the drug is metabolised mainly by one enzyme

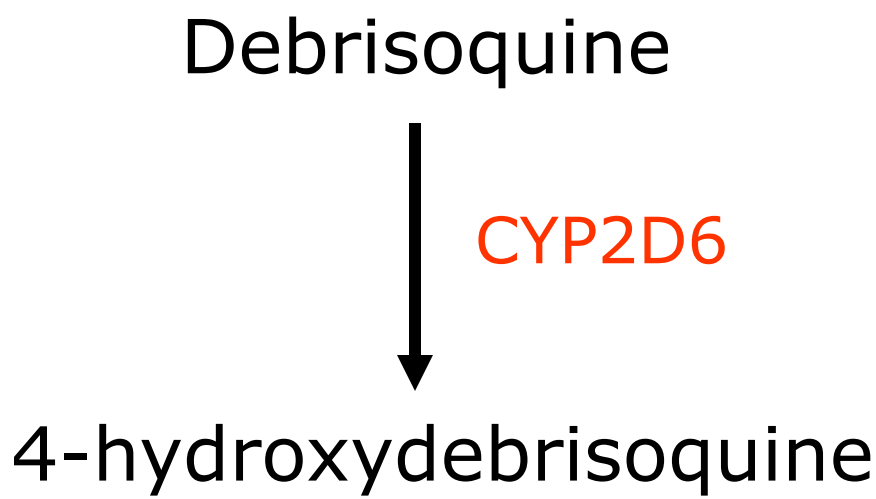
Population distribution of metaboliser status



Worldwide distribution of poor drug metabolisers (CYP2D6)



Debrisoquine is metabolised largely by one enzyme



Some drugs cleared by CYP2D6

ß-Adrenergic antagonists
e.g.metoprolol, bufuralol, propranolol

Neuroleptics
e.g. haloperidol, perphenazine

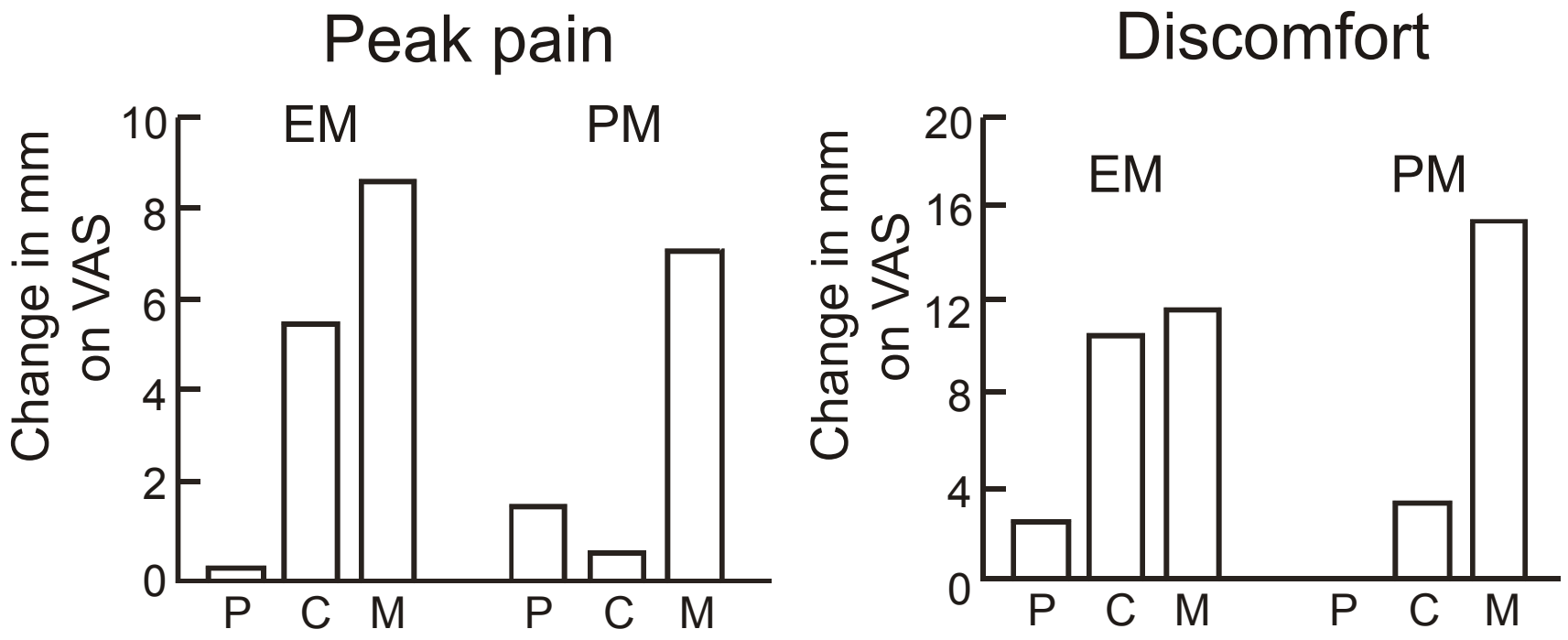
Anti-depressants
e.g. imipramine, amitriptyline, nortriptyline, paroxetine

Anti-arrhythmics
e.g. flecainide, encainide

Miscellaneous drugs
e.g. dextromethorphan, debrisoquine, sparteine, codeine

CYP2D6 phenotype reduces effectiveness of codeine analgesia

From Poulsen *et al*. (1996)

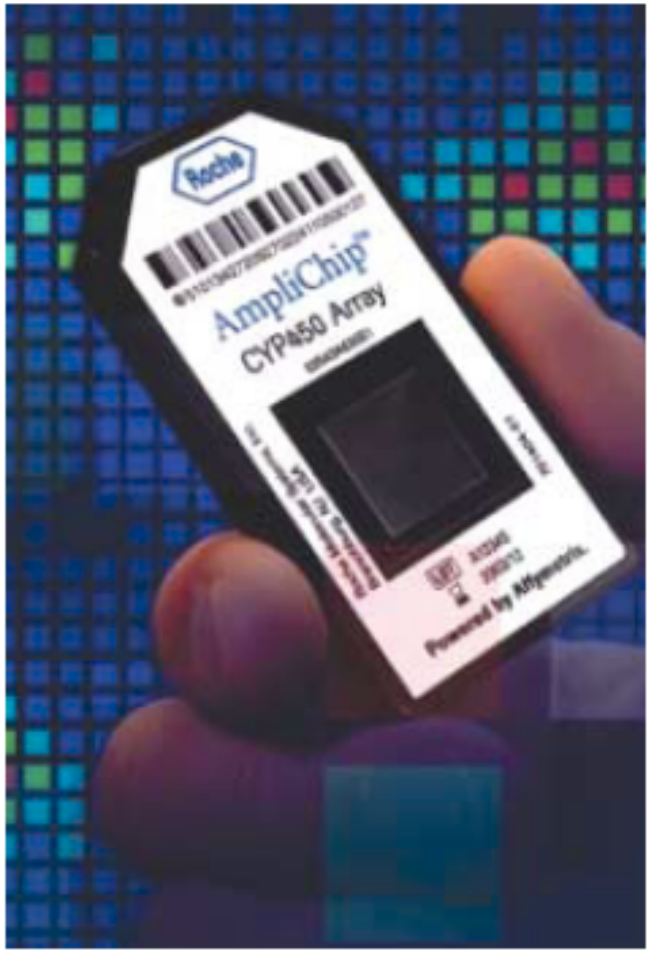


P=placebo; C=codeine; M=morphine

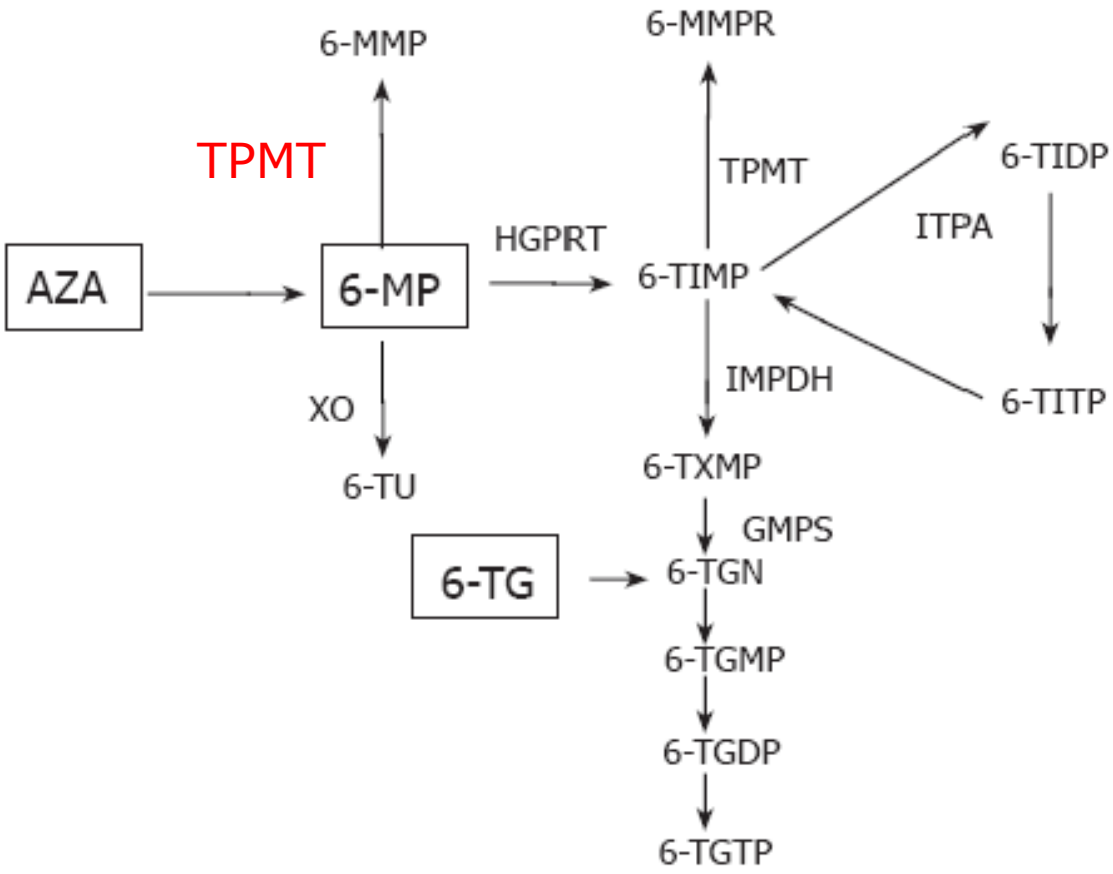
Poor metaboliser status can work both ways

	Poor metaboliser
Prodrug eg codeine activated by 2D6	Risk lack of effect
Active drugs inactivated by metabolism	Risk of toxicity

Genes on a chip



Thiopurine S-Methyltransferase (TPMT)



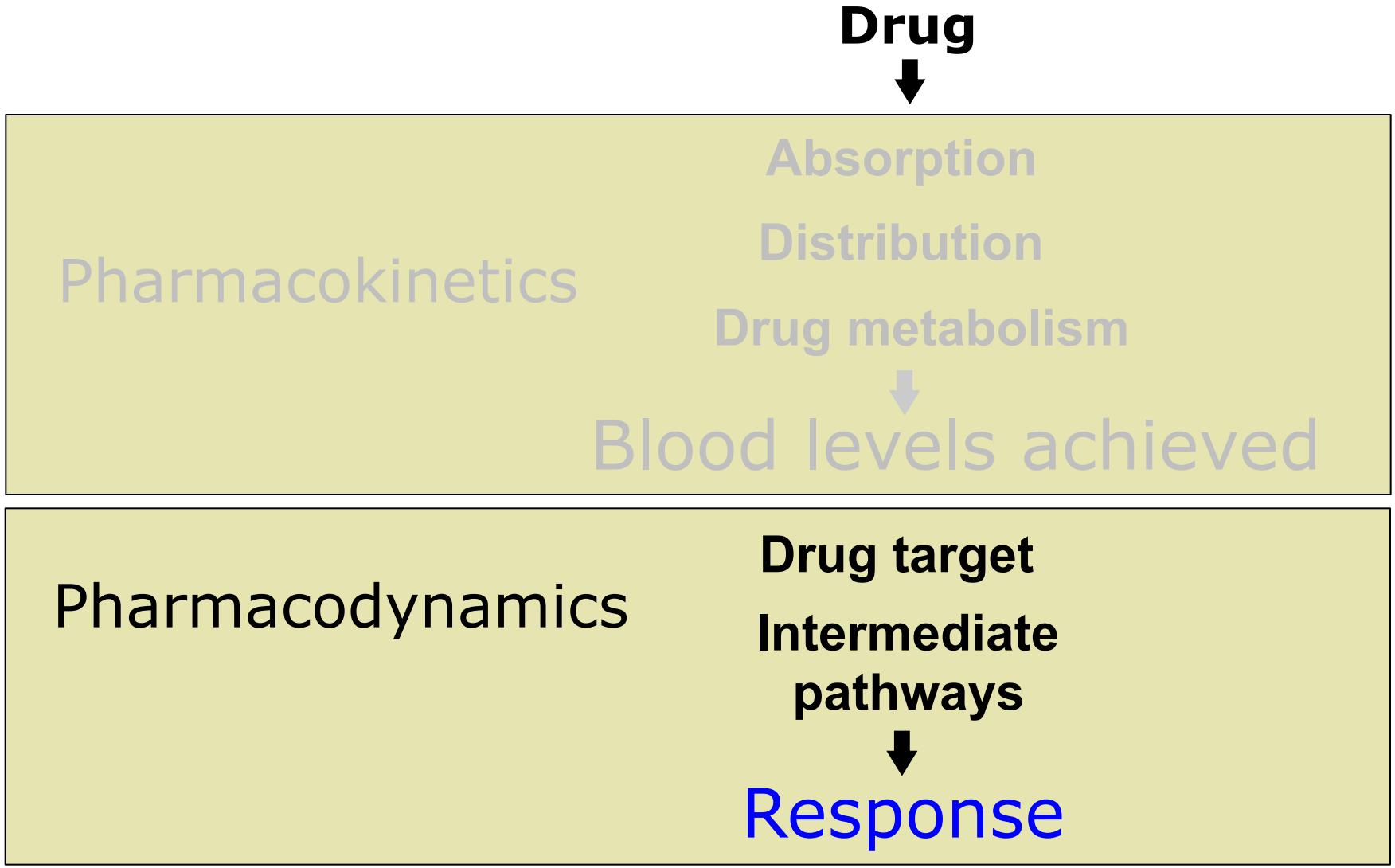
TPMT deficiency

- 1 in 300 (UK) have TPMT deficiency
- Several polymorphisms: G238C, G460A and A719G
- TPMT deficiency predicts severe neutropaenia following treatment with 6-mercaptopurine or azathioprine (but not other side effects)
- Some cases of severe neutropaenia occur with normal TPMT phenotype

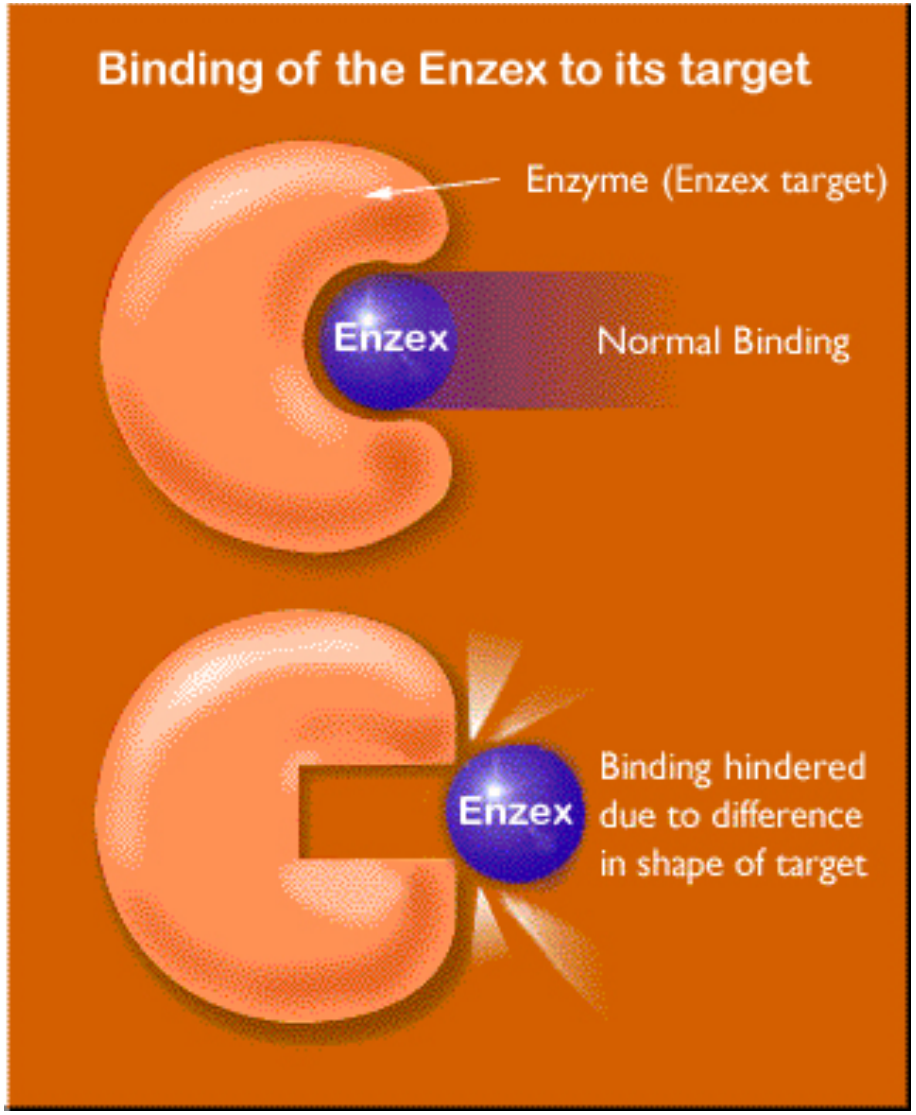
TPMT deficiency

- Azathioprine used in a wide range of inflammatory diseases, prescribed by specialists in respiratory medicine, dermatology, neurology, rheumatology, oncology, gastroenterology
- Product labelling amended to include reference to TPMT status, FDA have approved (2004) test for determination of TPMT status
- British Association of Dermatologists
  - Pretreatment TPMT determination in all patients requiring azathioprine
- British Thoracic Society
  - No requirement for testing TPMT status in interstitial lung disease guidelines before prescribing azathioprine
- British Society of Gastroenterology
  - TPMT status determination 'cannot yet be recommended as a prerequisite to therapy'

Genetic variation can influence patient response at two levels



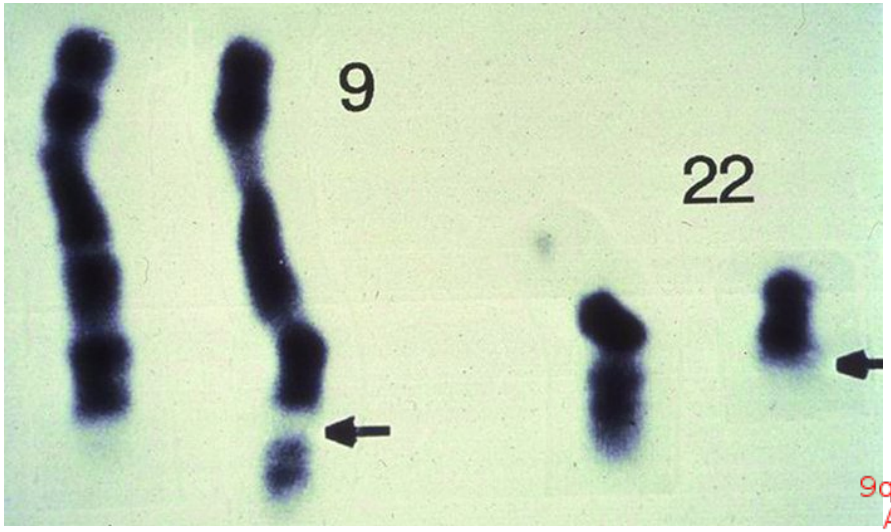
Genetic variation in drug target

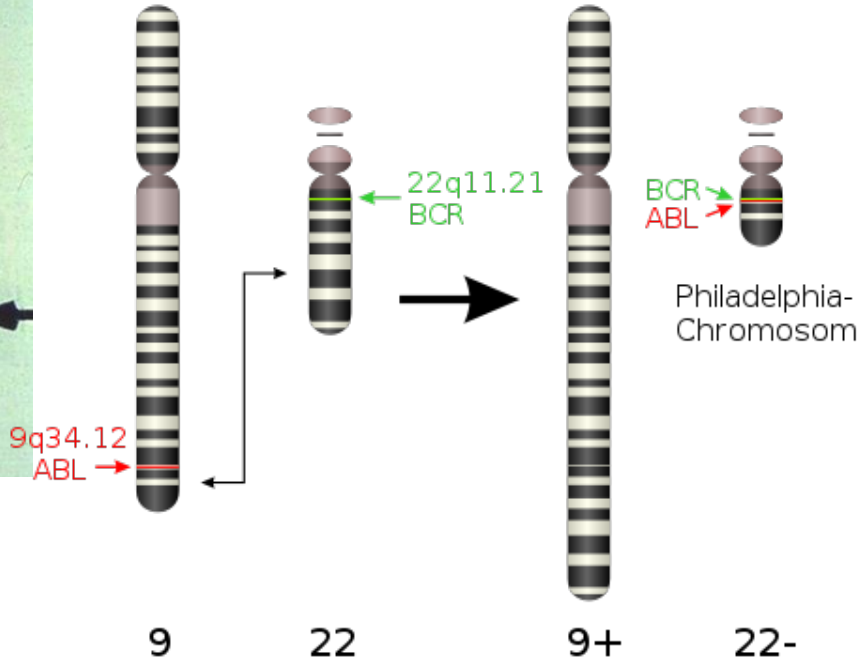


Genomic variation affecting drug targets

- Malignancy
  - Gleevec
  - Herceptin
- Infectious diseases

Imatinib (Gleevec): designer drug





Genomics can be used identify good responder subgroups in cancer

Breast cancer – Herceptin

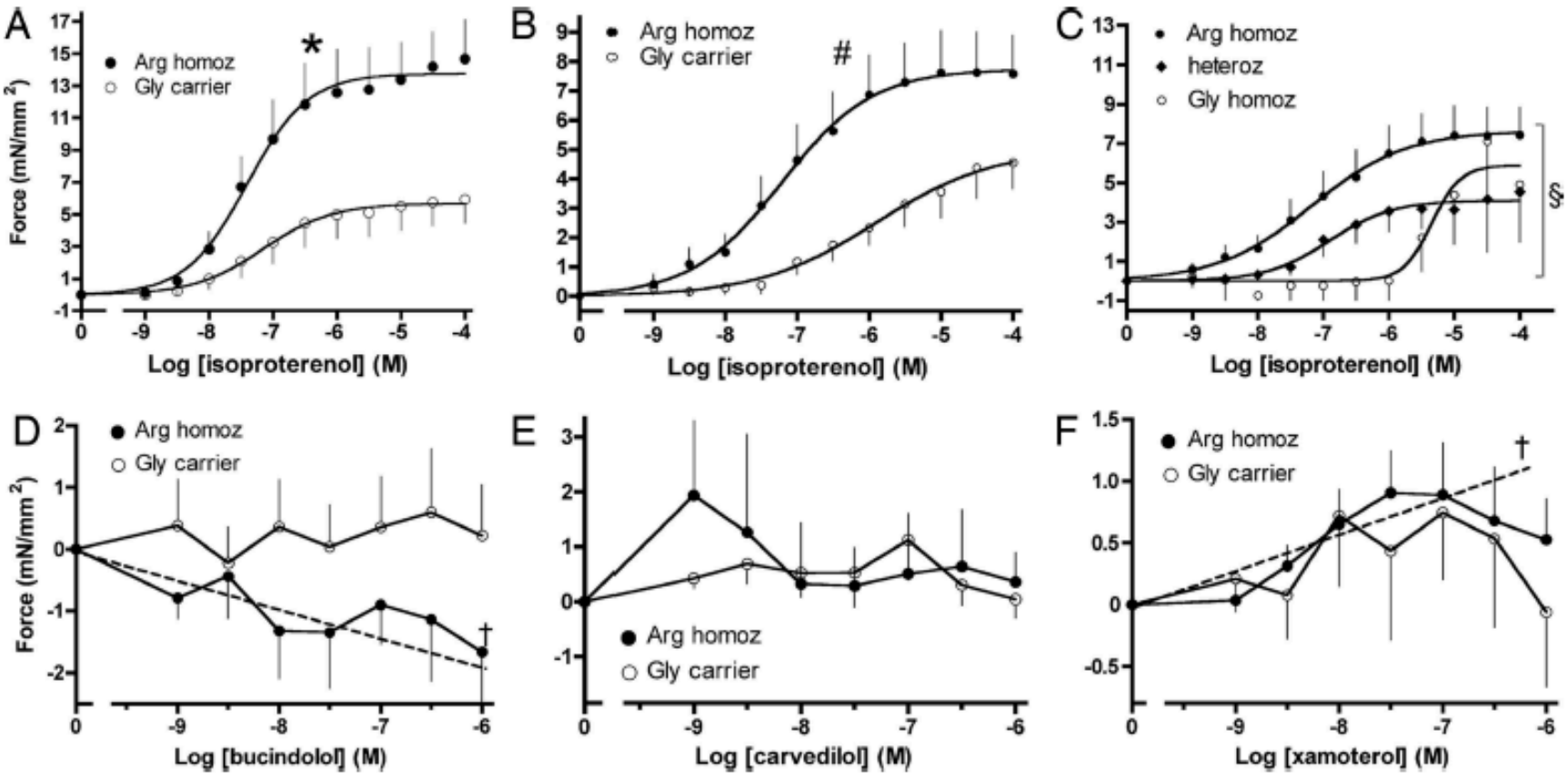
Patients who respond best are those with tumours that overexpress the *ERBB2* (also known as *HER2/neu)* gene

A polymorphism within a conserved β_1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure

Stephen B. Liggett*†, Jeanne Mialet-Perez‡, Surai Thaneemit-Chen§, Stewart A. Weber¶, Scott M. Greene¶, Danielle Hodne¶, Bradley Nelson¶, Jennifer Morrison¶, Michael J. Domanski‖, Lynne E. Wagoner‡, William T. Abraham**, Jeffrey L. Anderson††, John F. Carlquist††, Heidi J. Krause-Steinrauf§, Laura C. Lazzeroni§, J. David Port¶, Philip W. Lavori§, and Michael R. Bristow¶

species		% identity
Homo sapien	R S P D F R K A F Q R/G L L C C A R R A	100
Ovis aries	R S P D F R K A F Q R L L C C A R R A	100
Bos taurus	R S P D F R K A F Q R L L C C A R R A	100
Rattus norvegicus	R S P D F R K A F Q R L L C C A R R A	100
Mus musculus	R S P D F R K A F Q R L L C C A R R A	100
Pan troglodytes	R S P D F R K A F Q R L L C C V R R A	94
Rhesus macaque	R S P D F R N A F Q R L L C C A R R A	94
Canis familiaris	R S P D F R R A F Q R L L C C A R R A	94
Felis catus	R S P D F R K A F Q R L L C F A R R A	94
Sus scrofa	R C P D F R K A F Q R L L C C A R R V	94
Tetraodon nigroviridis	R S P D F R K A F K R L L C C A R Q A	84
Xenopus laevis	R S P D F R K A F K R L L C C P K K A	78
Meleagris gallopavo	R S P D F R S A F K R L L C F P R K A	78

A polymorphism within a conserved β_1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure



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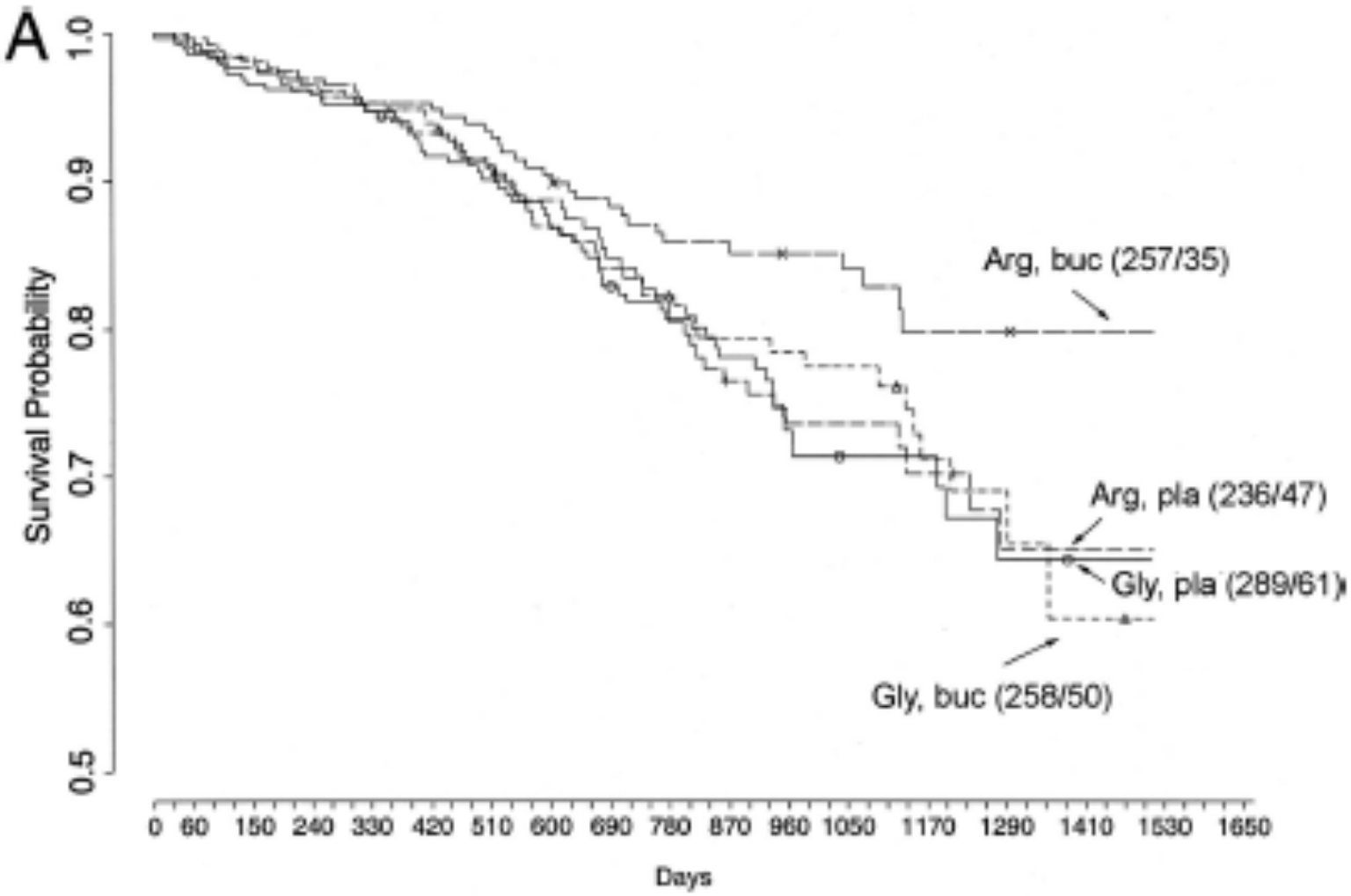
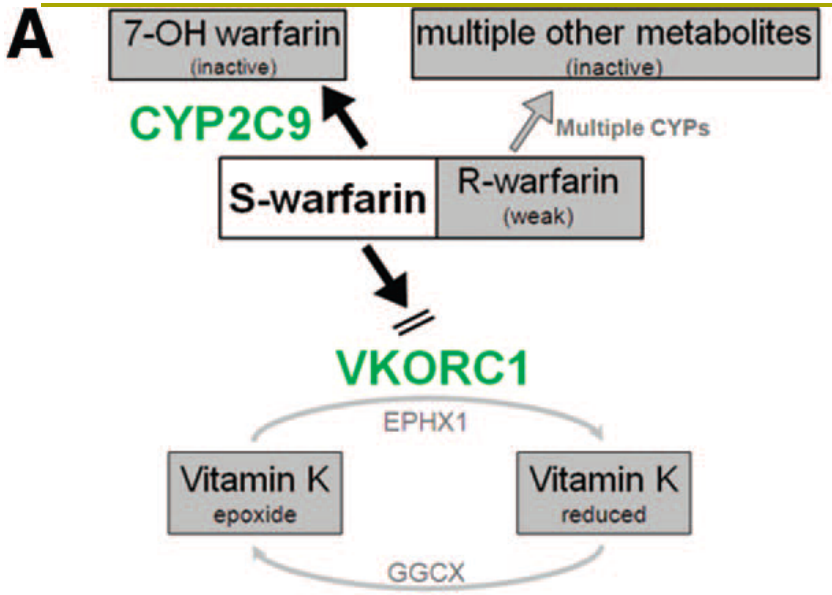
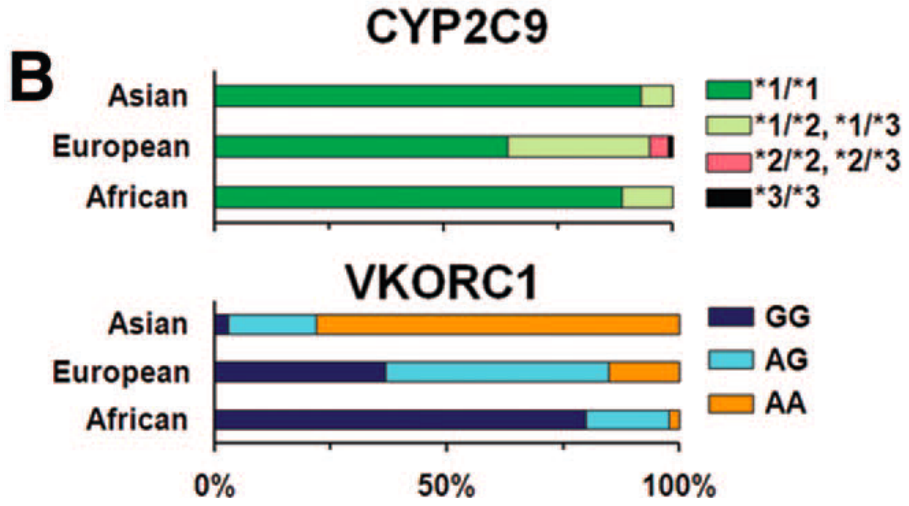
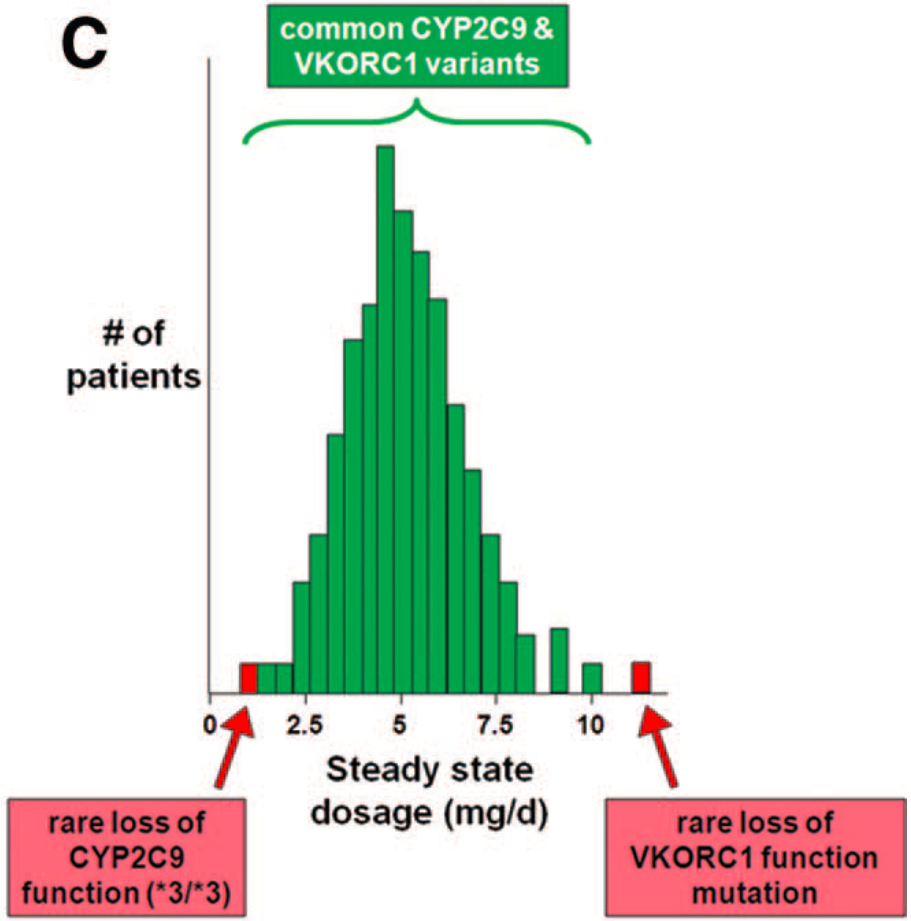


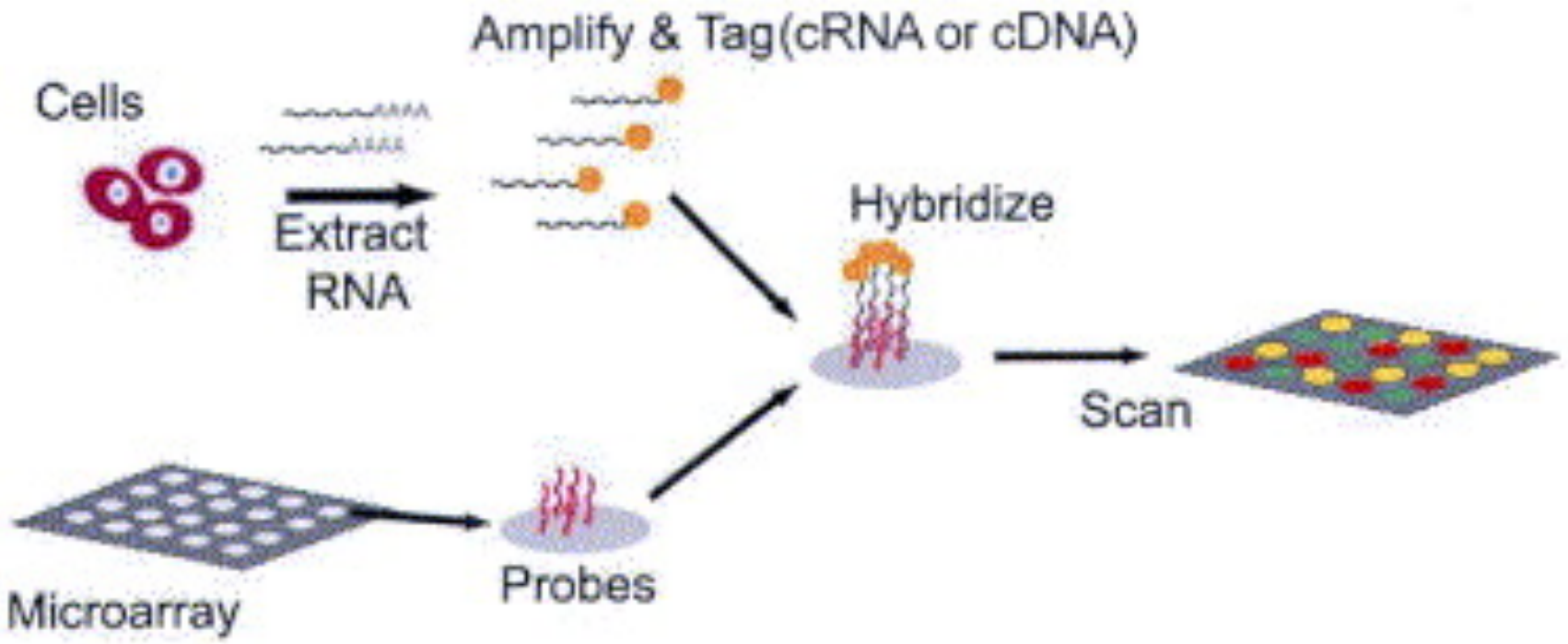
PK and PD variants and warfarin dose





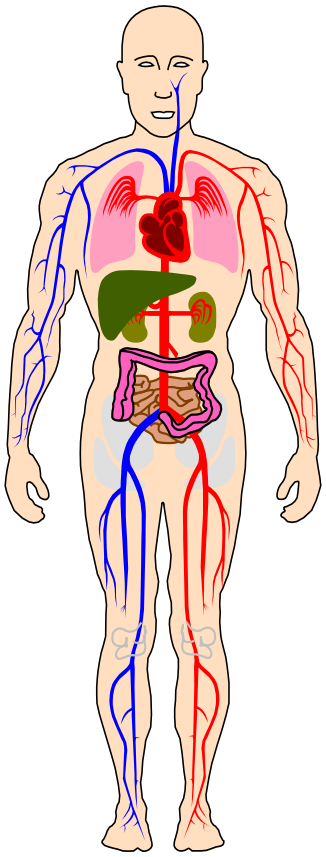


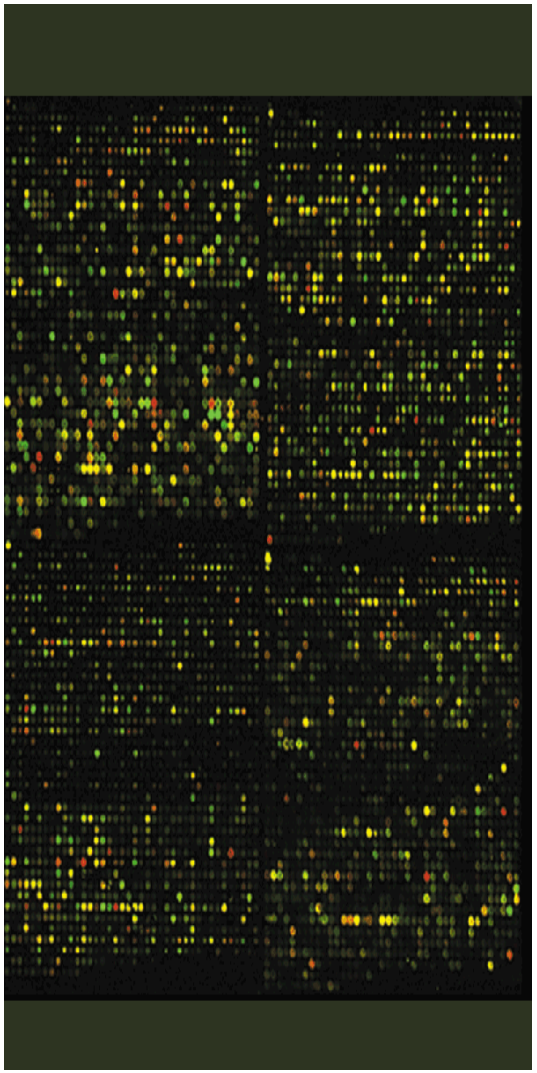
Gene expression analysis



Genetics can be used for more accurate diagnosis of cancer type

A





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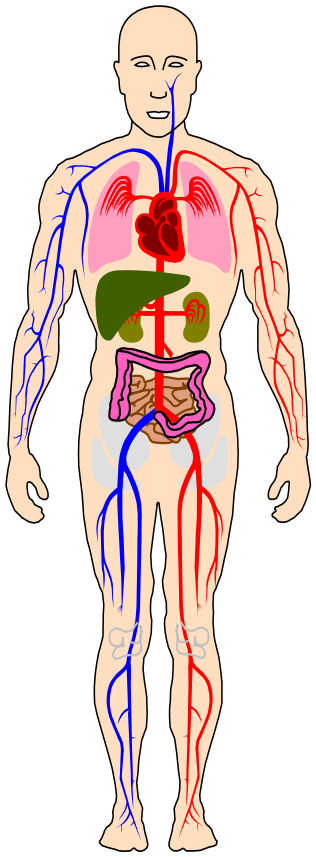
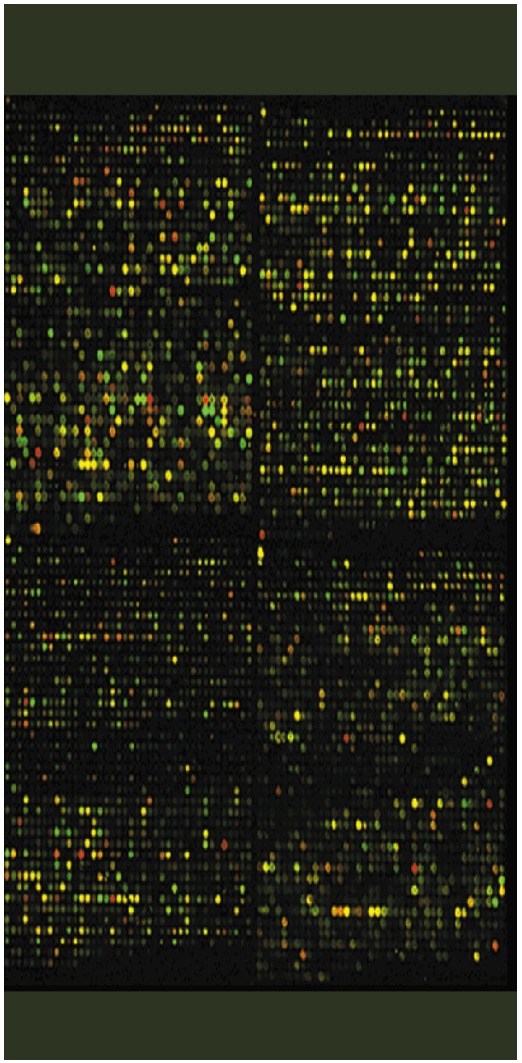
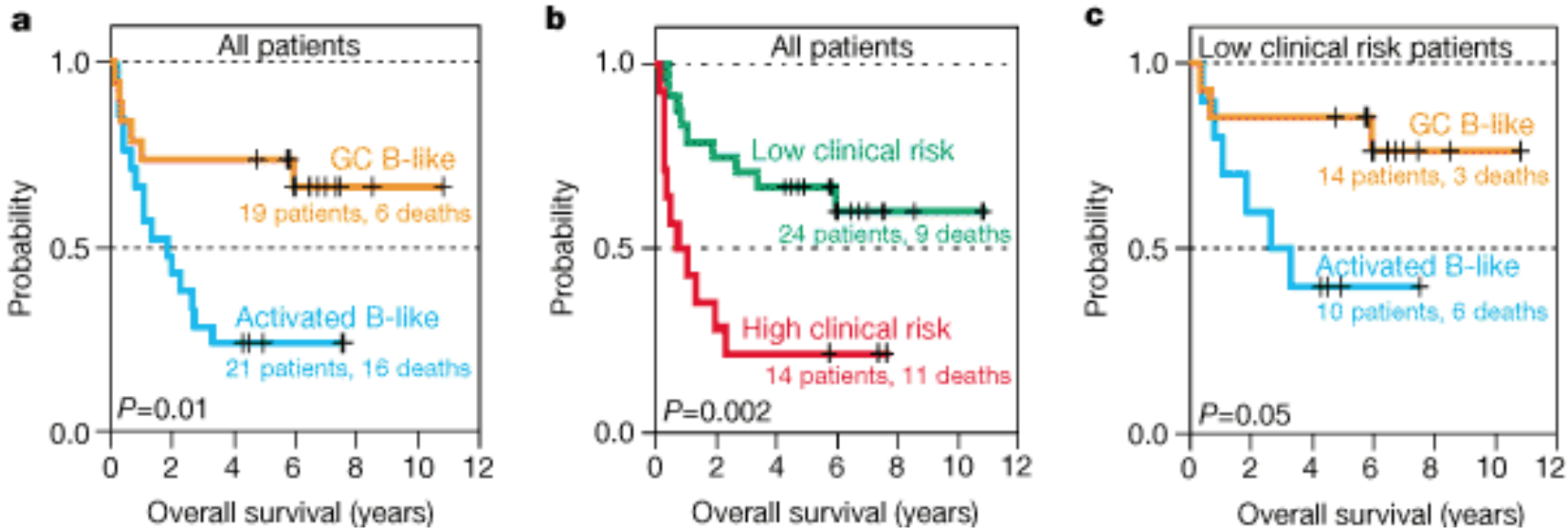




Survival according to gene expression



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

BACKGROUND

Oncogenic fusion genes consisting of *EML4* and anaplastic lymphoma kinase (*ALK*) are present in a subgroup of non–small-cell lung cancers, representing 2 to 7% of such tumors. We explored the therapeutic efficacy of inhibiting ALK in such tumors in an early-phase clinical trial of crizotinib (PF-02341066), an orally available small-molecule inhibitor of the ALK tyrosine kinase.

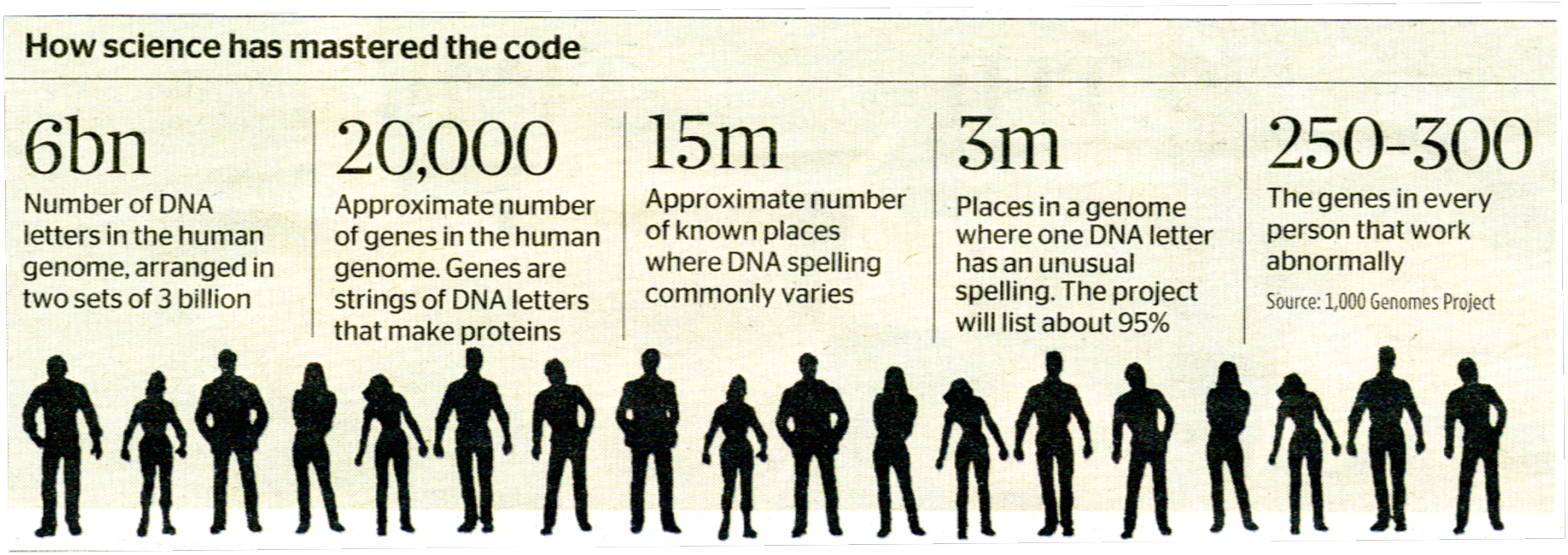
CONCLUSIONS

The inhibition of ALK in lung tumors with the *ALK* rearrangement resulted in tumor shrinkage or stable disease in most patients. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

Gene expression data and clinical practice

	Application available now	Potential or emerging application
Oncology		
Breast	Predict recurrence	Predict response to therapy
Lymphoma	Classify / guide therapy	Classify subtypes/ guide therapy
Unknown primary		Assess prognosis
Neuroblastoma		
Infectious disease		
HIV	Classify virus	Predict response to therapy
SARS		
Hepatitis C		
Cardiovascular	?	
Hypertension		
Atherosclerosis		
Cardiac Failure		

Nobody is perfect



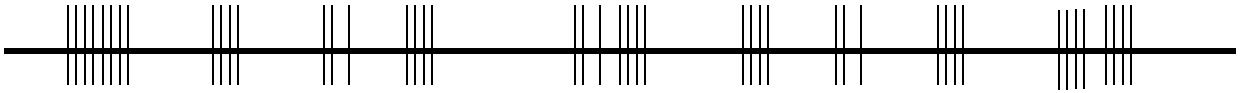
What is a SNP

Different people can have a different nucleotide or base at a given location on chromosome

. . . G G T A A C T G . . . .

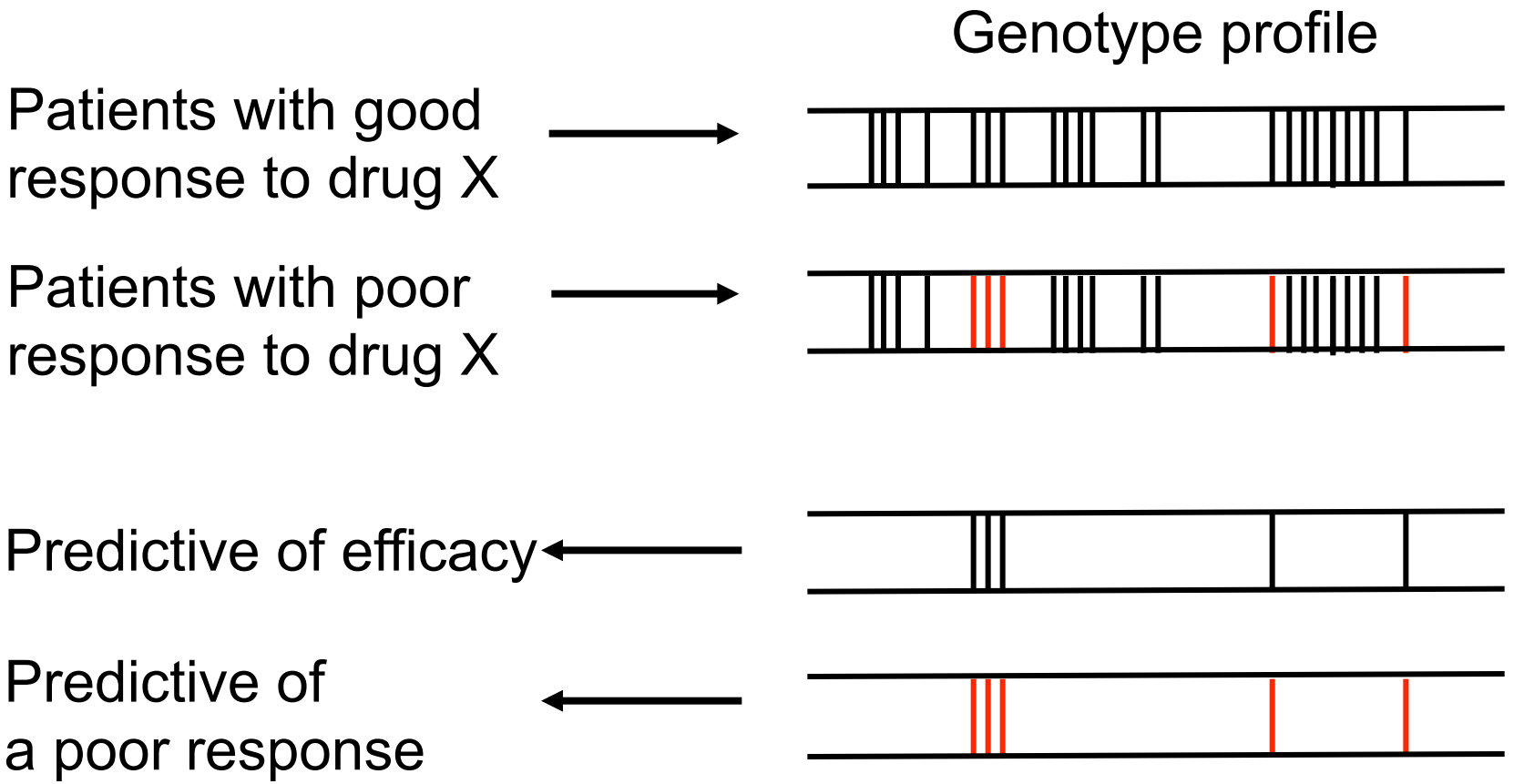
. . . G G C A A C T G . . . .

What is a SNP map

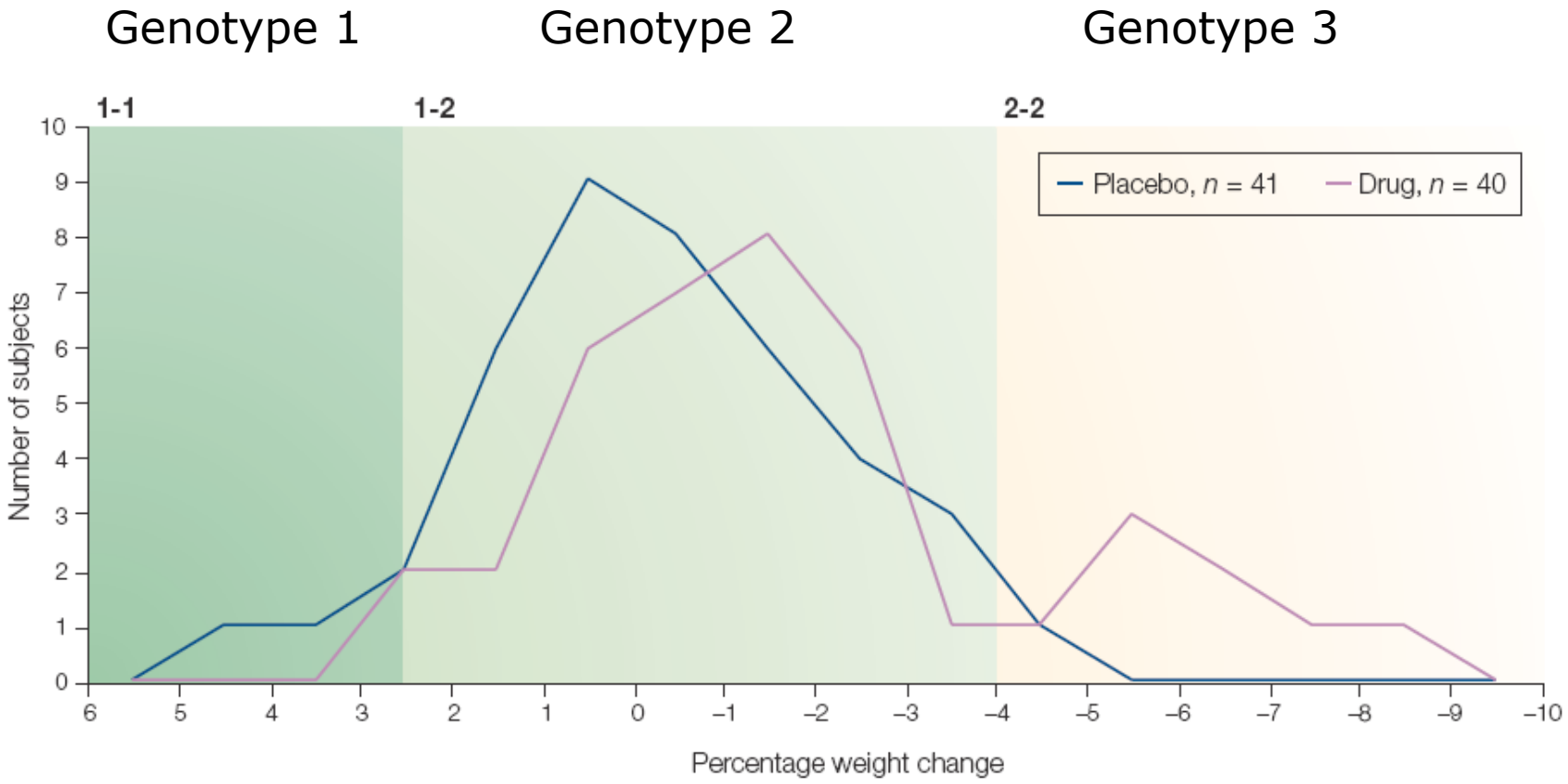


Location of SNPs on human DNA

How a SNP map can be used to predict a response to a drug



Distribution of weight change by genotype



Pharmacogenomics and adverse events

Drug	Adverse Drug Reaction		Genetic Risk Factor		
	Reaction	Prevalence	Risk Allele	Freq.[1]	Effect[2]
Clopidogrel	Cardiovascular events	0.13	*CYP2C19*2/3/4/5*	0.03	3
Gefitinib	Diarrhea	0.28	*ABCG2* Q141K	0.07	5
Isoniazid	Hepatotoxicity	0.15	*CYP2E1*1 & NAT2*	0.13[3]	7
Augmentin	Hepatotoxicity	<0.001	*HLA-DRB1*1501*	0.20	10
Irinotecan	Neutropenia	0.20	*UGT1A1*28*	0.32	28
Ticlopidine	Hepatotoxicity (cholestatic)	<0.001	*HLA-A*3303*	0.14	36
Tranilast	Hyperbilirubinemia	0.12	*UGT1A1*28*	0.30	48
Flucloxacillin	Hepatotoxicity	<0.001	*HLA-B*5701*	0.04	81
Allopurinol	Severe cutaneous reaction	<0.001	*HLA-B*5801*	0.15	678
Abacavir	Hypersensitivity reaction	0.08	*HLA-B*5701*	0.04	>1000
Carbamazepine	Stevens-Johnson syndrome	<0.001	*HLA-B*1502*	0.04	>1000

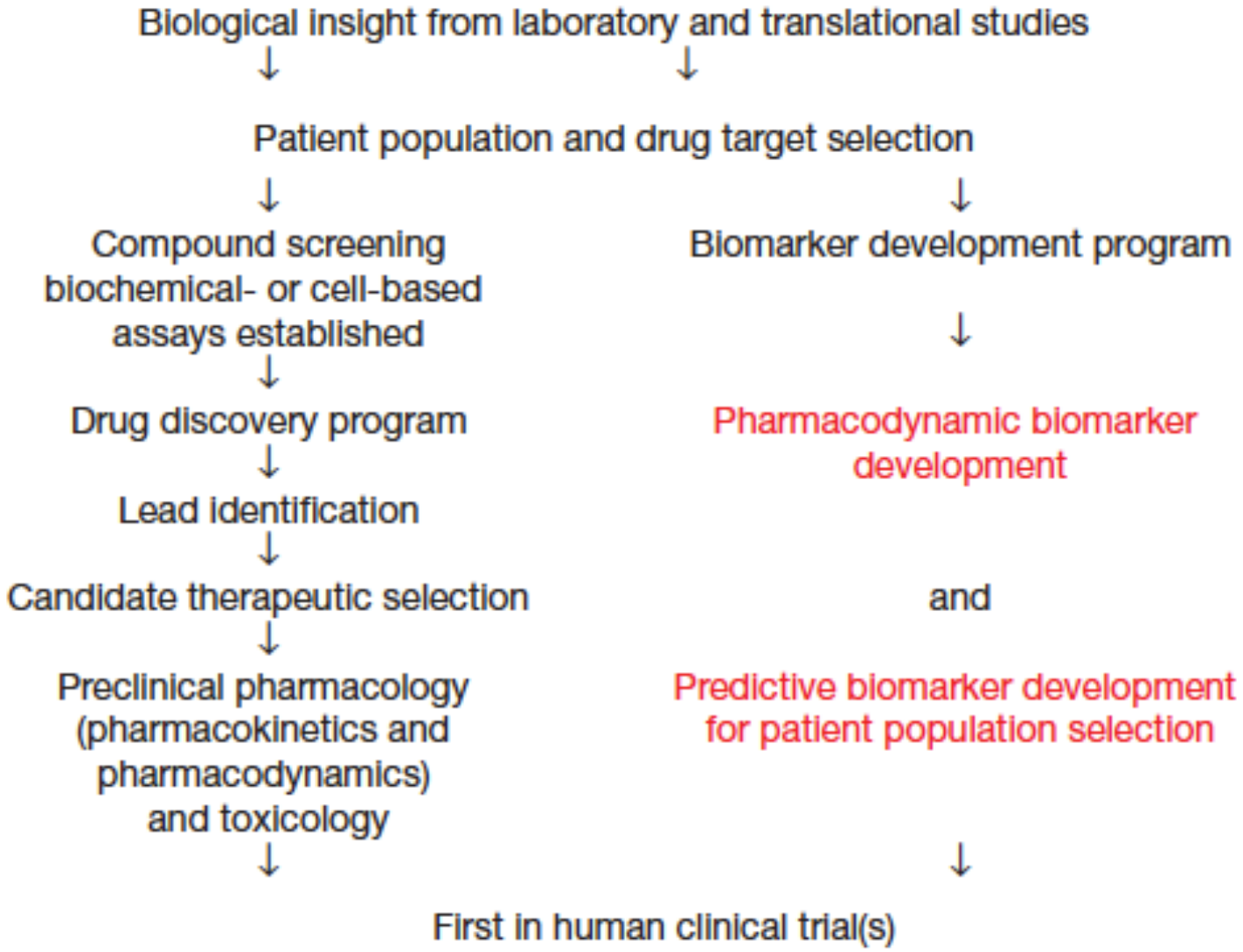
Drugs with pharmacogenomic tests in label

Antiviral	Abacavir	HLA-B*5701
	Maraviroc	CCR5
Cardiology	Warfarin	2Cp, VKCOR1
Neuropharm	Carbemezepine	HLA-B*1502
Oncology	Trastuzumab	HER2
	Irotecan	UGT1A*28
	Azothioprine	TMPT status
	Gefitinib	EGFR status
	Cetuximab	KRAS status
	Panitumumab	
Pain	Codeine	2D6

Genomics: A powerful tool for drug target identification and validation

- 7,000 rare diseases worldwide
- Medicines for only 80-90 of them
- Know the cause, have the target, can recruit the right patients

Recommended schema for anti-cancer drug development



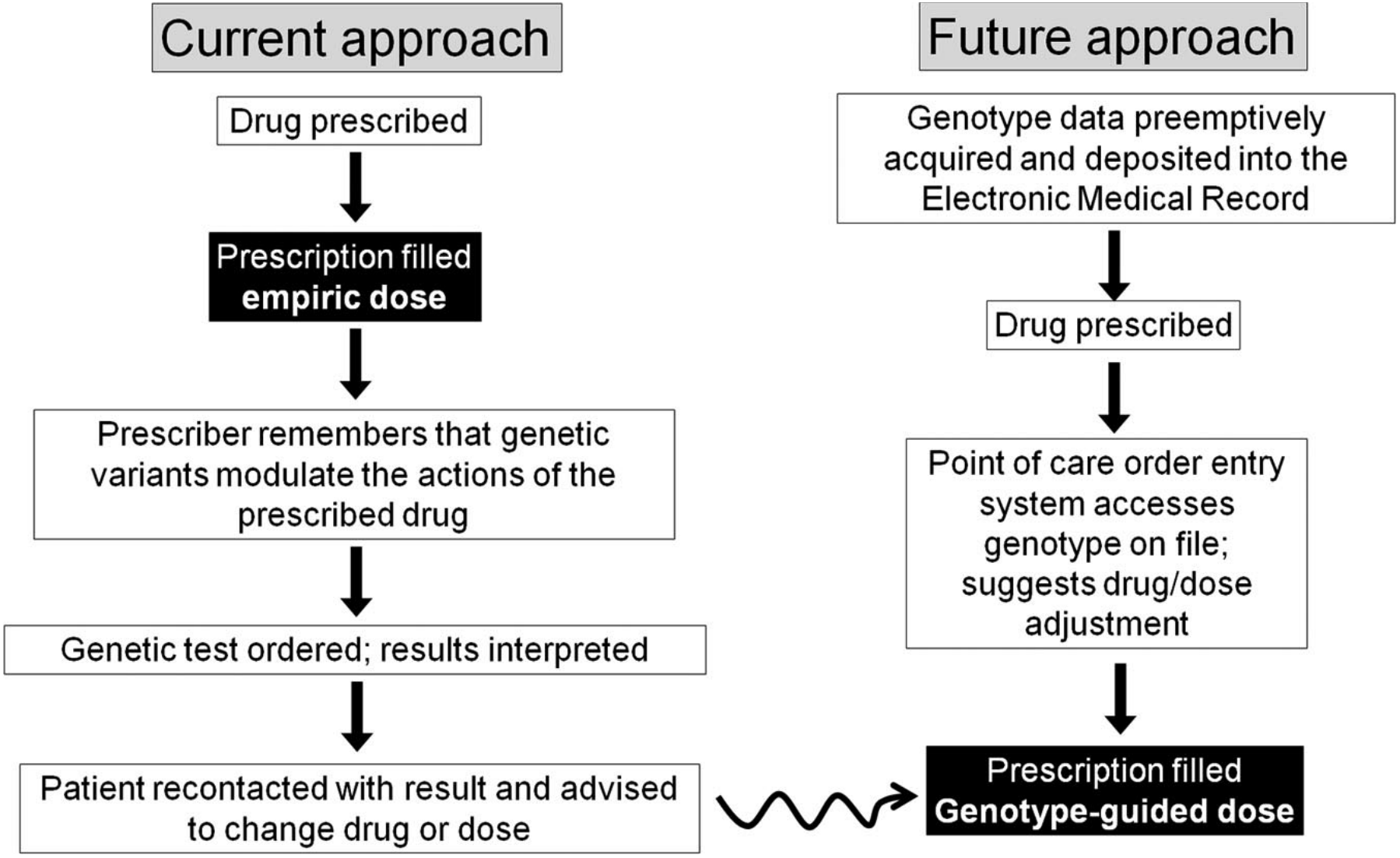
Hurdles to implementation

- Physicians
  - Education - number of variants growing
  - Needs a laboratory test – inconvenience and associated costs
- Regulators
  - The level of evidence required to adopt a specific genetic test as a guide to practice is not established.
- Pharmaceutical companies
  - Dissects the market
- Patients
  - Suspicion and sensitivity to genetic testing

Francis Collins

"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 find 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."

Current and future approachs



References

- Roden et al Pharmacogenomics: The Genetics of Variable Drug Responses Circulation 2011; 123: 1661

Use of pharmacogenomics to deliver right medicine to right patient