Pharmacogenomics

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Glaxo chief: Our drugs do not work on most patients

BY STEVE CONNOR
Science Editor

MOST PRESCRIPTION medicines do not work on most people who take them, a senior executive with Britain's biggest drug company has admitted.

Allen Roses, worldwide vice-president of genetics at GlaxoSmithKline (GSK), said fewer than half the patients prescribed some of the most ex-pensive drugs actually derived any benefit from them.

It is an open secret within the drugs industry that most of its products are ineffective in most patients, but this is the first time such a senior drug company employee has gone public. His comments come days after it emerged that the NHS drugs bill has soared by nearly 50 per cent in three years, rising by £2.3bn a year to an annual cost to the taxpayer of £7.2bn. GSK announced last week that it had 20 or more new drugs under development which could each earn the company up to US$1bn (£600m) a year.

Dr Roses, an academic geneticist from Duke University in North Carolina, spoke at a recent scientific meeting in London where he cited figures on how well different classes of drugs work. Drugs for Alzheimer's disease work in fewer than one in three patients, whereas cancer drugs are only effective in a quarter of patients. Drugs for migraines, osteoporosis, and arthritis work in about half the patients, he said. Most drugs work in fewer than one in two patients, mainly because the recipients carry genes that interfere with the medicine, he said. "The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people," Dr Roses said. "I wouldn't say that most drugs don't work … Drugs out there on the market work, but they don't work in everybody."

Some industry analysts said Dr Roses' comments were reminiscent of the 1991 gaffe by Gerald Ratner, the jewellery boss who famously said his high street shops were successful because they sold "total crap". But others believe Dr Roses deserves credit for being honest about a little-publicised fact known to the drugs industry for many years.

"Roses is a smart guy and what he is saying will surprise the public but not his colleagues," one industry scientist said. "He is a pioneer of a new culture within the drugs business based on using genes to test for who can benefit from a particular drug."

Dr Roses has formidable reputation in the field of "pharmacogenomics", the application of human genetics to drug development, and his comments can be seen as an attempt to make the industry realise that its future rests in being able to target drugs on a smaller number of patients with specific genes. The idea is to identify "responders" - people who benefit from the drug - with a simple and cheap genetic test that can eliminate those non-responders who might benefit from another drug.

This goes against a marketing culture within the industry that relies on selling as many drugs as possible to the widest number of patients, a culture that made GSK one of the most profitable pharmaceuticals companies, but which also means most of its drugs are at best useless, and even possibly dangerous, for many patients.

Dr Roses said doctors treating patients routinely applied a trial-and-error approach which says that if one drug does not work there is always another. "I think everyone has it in their experience that multiple drugs have been used for their backache or whatever," he said.

"It's in their experience, but they don't quite understand why. The reason why is because they have different susceptibilities to the effect of that drug and that's genetic. Neither those who pay for medical care nor patients want drugs to be prescribed that do not benefit the recipient. Pharmacogenetics has the promise or removing much of the uncertainty."

Further report, pages 18-19
Leading article, page 30

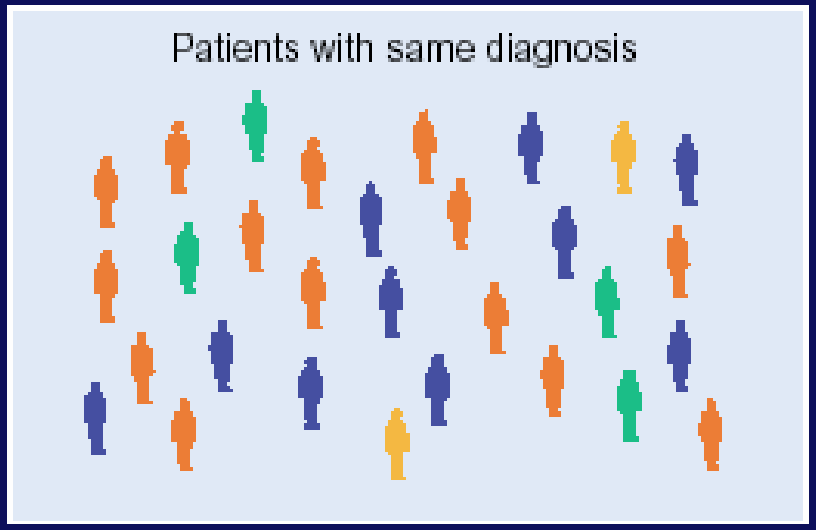
Therapeutic Response Rates

Disease	Drug Class	Rate of Response (%)
Asthma	Beta-agonists, others	25-60
Solid cancers	Various	0-30
Depression	SSRIs, tricyclics, others	60-80
Diabetes	Sulfonylureas, others	25-50
Arthritis	NSAIDs, COX-2 inhibitors, others	50-80
Migraine	Triptans, NSAIDs, ergots	40-70
Schizophrenia	Various	25-75
Major drug toxicity	Various	2 million hospitalized patients/y 4th to 6th leading cause of death in the United States in 1994[1]

COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

1. Lazarou J, et al. *JAMA.* 1998;279:1200-1205.

Clinical Potential of Pharmacogenomics



1.

Predicted good response to tested drug

2.

Predicted poor or nonresponse

Use different drug

3.

Predicted increased toxicity risk

Decrease dose or use different drug

Johnson JA. *Trends Genet.* 2003;19:660-666.

History

- Started with observations of adverse reactions in certain patients receiving standard drug doses
  - Primaquine hemolysis in mainly black-American WWII soldiers
    - G6PD deficiency (*Science.* 1956;124:484)
  - Isoniazid neuropathy
    - Slow acetylators (*N*-acetyltransferase-2) (*Am Rev Tuberc.* 1954;70:266)
  - Suxamethonium prolonged apnea
    - Plasma cholinesterase abnormality (*Lancet.* 1956;211:576)
  - Life-threatening hypotension from debrisoquine
    - CYP2D6 deficiency (*Lancet.* 1977;2:584-586)

1. Alving AS, et al. *Science.* 1956;124:484-485; 2. Hughes HB, et al. *Am Rev Tuberc.* 1954;70:266-273; 3. *Lancet.* 1956;211:576; 4. Mahgoub A, et al. *Lancet.* 1977;2:584-586.

Definitions

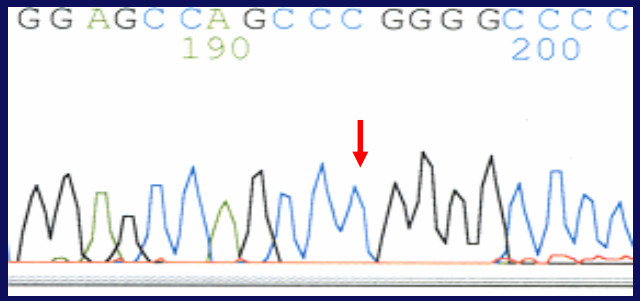
- Pharmacogenetics
  - A discrete inherited trait related to drug absorption and disposition, as well as response
- Pharmacogenomics
  - The application of genome-wide SNP scans and gene expression analyses (information from the whole genome) to study variations that influence drug action (responses, new drug targets, etc)

SNP = single nucleotide polymorphism.

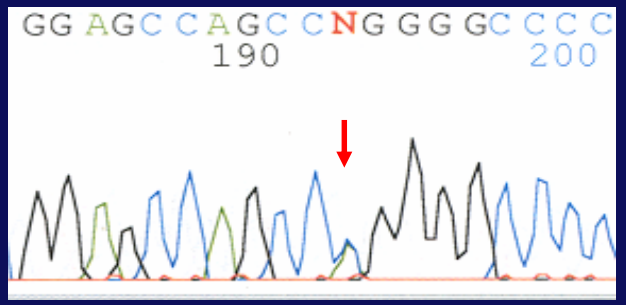
Genetic Variants

- Mutation: a rare DNA variant (<1% of population)
- Polymorphism: a common DNA variant (>1% of population)
  - Base substitution, deletion or insertion
  - Most common are SNPs
  - May be in coding or non-coding region
  - Alter amino acid (non-synonymous) or not (synonymous)
  - May alter function or expression level of protein

C/C



C/A



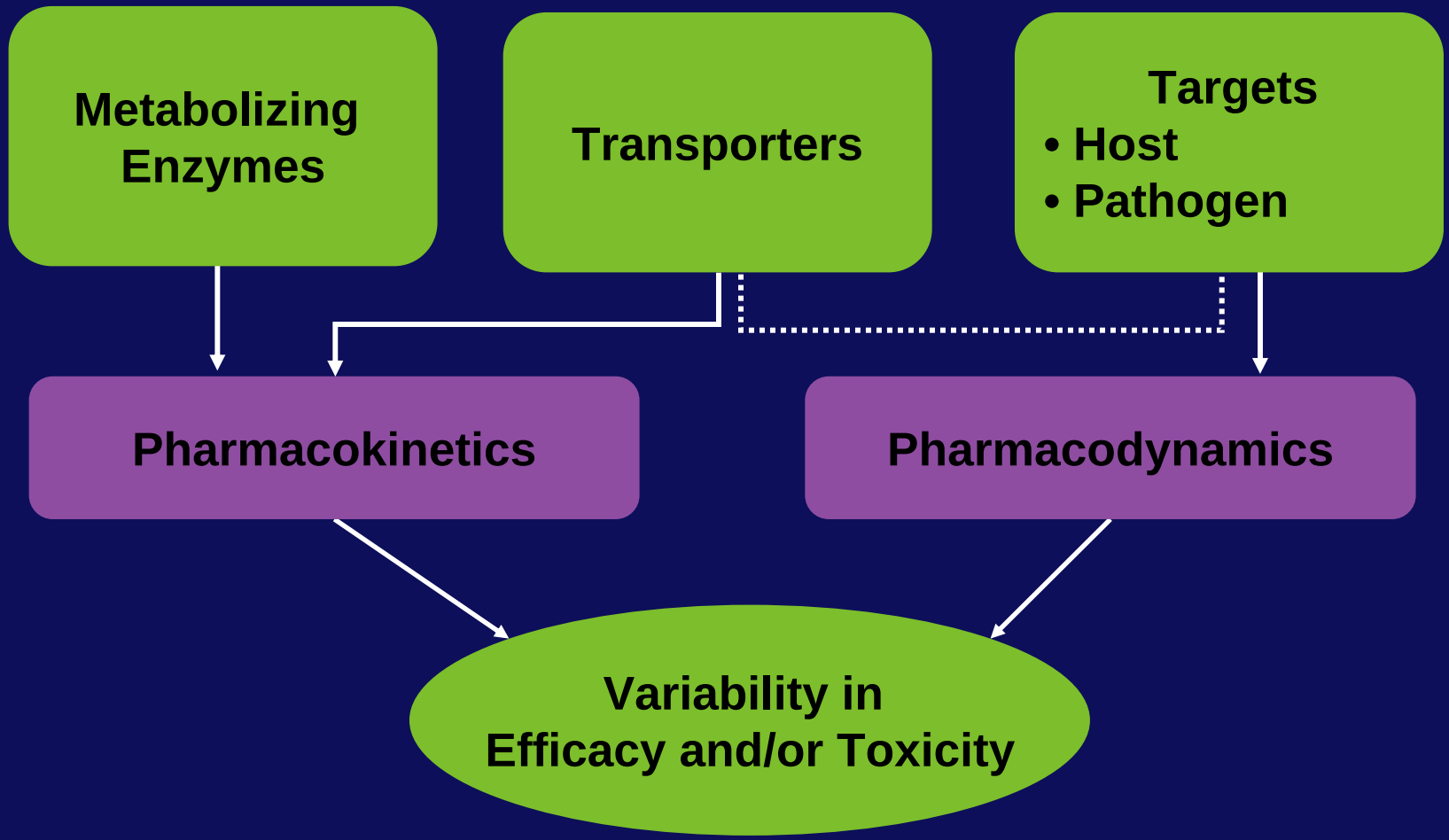
Pharmacokinetic Variability

- Key principle: the same dose does not produce the same concentrations among patients due to interpatient differences in absorption, distribution, metabolism and excretion
- Factors that can exaggerate pharmacokinetic variability
  - Drug-food interactions
  - Drug-drug interactions
  - Enzyme induction/inhibition
  - Altered GI, renal and hepatic function
  - Pregnancy
  - Sex differences in pharmacokinetics
  - Genetic differences in pharmacokinetics

Genetics and Therapeutics

- Pharmacogenetics/pharmacogenomics
  - Identifying genetic correlates that may account for differences in pharmacologic response among individuals
    - Metabonomics
    - Toxicogenomics
- Predictive medicine
  - Genetic testing for predisposition to disease or variation in response to a therapeutic intervention
    - “Therapy with the right drug at the right dose in the right patient”

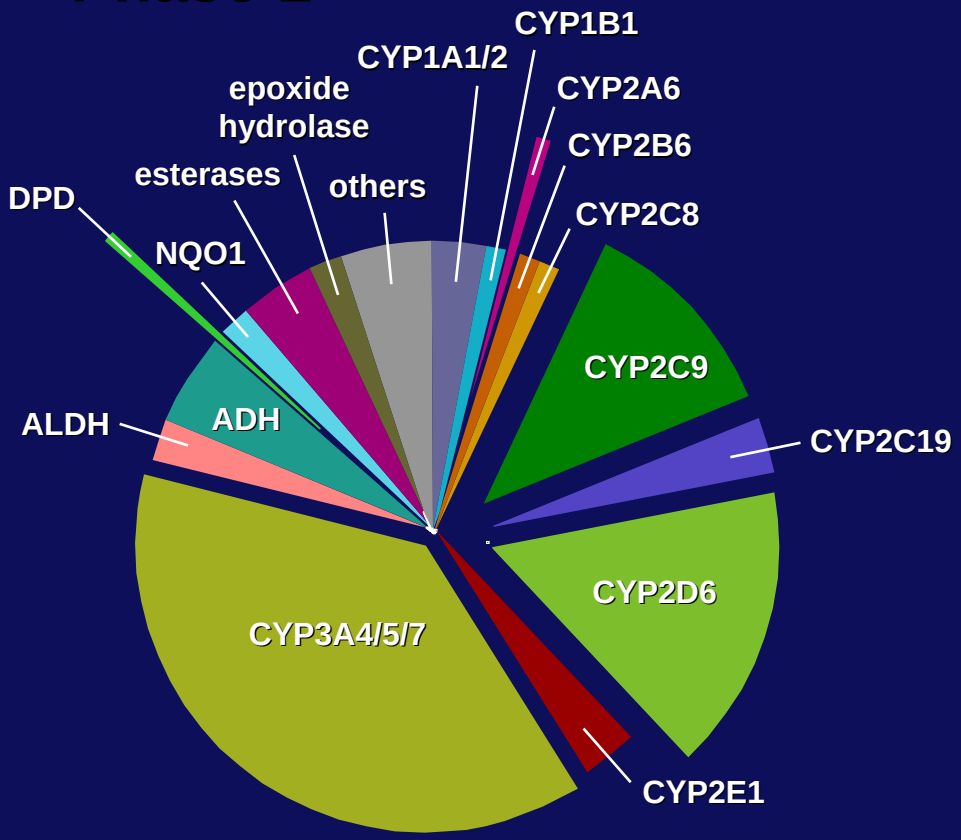
Pharmacogenomics



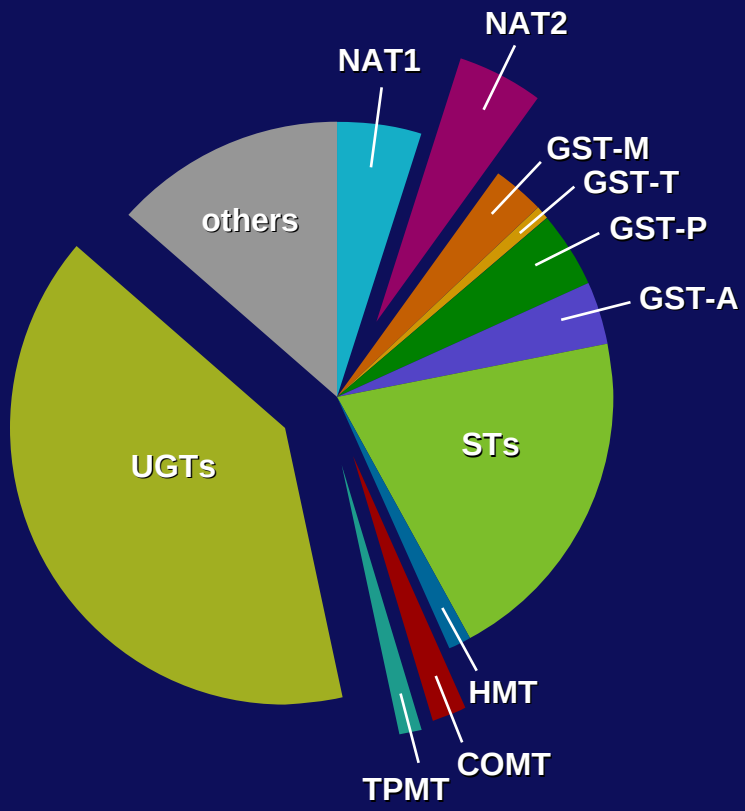
Modified from Johnson JA. *Trends Genet.* 2003;19:660-666.

Drug Metabolizing Enzymes

Phase 1



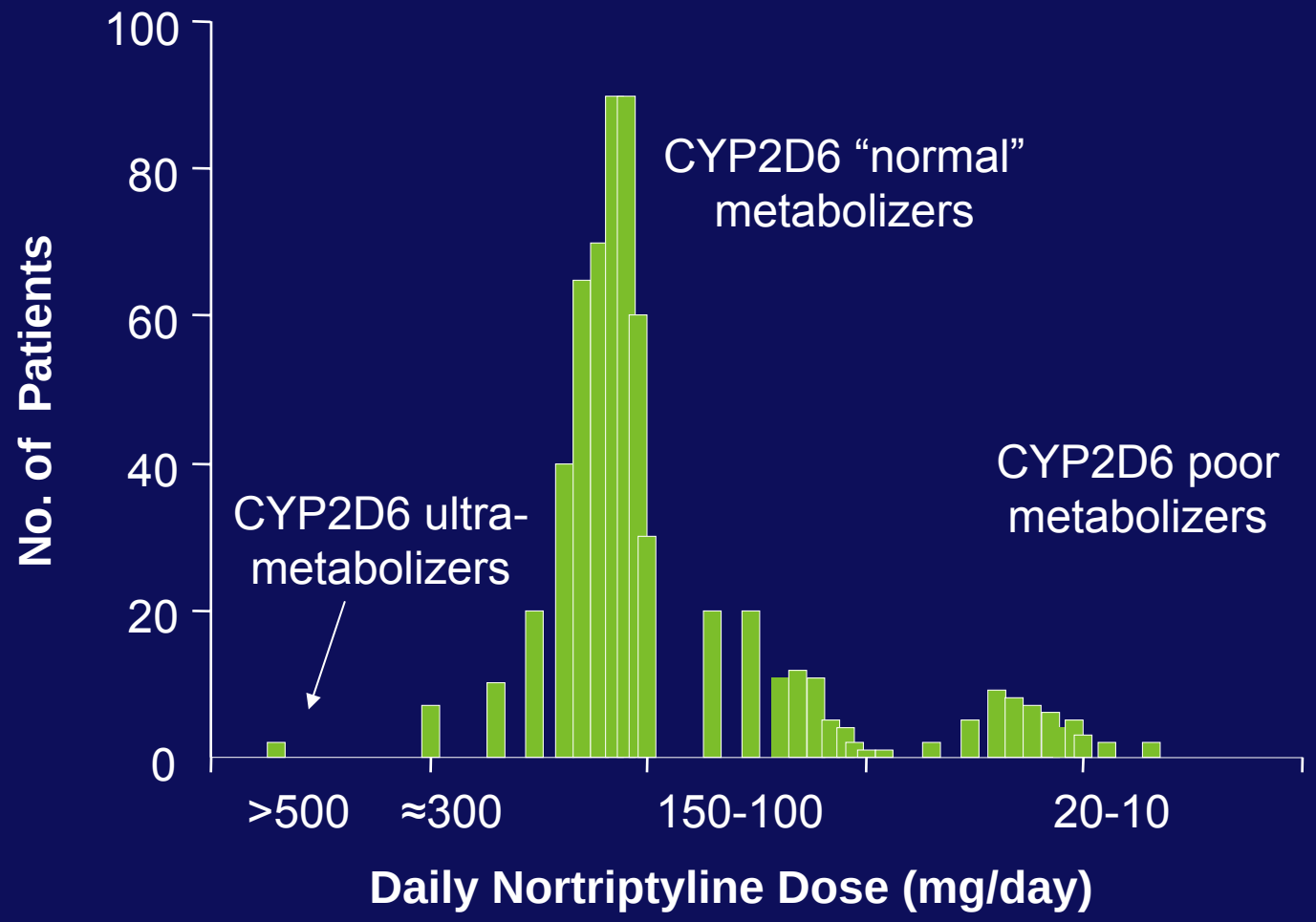
Phase 2



Extended = known polymorphisms that affect activity.
Polymorphisms present in all (?) enzymes.

Wilson JF, et al. *Nat Genet.* 2001;29:265-269.

Daily Dose Requirements of Nortriptyline



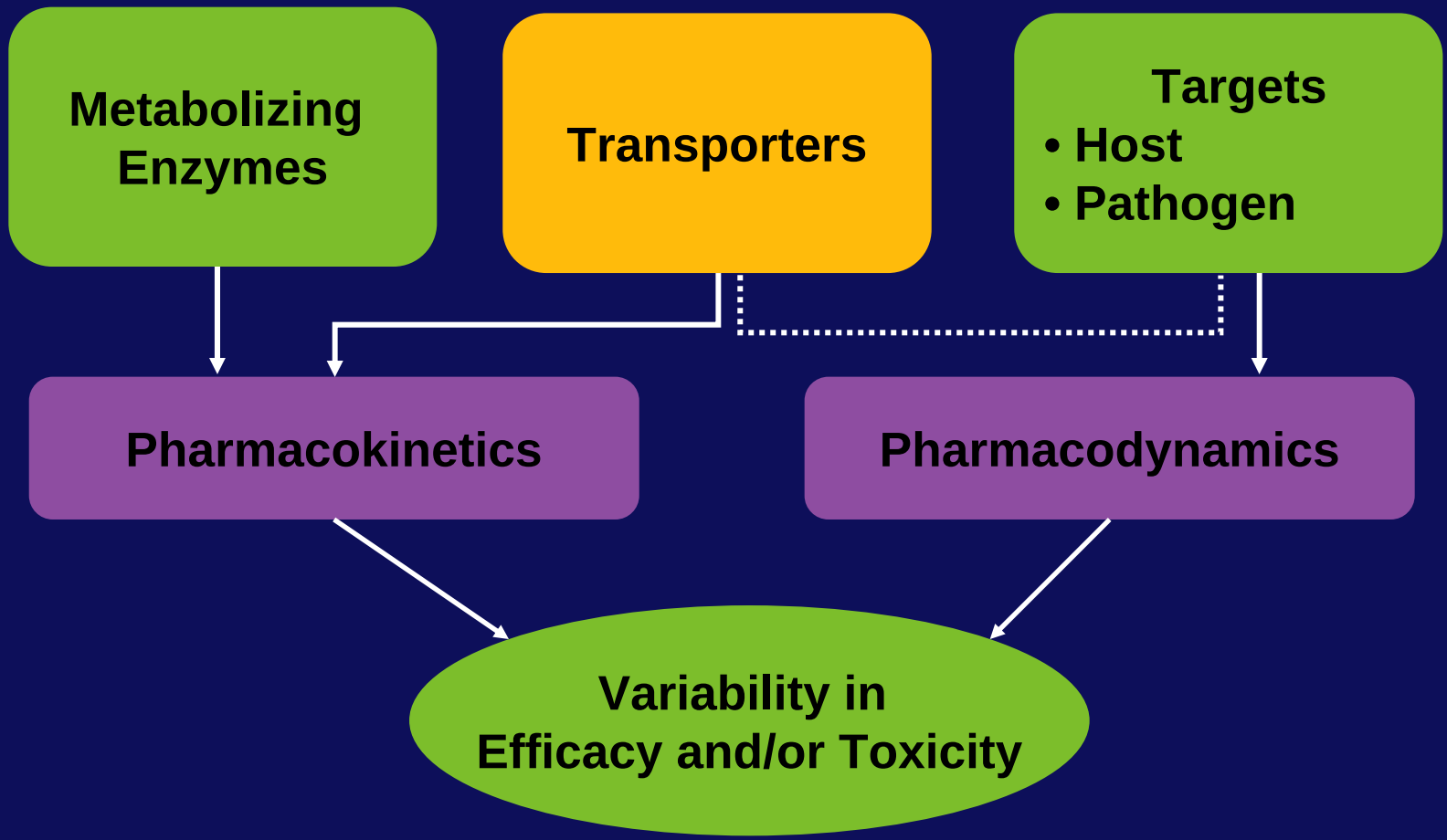
Kalow W. *Pharmacogenetics.* New York, NY: Marcel Dekker; 2001.

Voriconazole and Pharmacogenomics

- CYP2C19 is significantly involved in the metabolism of voriconazole
- Poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCτ)
  - Poor metabolizers: 15% – 20% of the Asian population and 3% – 5% of Caucasians and blacks
- Most frequent adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain and respiratory disorder
- 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances

Voriconazole (Vfend) package insert, December 23, 2003.

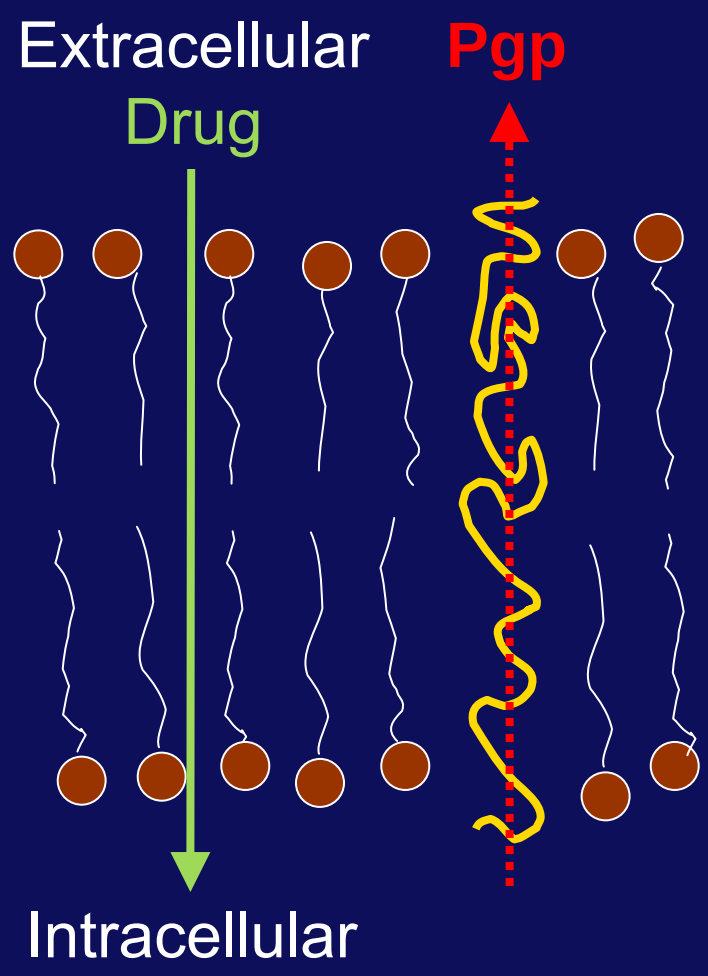
Pharmacogenomics



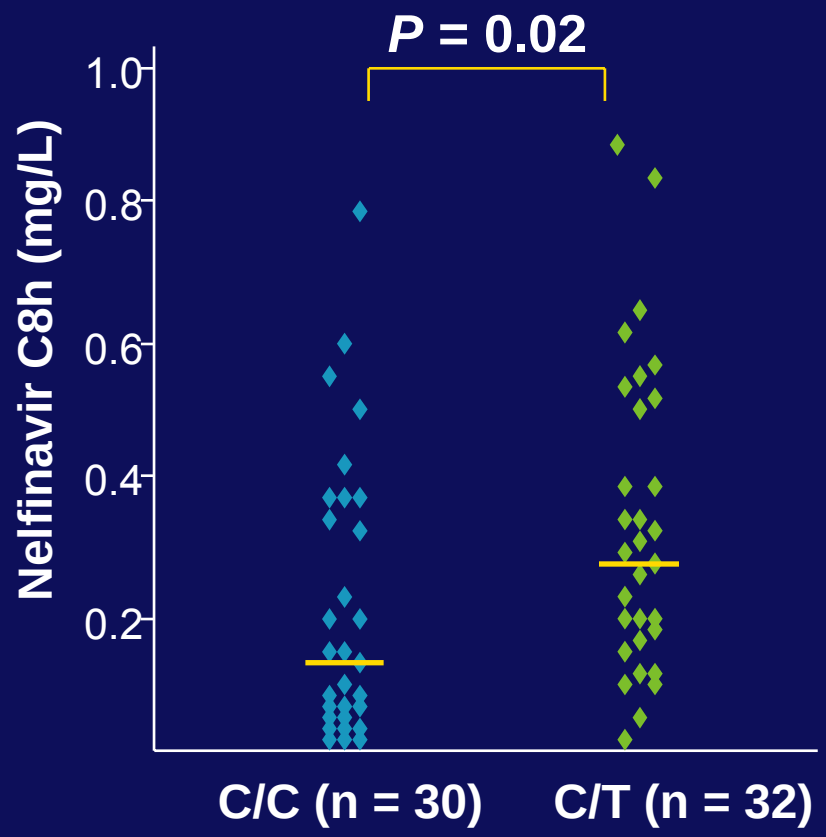
Modified from Johnson JA. *Trends Genet.* 2003;19:660-666.

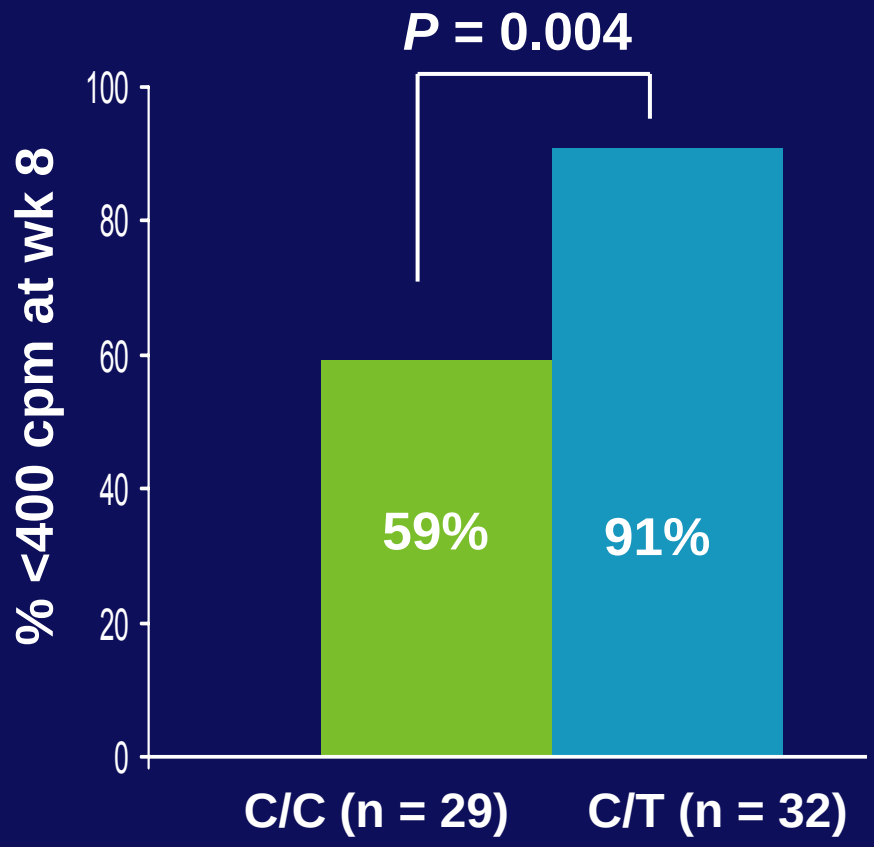
The Role of P-Glycoprotein (Pgp) in the Absorption and Distribution of Drugs

- Encoded by MDR1 gene; a member of the ATP-binding cassette family of membrane transporters
- Found in blood-brain barrier, gut, lymphocytes, renal tubules, etc
- Principal function is cellular efflux of substrates; protects cells from xenobiotics
- 2 SNPs identified: 3435C->T (synonymous) and 2677G->T (nonsynonymous); 3435 is in linkage disequilibrium with 2677
- SNPs are associated with reduced Pgp function, although the results are variable



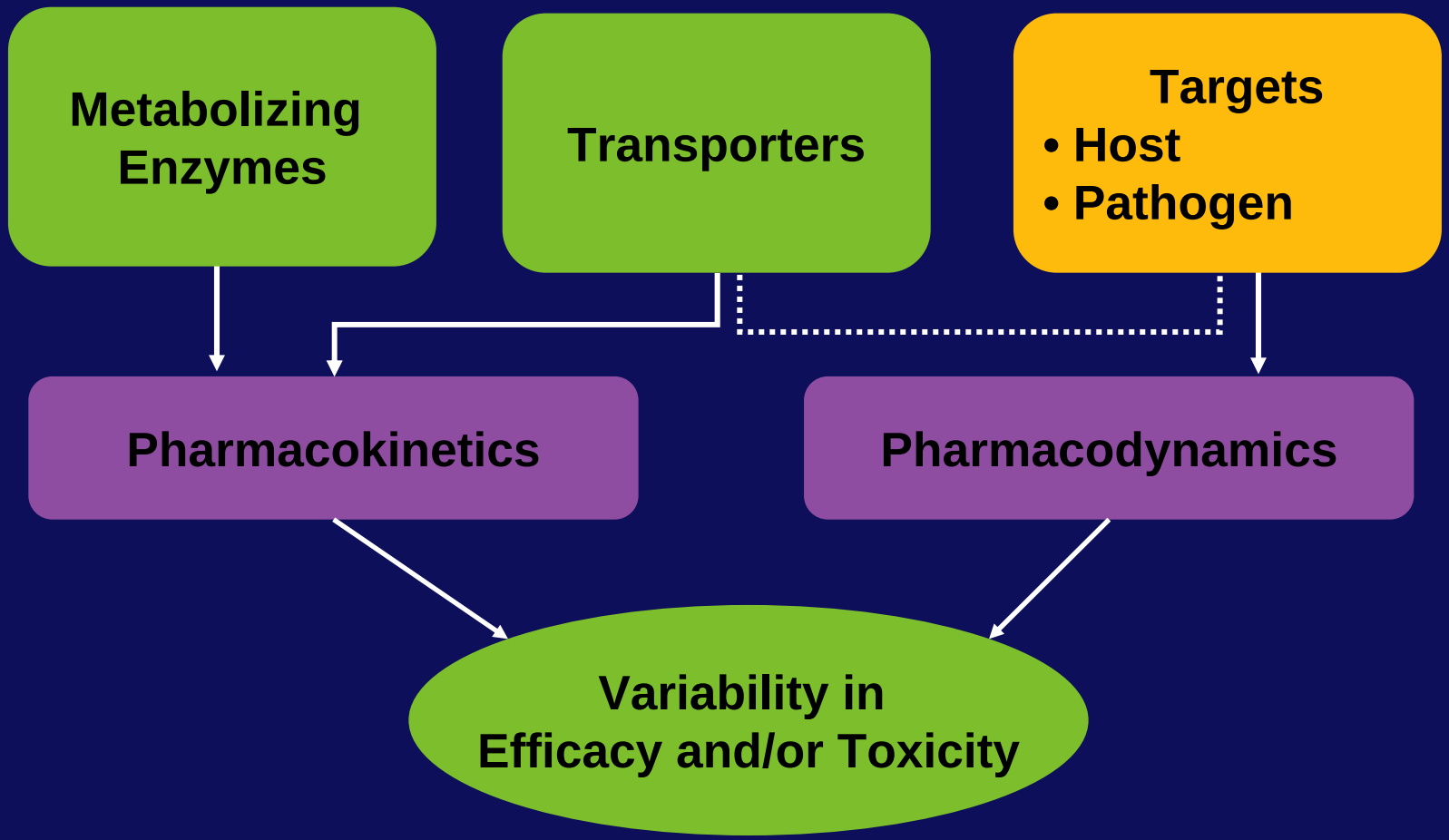
Nelfinavir Trough Levels, HIV RNA Response and Pgp Polymorphisms





Saitoh A, et al. *AIDS.* 2005;19:371-380.

Pharmacogenomics



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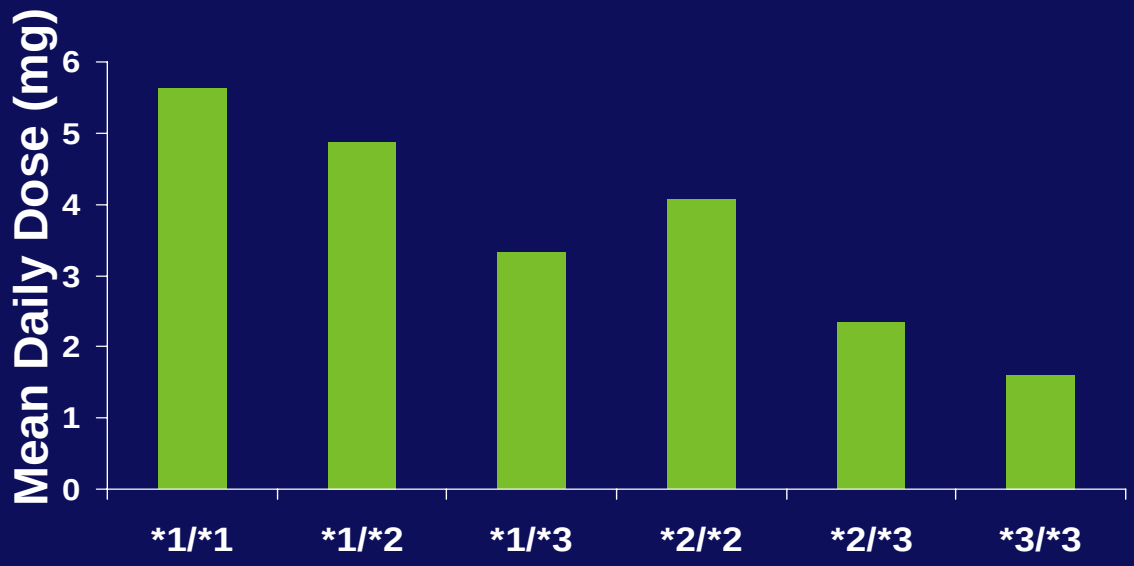
Association Between *CYP2C9* Genetic Variants and Warfarin Therapy*

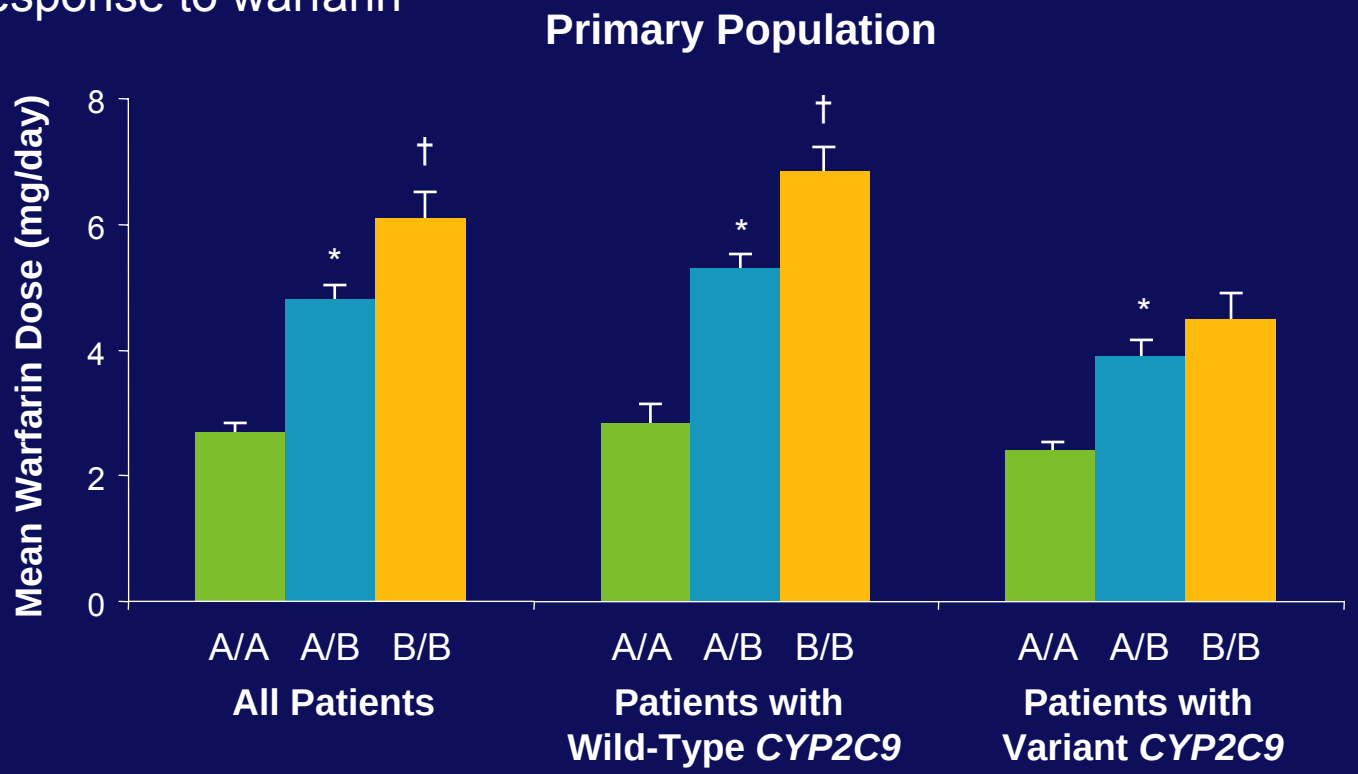


End Point	Finding	Hazard Ratio
Time to stable dosing	CYP variants had longer time to achieve stable dosing	0.65
Time to bleeding event	CYP variants had an increased risk of bleeding	3.94

Higashi MK, et al. *JAMA.* 2002;287:1690-1698.

Effect of *VKORC1* Haplotypes on Warfarin Dose*

- Vitamin K epoxide reductase complex 1 *(VKORC1)* recycles reduced vitamin K, essential for the synthesis of clotting factors II (prothrombin), VII, IX and X
- The *VKORC1* gene encodes the primary warfarin-sensitive component, and polymorphisms have been discovered that influence the pharmacodynamic response to warfarin



Rieder MJ, et al. *N Engl J Med.* 2005;352:2285-2293.

Abacavir Hypersensitivity and HLA Polymorphisms

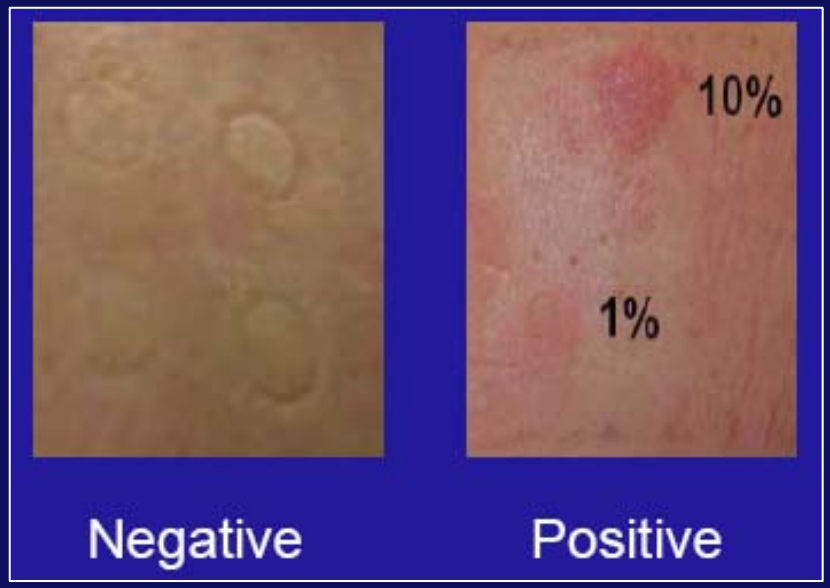
	Abacavir Hypersensitive	Abacavir Tolerant	OR
HLA-B 5701	14 (78%)	4 (2%)	117
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73
HLA-B 5701, HLA-DR7, HLA-DQ3	13 (72%)	0 (0%)	822

HLA = human leukocyte antigen; OR = odds ratio.

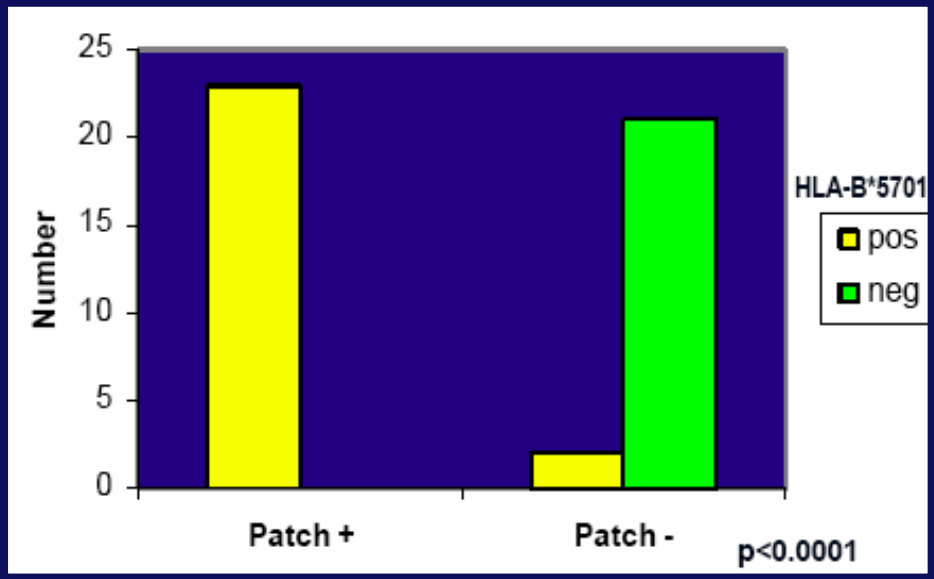
Mallal S, et al. *Lancet.* 2002;359:727-732.

Patch Test for Abacavir Hypersensitivity

Patch Testing to 1% and 10% Abacavir



HLA-B*5701 Presence According to Patch Test

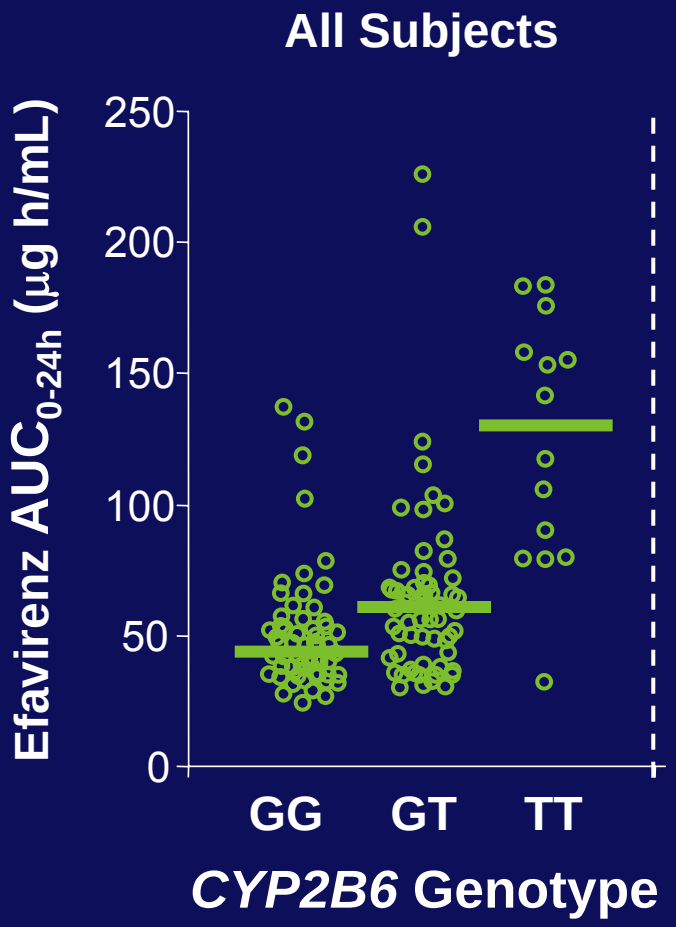


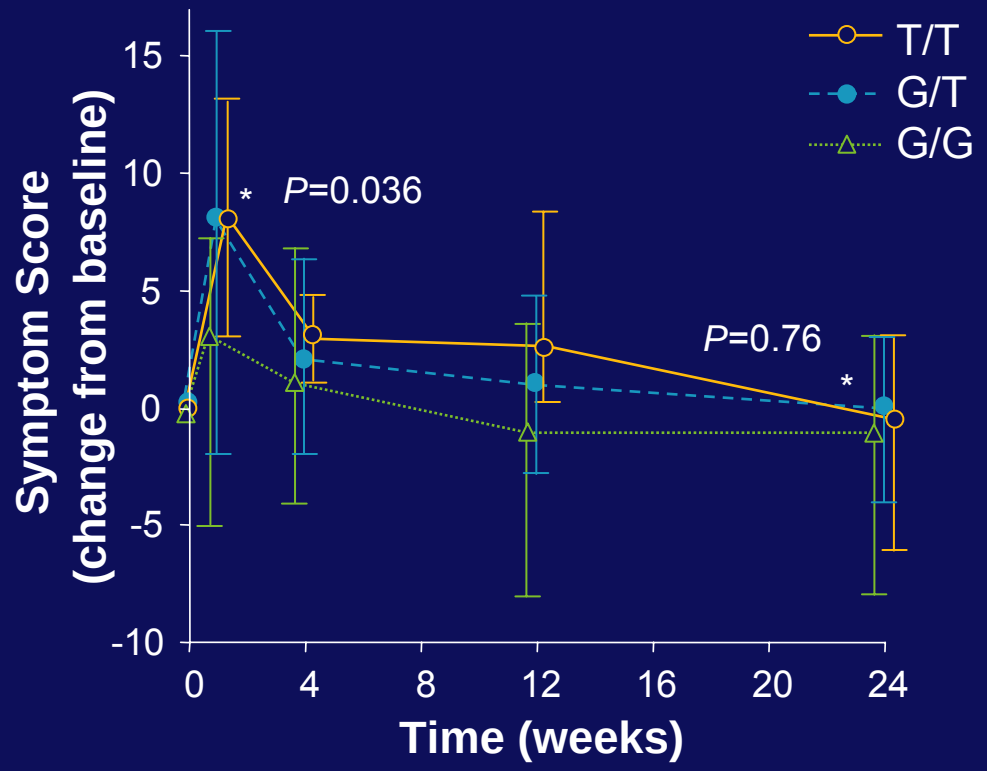
Phillips E, et al. 7th International Wkshp on HIV Clinical Pharmacology, Lisbon, April 20, 2006.

Rules of Pharmacogenomics

- Population
- Power
- Strength of association
- Dose-response
- Biologic plausibility

EFV, CNS Symptoms and *CYP2B6*

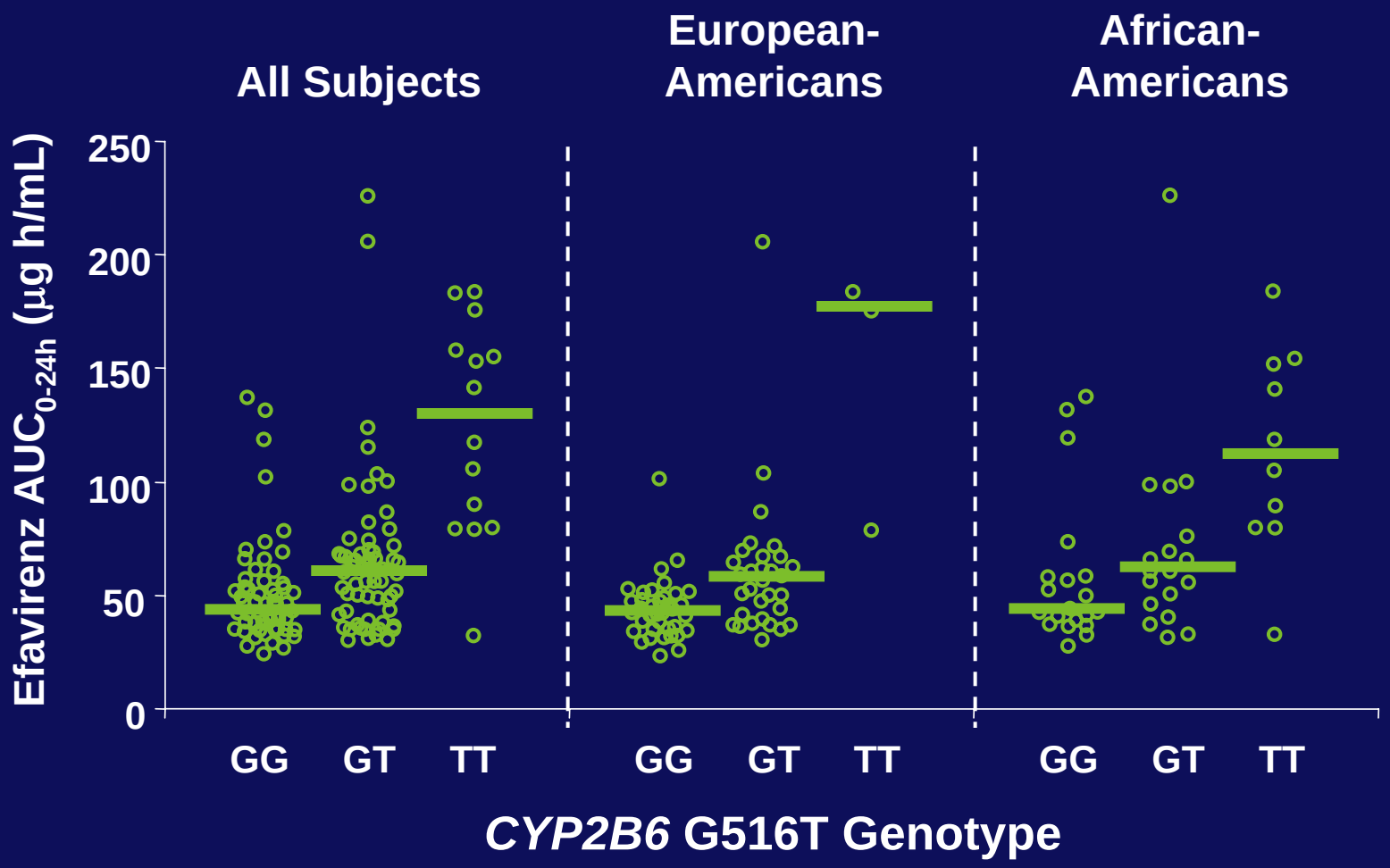




G/G	83	77	74	75	69
G/T	60	59	52	50	47
T/T	14	14	14	14	14

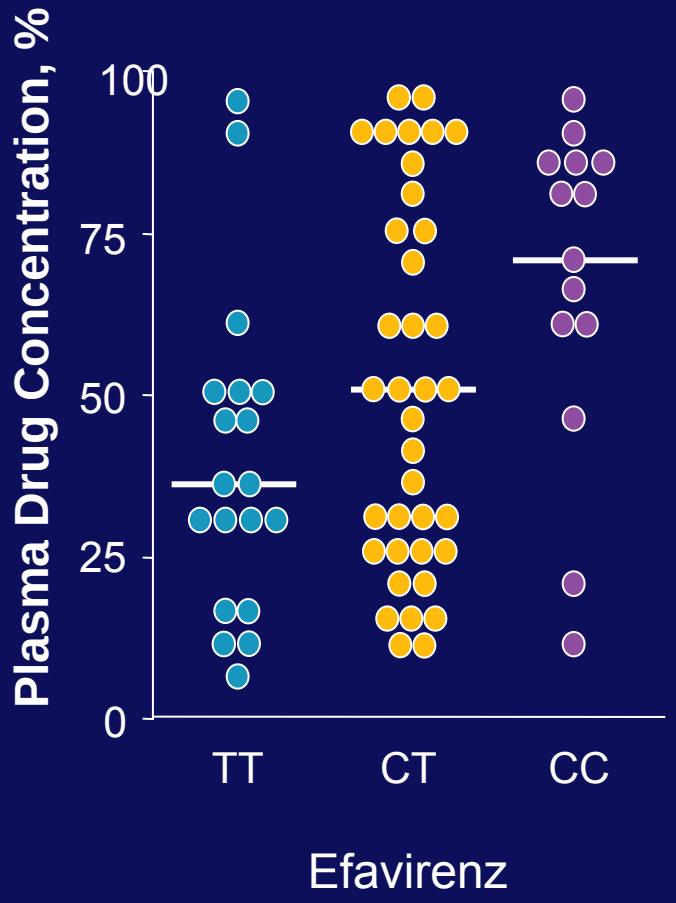
Haas DW, et al. *AIDS.* 2004;18:2391-2400.

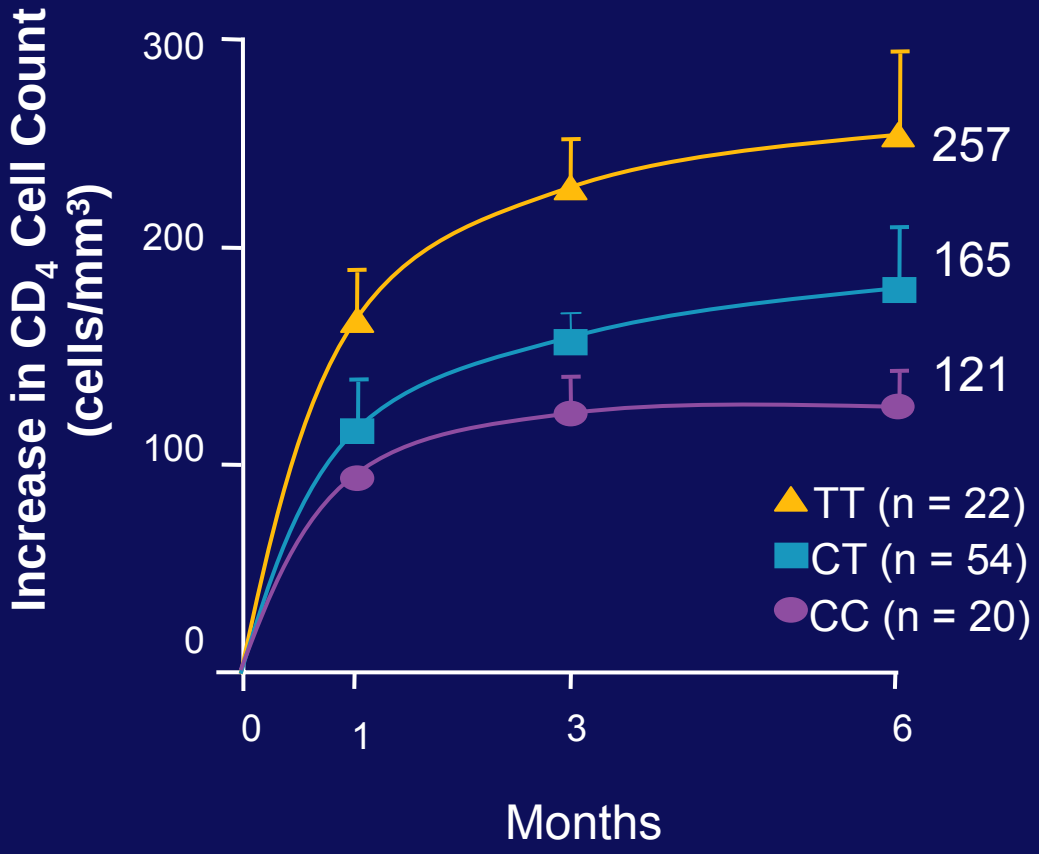
Efavirenz Concentrations and Polymorphisms in *CYP2B6*



Haas DW, et al. *AIDS.* 2004;18:2391-2400.

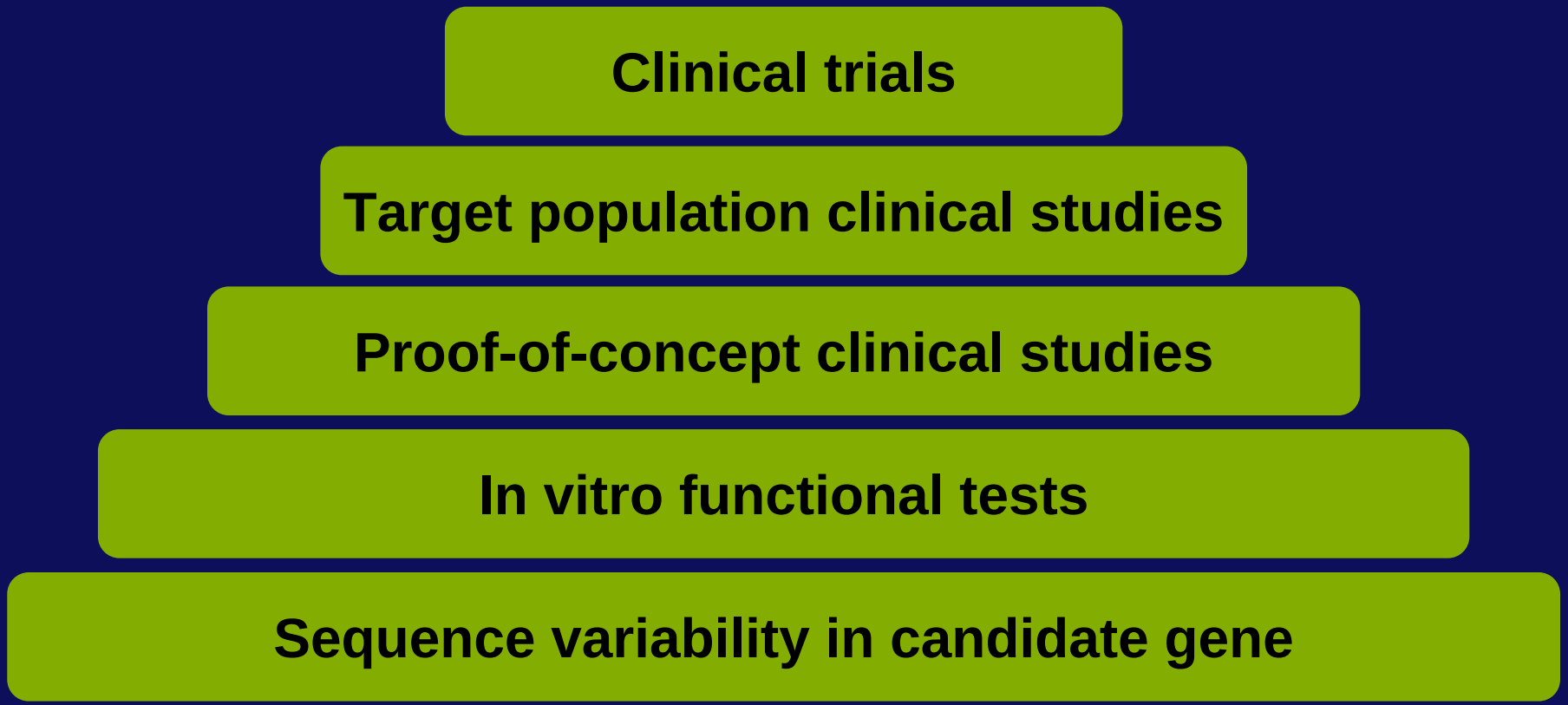
P-Glycoprotein Polymorphisms (3435 C/T) Efavirenz Conc and CD4 Response





Fellay J, et al. *Lancet*. 2002;359:30-36.

Pharmacogenetics: From Research to Clinical Practice



Modified from Johnson JA. *Trends Genet.* 2003;19:660-666.

Summary

- The field of pharmacogenomics is rapidly evolving
- There is no single best strategy or method for pharmacogenomic discovery or validation
- Pharmacogenomic approaches have the potential to provide profound clinical benefits, but this is not guaranteed
- To eventually bring pharmacogenomic assays to clinical practice, the careful design of studies will be more important than the technology applied

And Here Is My Sequence . . .