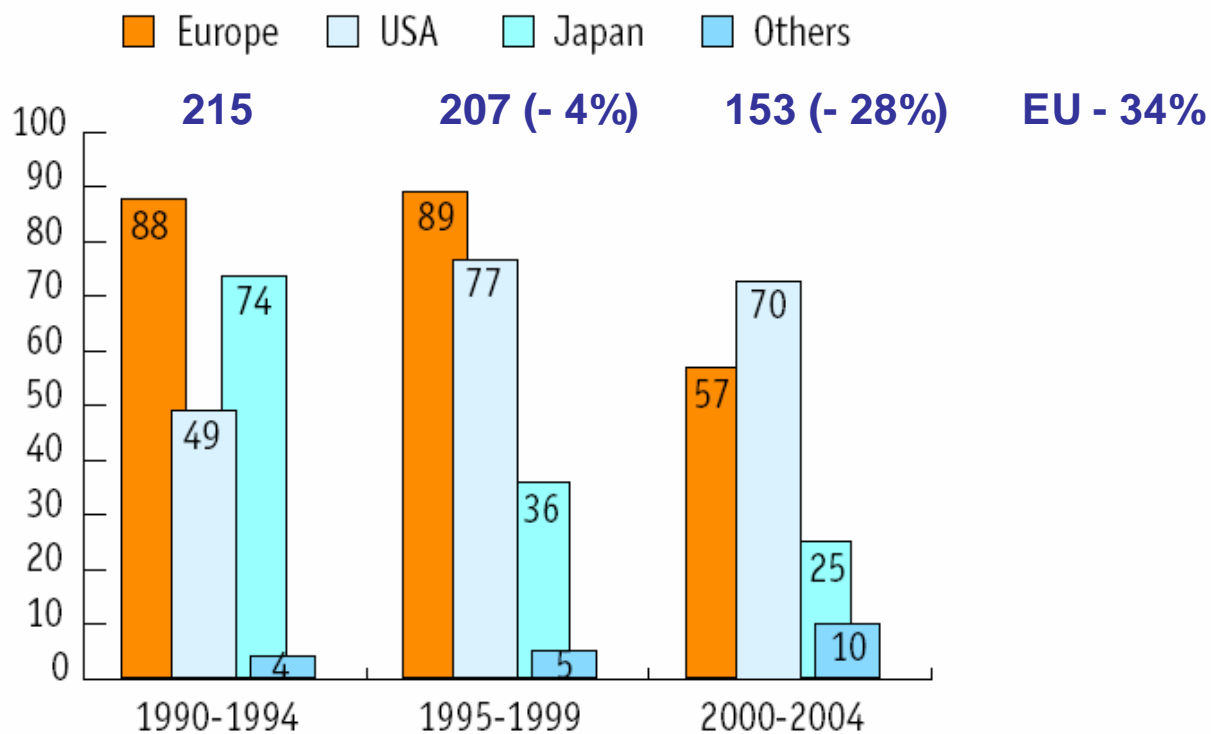


# Farmacogenetica ed Efficacia Terapeutica

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## NEW CHEMICAL OR BIOLOGICAL ENTITIES (1990-2004)



Source: SCRIP – EFPIA calculations (according to nationality of mother company)

## Fenotipo: Sicurezza

Nel 2007, 28 farmaci ritirati dal commercio per ADR letali (TdP)

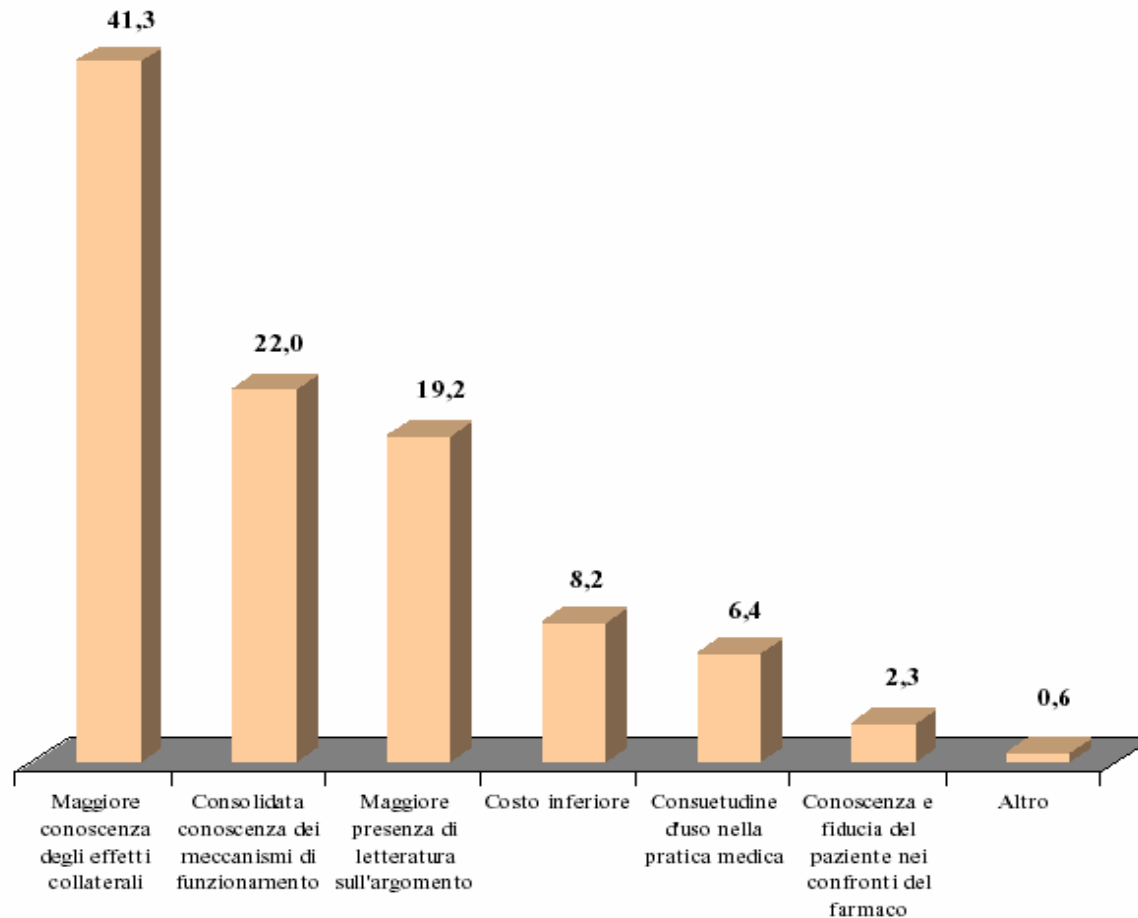
16% dei farmaci in commercio è associato a ADR gravi, riportate sul scheda tecnica (Spear B, 2001)

>100 000 morti all'anno negli USA rappresenta la quarta causa di morte dopo malattie cardiovascolari, tumori e ictus (Lazarou et al, 1998)

ADR lievi/moderate ↓ la compliance influenzando la risposta (Spear B, 2001)

# Motivazioni per preferire un farmaco

Fig. 9 - Le principali motivazioni che spingono a preferire un farmaco noto in presenza di due farmaci con caratteristiche terapeutiche simili (val.%)



# Casi Recenti

- Rofecoxib
- Cerivastatina

# Variabilità nella efficacia terapeutica dei farmaci

	% pazienti scarsa risposta
Antagonisti dell'angiotensina 2	10-25%
ACE inibitori	10-25%
Beta-bloccanti	15-25%
Antidepressivi triciclici	20-50%
Agonisti beta-2 adrenergici	40-70%

# La variabilità individuale nelle risposte ai farmaci è dovuta a fattori:

Fisiologici

età, sesso, peso corporeo, condizione fisica

Patologici

malattie, livello di funzionalità epatica o renale

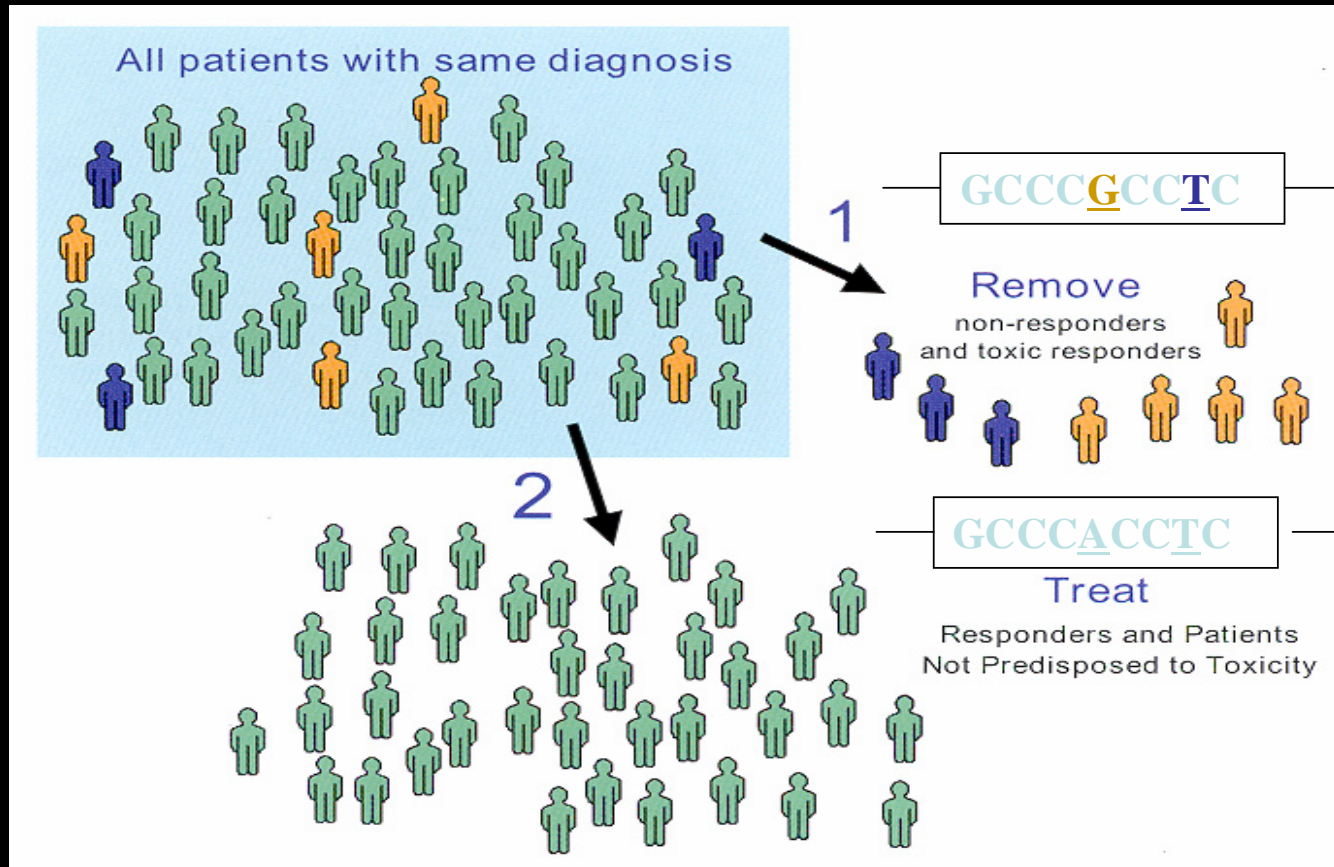
Ambientali

dieta, alcool, tabacco, altri farmaci

Genetici

polimorfismi

# Pharmacogenetic Strategy Applied to the Practice of Medicine

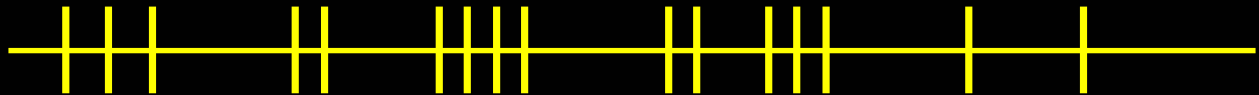


# Genotipo

SNP - Single Nucleotide Polymorphisms



...GG**T**AAC TG...  
...GG**C**AAC TG...



# Associazione (SNP)

Responders



No responders



Predittivi della  
presenza del fenotipo



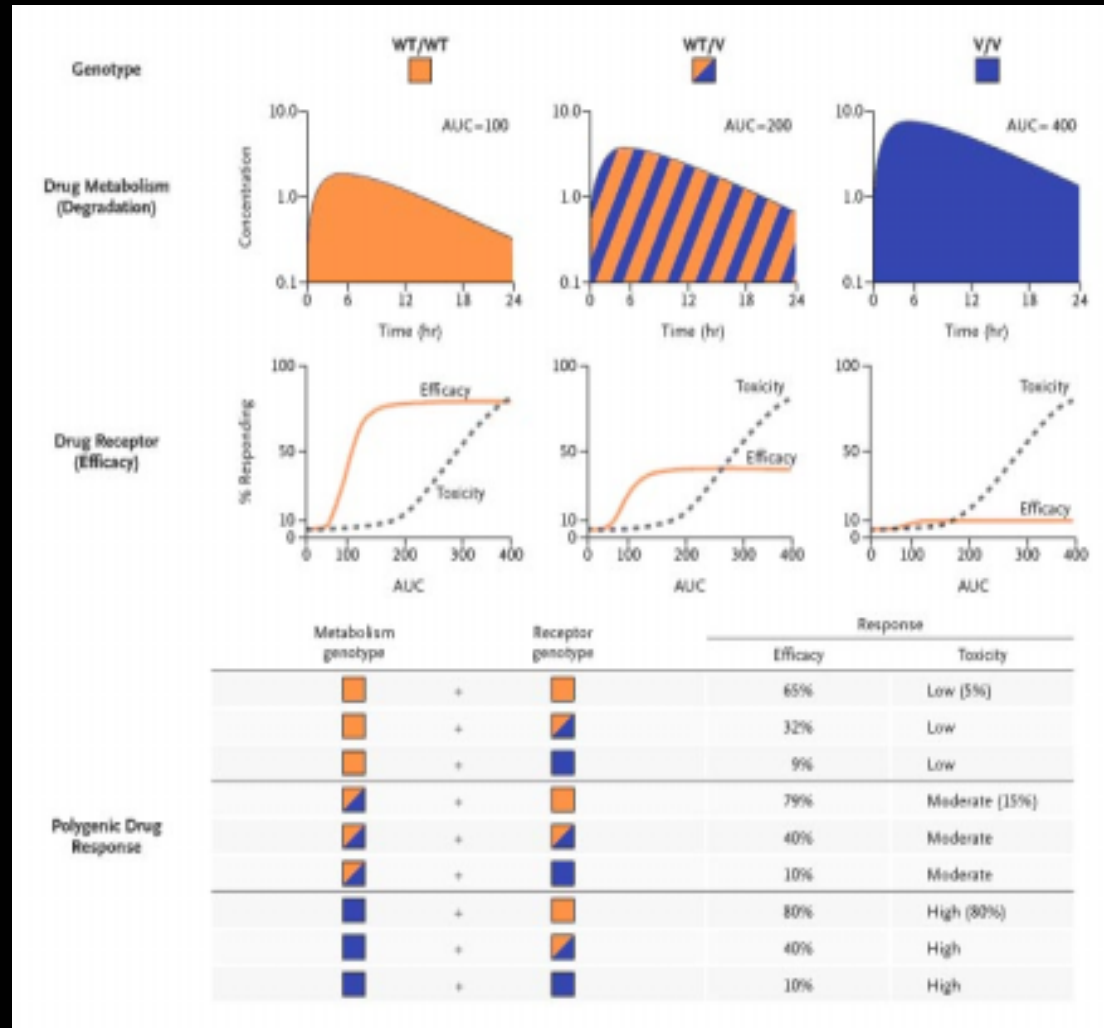
T

Predittivi dell'assenza  
del fenotipo



A

# Risposta al farmaco: determinanti poligenici



# Farmacogenetica



genotipo  
SNPs

Associazione



fenotipo  
Risposta al farmaco

Marker predittivi

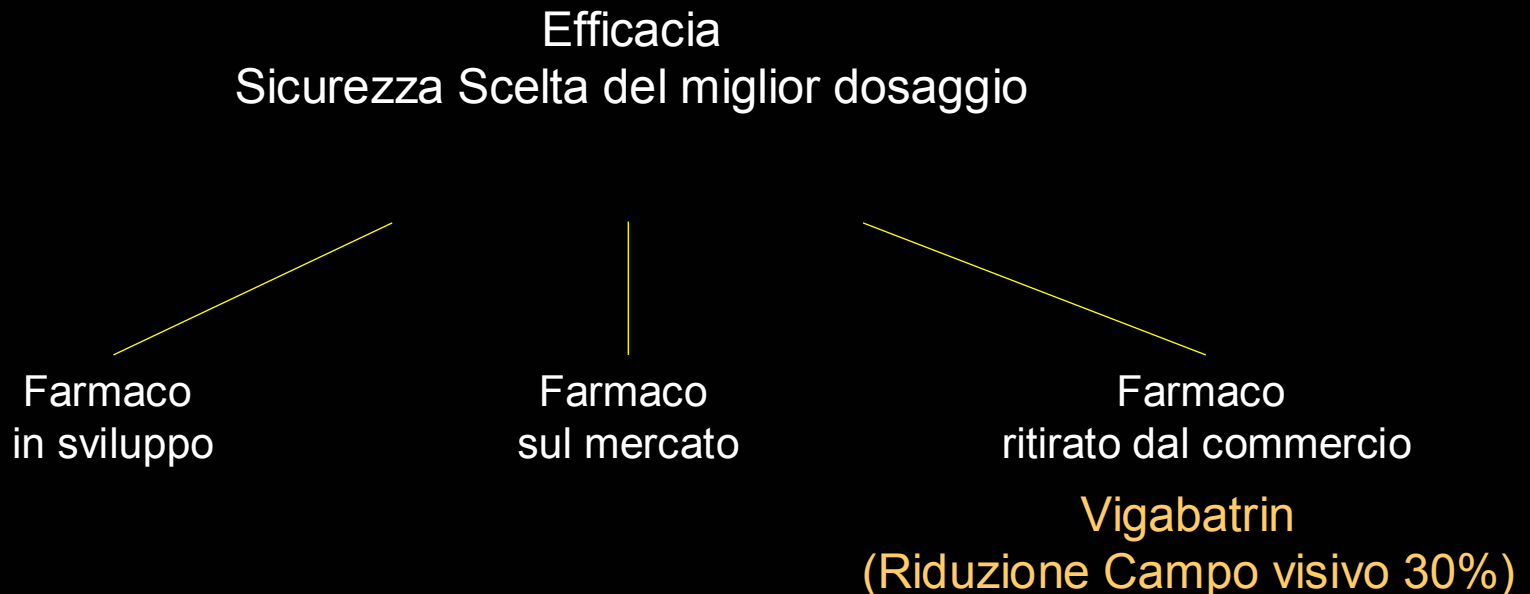


Terapia personalizzata

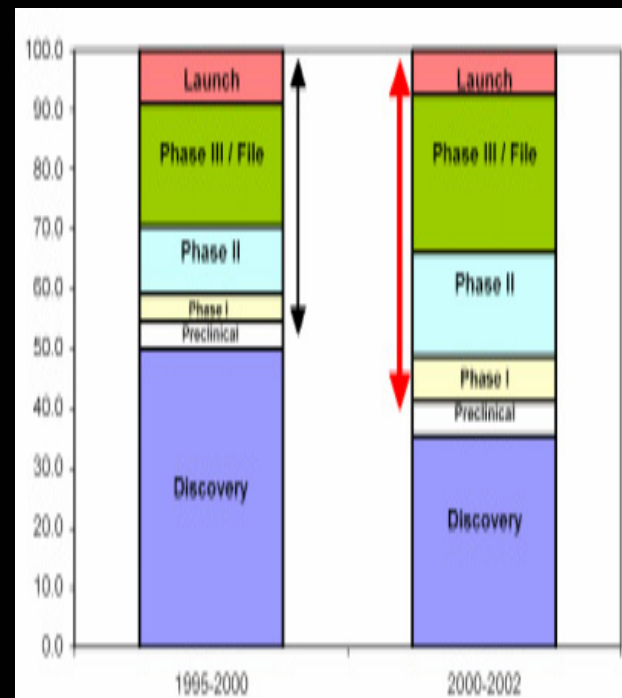
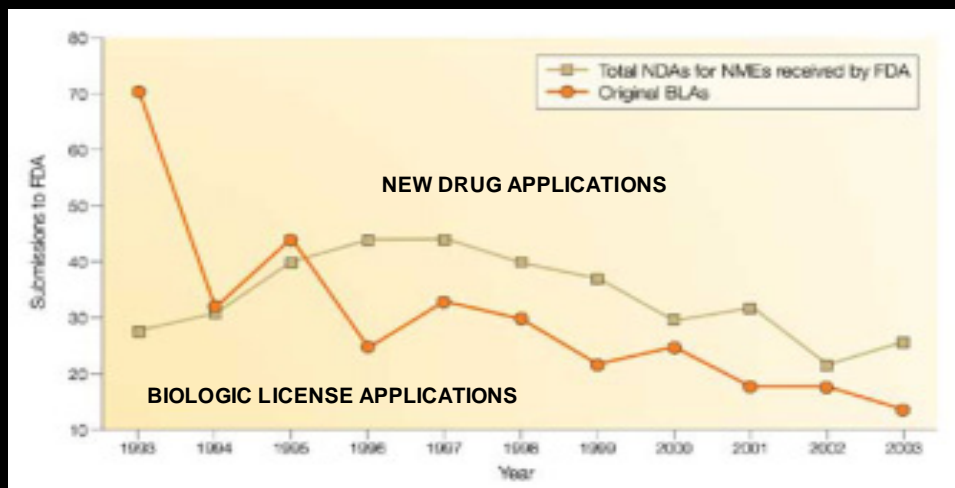
'right medicine, right dose, to right patient'

# Per quali farmaci dobbiamo sviluppare PGX test?

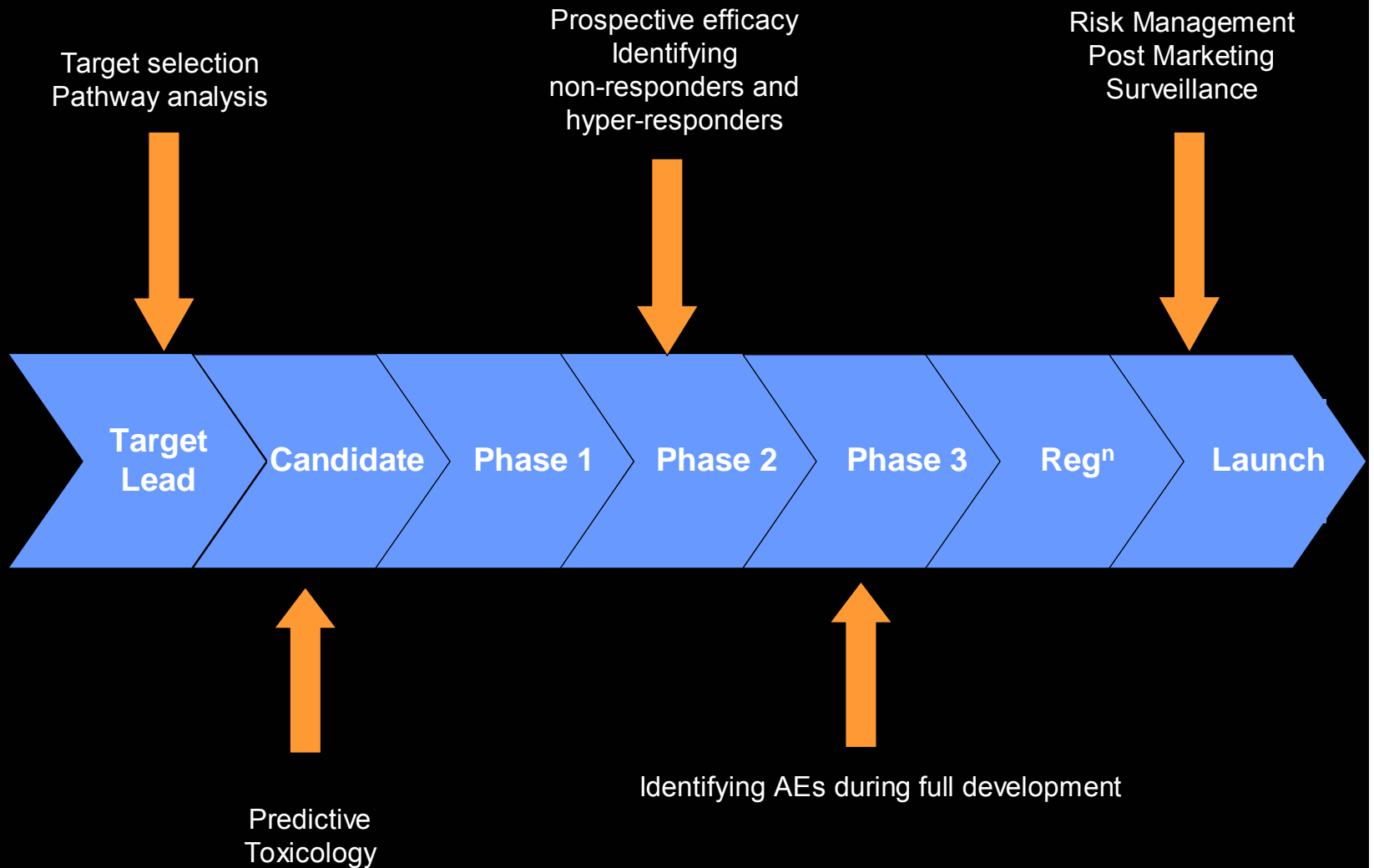
1. Consistente variabilità interindividuale
2. Indice terapeutico ristretto (warfarin)
3. ADR gravi ed inaspettate (carbamazepina-SJS)
4. Trattamento cronico con insorgenza dell'effetto ritardata nel tempo (SSRI)



# PGX e sperimentazione dei nuovi farmaci



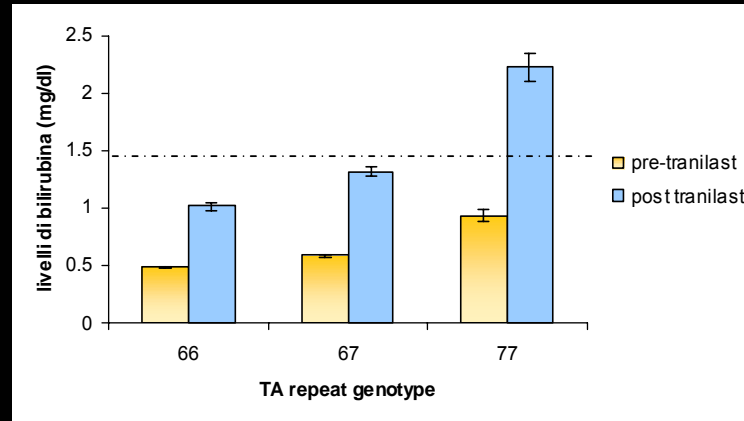
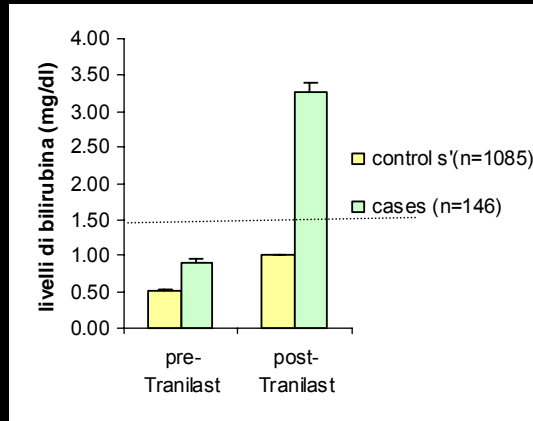
# Prospective efficacy/safety pharmacogenetics



# Tranilast and TATA box UGT1A1

## Esempio di ADR comuni durante trials

Durante Phase III: 12% dei pazienti ↑ bilirubina

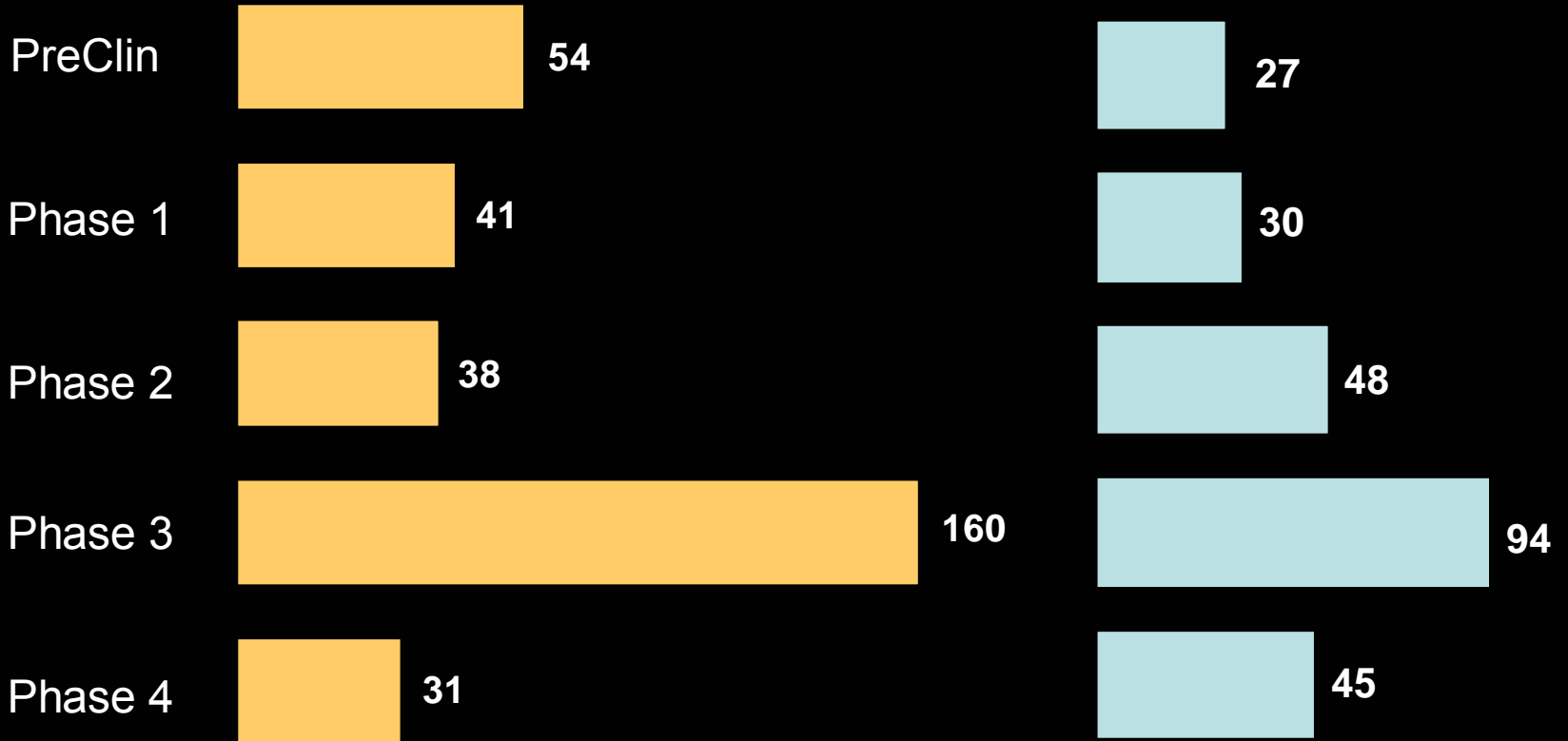


7- repeat in TATAA box of *UGT1A1* (UDP-glucuronosyltransferase 1)

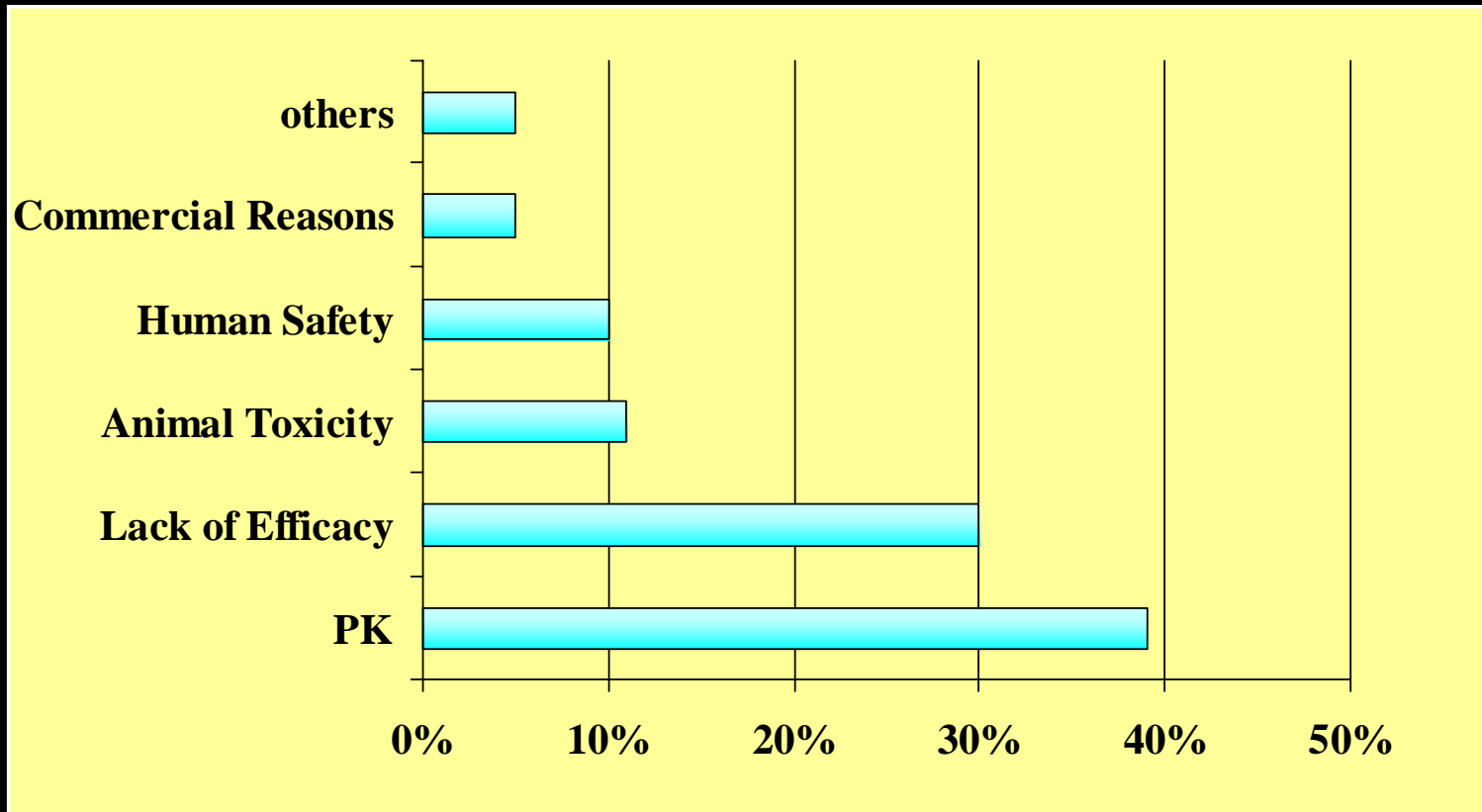
# Development Cost Benefits from Pharmacogenetics

Base Case, Total = \$324M

With PGx, Total = \$245M



# During Drug Development: PGX May Identify Failures in Advance



# PGX postmarketing: the abacavir case

Abacavir inibitore della trascrittasi inversa

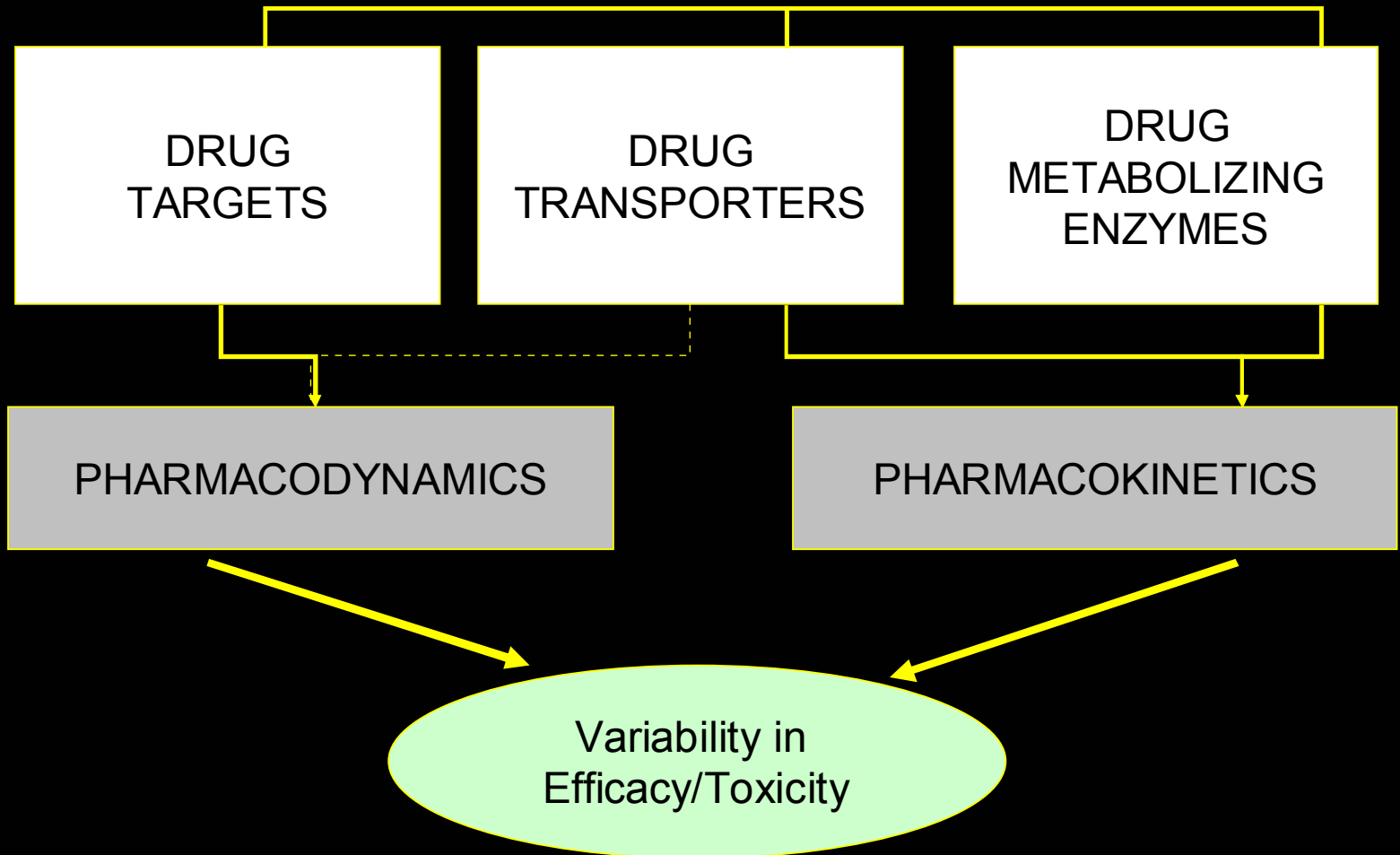
4.3 % dei pazienti trattati sviluppa Hypersensitivity Reaction potenzialmente letale

	<b>Abacavir hypersensitive (n=18)</b>	<b>Abacavir tolerant (n=167)</b>	<b>Odds ratio (95% CI)</b>	<b>p<sub>c</sub></b>
<i>HLA-B*5701</i>	14 (78%)	4 (2%)	117 (29–481)	<0.0001
<i>HLA-DR7, HLA-DQ3</i>	13 (72%)	6 (3%)	73 (20–268)	<0.0001
<i>HLA-B*5701, HLA-DR7, HLA-DQ3</i>	13 (72%)	0 (0%)	822 (43–15 675)	<0.0001
	..	..	..	..

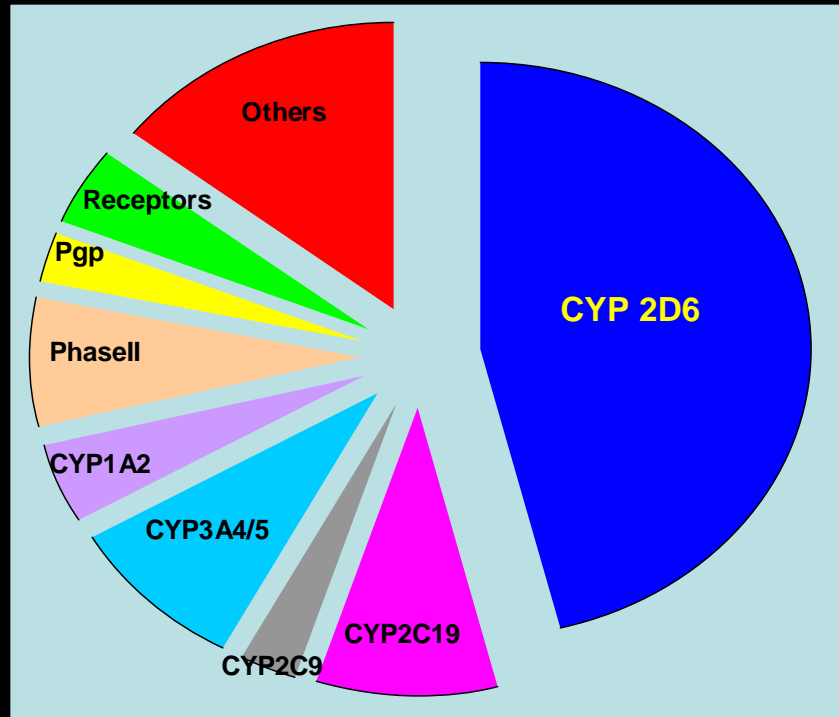
HLA-B57 allele is a significant predictor of the occurrence of the hypersensitivity reaction (Hetherington *et al.* 2002; Mallal *et al.* 2002).

Genetic testing è costo-efficace (Hughes *et al.* 2004).

# Candidate gene association study and PGX

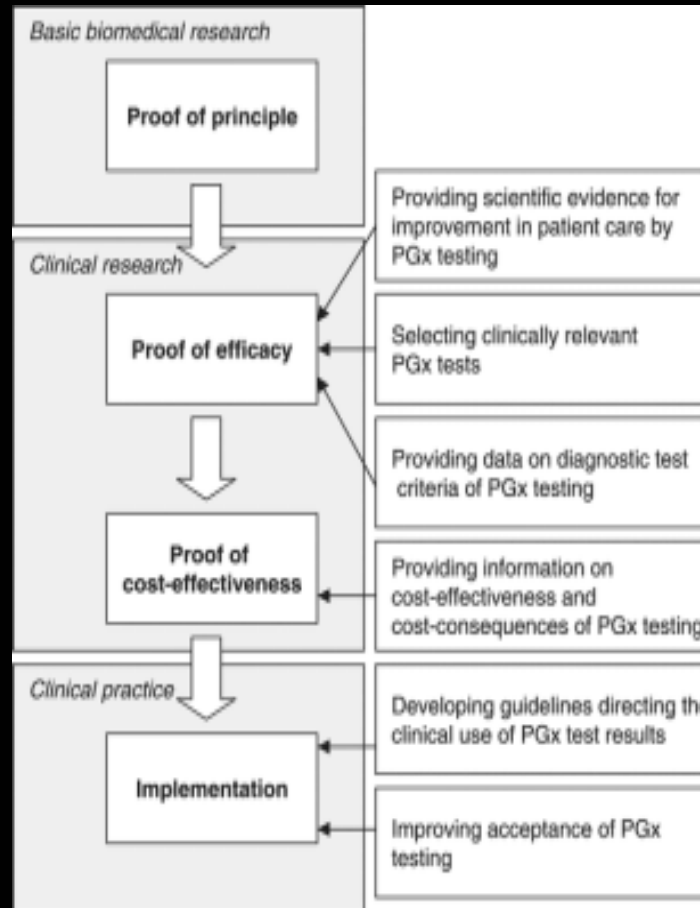


# Breakdown of Genotyping and Phenotyping in FDA Survey



- Genotyping and phenotyping performed in some submissions
- Phase II enzymes measured: NAT-2, UGT, GSTM1, etc
- Receptors: Dopamine, 5-HT, beta-adrenergic, alpha-1 adrenergic, potassium channels, etc
- Others: HMC, CETP, AAG, ApoE etc.

# PGX e pratica clinica



(Spear B, 2001)

# Warfarin

Test Category	Biomarker	Form	Associated Effect	N	Sensitivity	Specificity	PPV	NPV	R <sup>2</sup>	Ref
PGx tests	CYP2C9*3 polymorphism	SNPs	Risk of bleeding complication	185	0.17	0.94	0.40	0.82	NA	[19]
	Carrier of a CYP2C9 and VKORC1 polymorphism	SNPs	Acenocoumarol-induced overanticoagulation (INR>6)	226	0.48 <sup>a</sup>	0.81 <sup>a</sup>	0.20 <sup>a</sup>	0.94	39.1	[70]
	5-lipoxygenase (Alox5) genotype	Tandem repeat	Response to leukotriene antagonist ABT761	221	1 <sup>a</sup>	0.17 <sup>a</sup>	0.52 <sup>a</sup>	1 <sup>a</sup>	NA	[71]
	UGT1A1-3156AA genotype	SNP	Grade 4 neutropenia and irinotecan in whites	66	0.50	0.96	0.60	0.95	24	[72]
	β1 receptor Arg389Arg genotype	SNPs	Reduction in daytime diastolic blood pressure	40	0.78 <sup>ab</sup>	0.82 <sup>ab</sup>	0.78 <sup>ab</sup>	0.82 <sup>ab</sup>	15.8	[73]
	HLA-B*5701 genotype	SNPs	Hypersensitivity to abacavir in whites	1821	0.46–0.94	0.90–0.98	0.19–0.81	0.97–0.99	NA	[74]

(Spear B, 2001)

## PGX test approvati dalla FDA ed in commercio

### PK test

1. 2005 AmpliChip® per comuni polimorfismi su CYP2D6 and CYP2C19
1. Thiopurine Methyltransferase (TPMT)- activity

### PD test

1. Human Epidermal Growth Factor Receptor 2 (HER2)-overexpression (Fish test)

chemoterapici

Predisposizione genica acquisita

Studi retrospettivi

recenti

FDA ha approvato 22 molecole includendo i risultati di PGX

# Nuove prospettive

candidate gene-based studies

genome-wide scan association studies



Biomarkers su tutto il genoma

Importante per studiare nuovi target

↑ numerosità ————— studi multicentrici

1. Human genome
2. Dense genotyping chips
3. Well characterized clinical samples

## ARTICLES

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# **Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls**

The Wellcome Trust Case Control Consortium\*

Coronary Artery Disease  
Hypertension  
Rheumatoid arthritis  
Diabetes I and II

Breast cancer  
Multiple sclerosis  
Ankylosin spondylitis  
Autoimmune thyroid disease

**Pharmacogenetics**