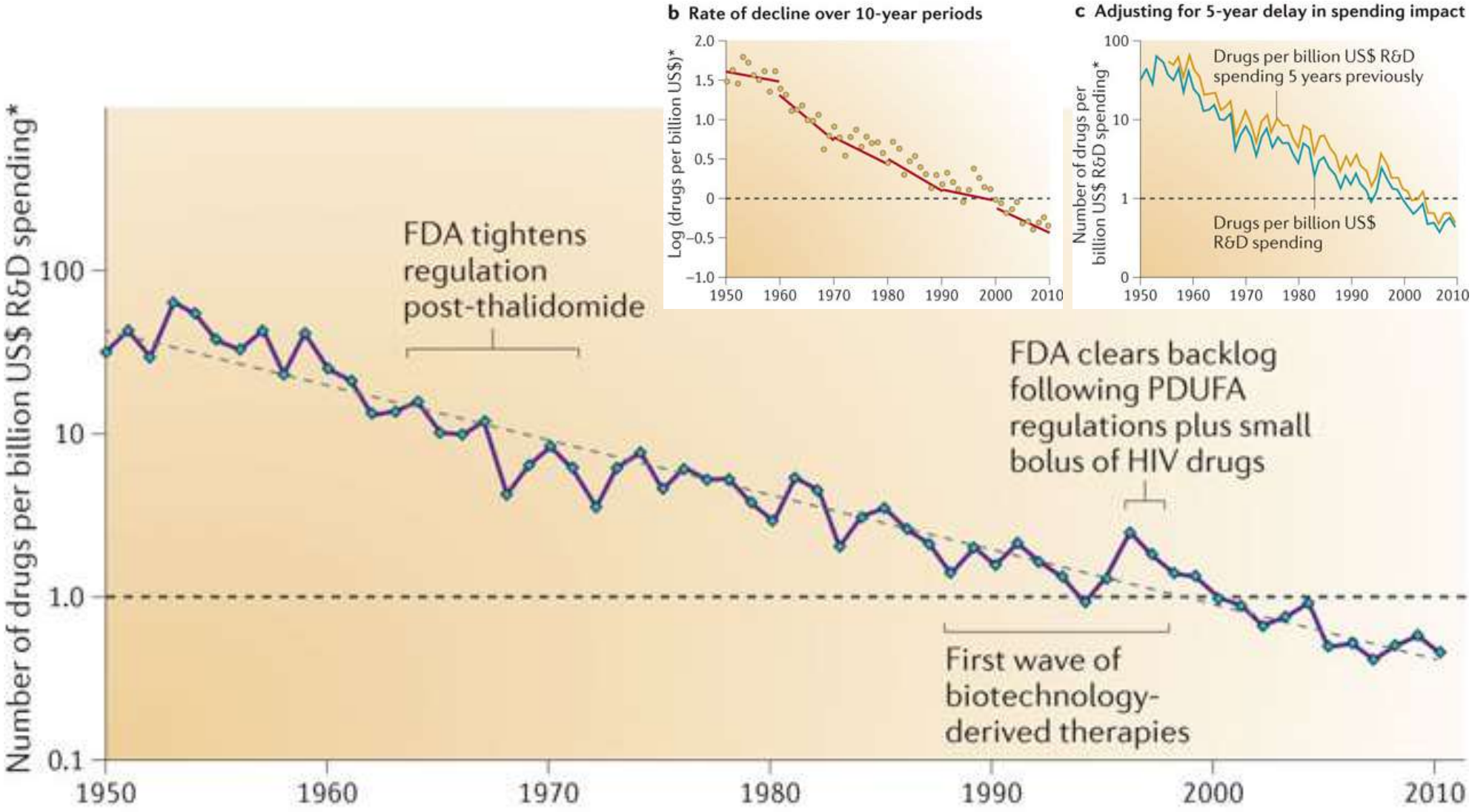
Rapid Transition from Bench to Bedside
an overview:
what is new, what has proven its value,
what are the latest trends in translational medicine

Jochen Theis, MD, FFPM
InHeCon

Translational Medicine

- the big picture
- what has proven its value
- what is new
- what are the latest trends
- rapid transition from the bench to the bedside
- your views

Overall Trend in R&D efficiency (inflation adjusted)



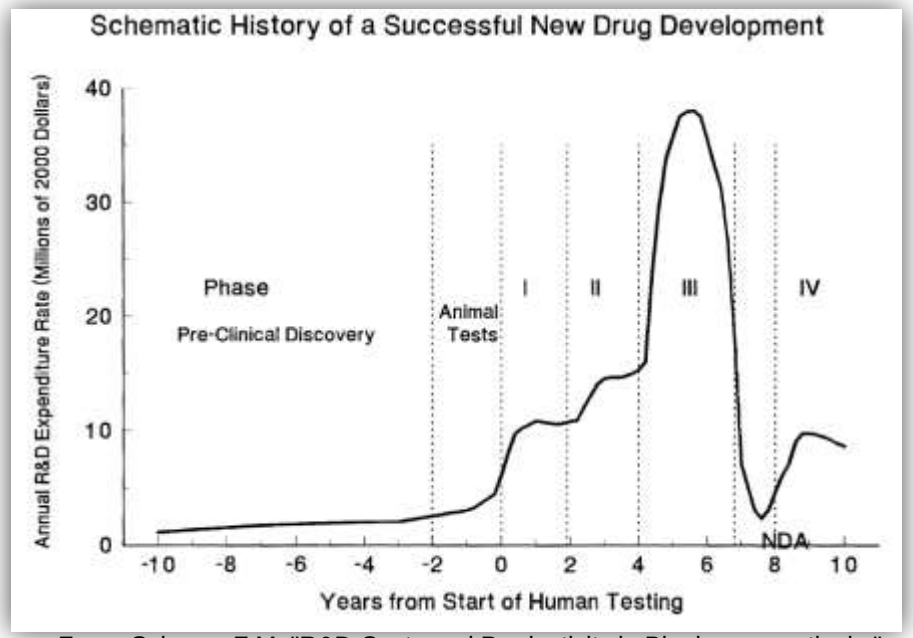
Jack W. Scannell, Alex Blanckley, Helen Boldon & Brian Warrington. Nature Reviews Drug Discovery 11, 191-200 (March 2012)

Pharma R&D Productivity

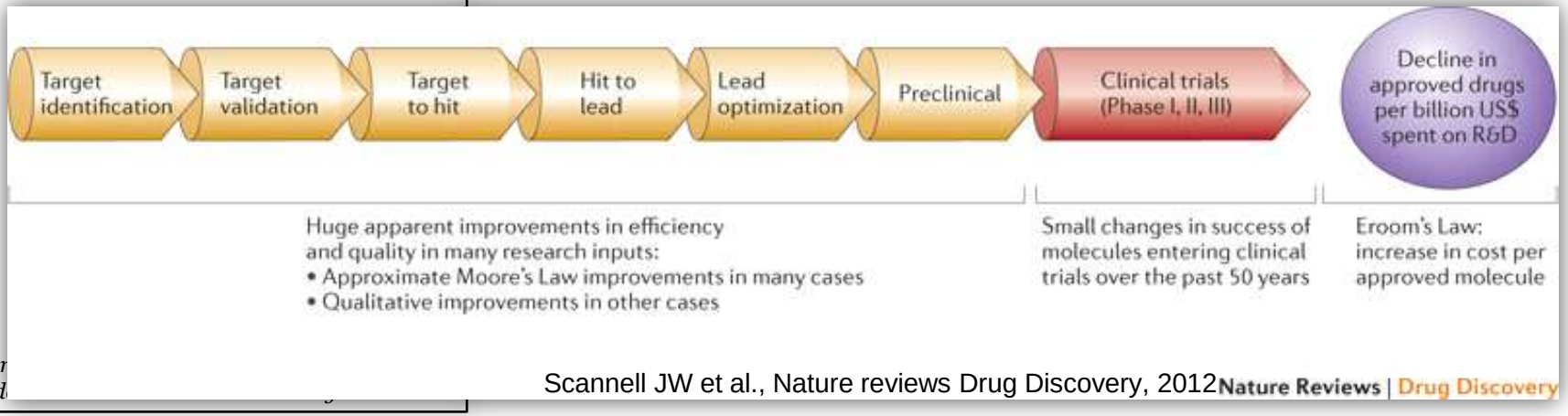
Research Spending Per New Drug

Company	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	5	11,790.93	58,955
GlaxoSmith Kline	10	8,170.81	81,708
Sanofi	8	7,909.26	63,274
Roche Holding AG	11	7,803.77	85,841
Pfizer Inc.	14	7,727.03	108,178
Johnson & Johnson	15	5,885.65	88,285
Eli Lilly & Co.	11	4,577.04	50,347
Abbott Laboratories			
Merck & Co Inc			
Bristol-Myers Squibb Co.			
Novartis AG			
Amgen Inc.			

Sources: InnoThink Cer
Thomson Reuters Fund



From: Scherer, F.M. "R&D Costs and Productivity in Biopharmaceuticals." HKS Faculty Research Working Paper Series RWP11-046, December 2011



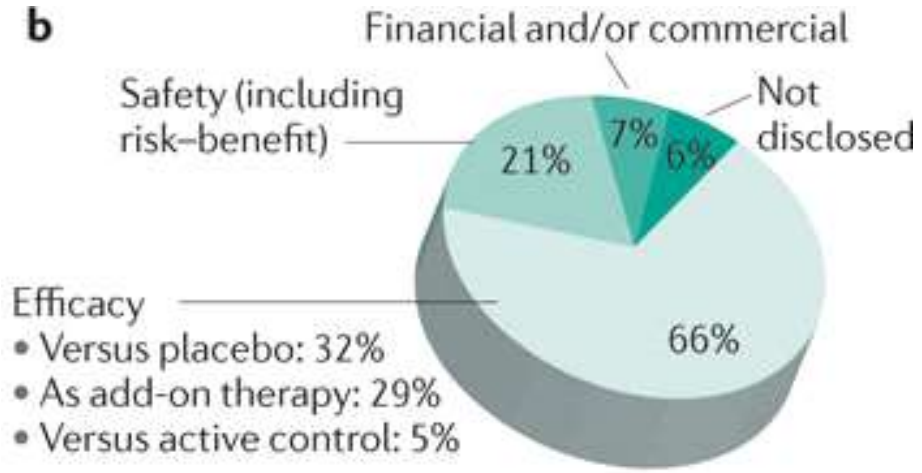
Scannell JW et al., Nature reviews Drug Discovery, 2012


Is Drug Development in
Pharma R&D a Gamble ?

Key challenges to address R&D productivity

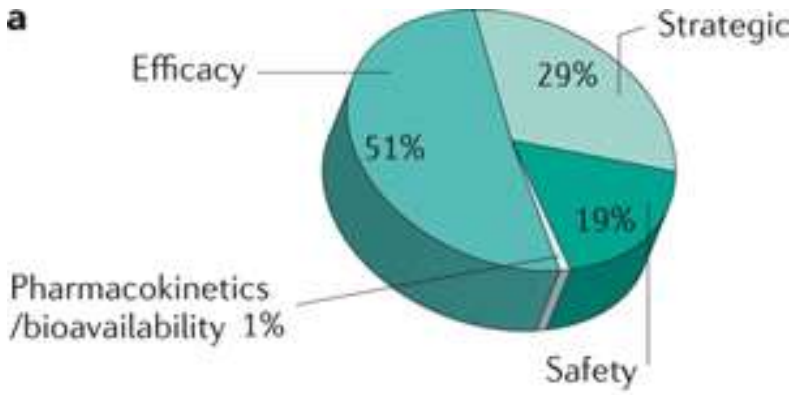
The average for the combined success rate at <u>Phase III and submission</u> has fallen to ~50% in recent years

Arrowsmith J, Nature Reviews Drug Discovery, 2011



<u>Phase II</u> success rates for new development projects have fallen from 28% (2006–2007) to 18% (2008–2009).

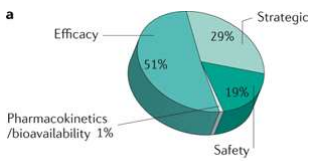
Arrowsmith J, *Nature Reviews Drug Discovery*, 2011



Translational Medicine . . .

- the big picture
- what has proven its value
- what is new
- what are the latest trends
- rapid transition from the bench to the bedside
- your views

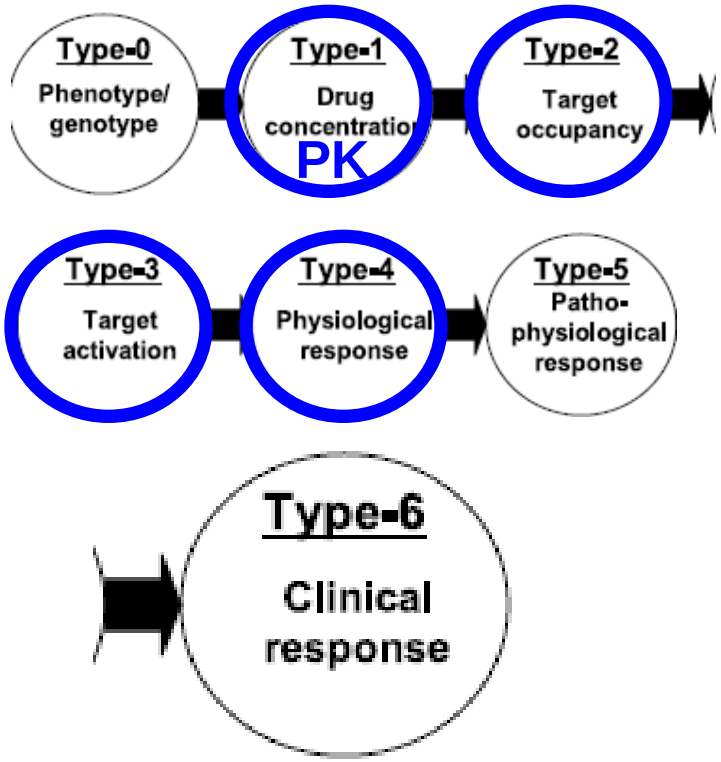
Evidence for Pharmacological Activity



A question based approach:

- Does the drug enter a relevant compartment?
- Does the drug interact with the target? – and at which dose/concentration?
- Does the drug have an effect on target-related pathways (second messenger etc.)?
- Which cascades are affected by the drug? - at which dose?
  - disease relevant?
  - adverse event relevant?

Mechanism-Based Pharmacokinetic-Pharmacodynamic Modeling - A New Classification of Biomarkers
Danhof et al., Pharm. Res. 22: 1432-7, 2005



Pharmacokinetics & Pharmacodynamics

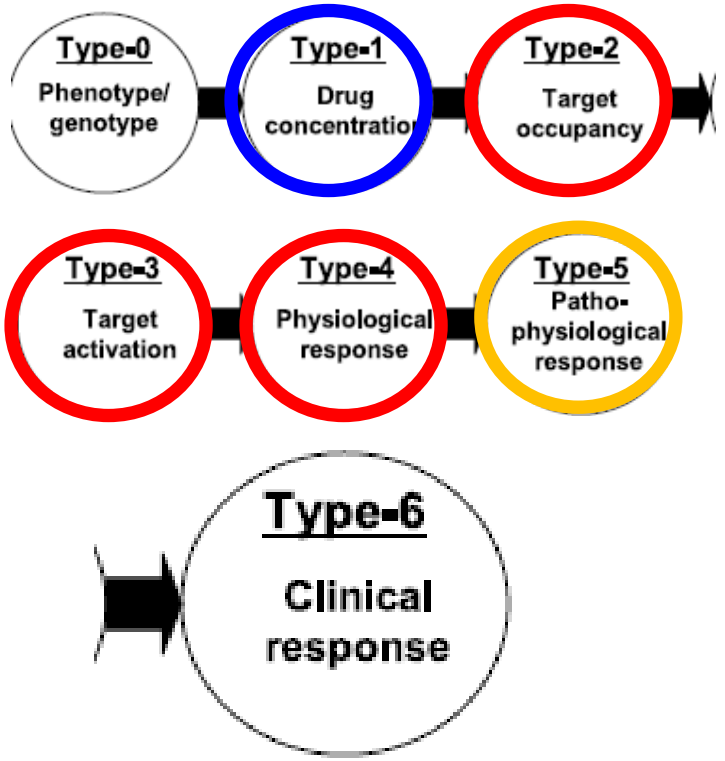
Phase I

- **Systemic Pharmacokinetics**
- **Target Occupancy**
- **Target Activation**
- **Pharmacological Response**

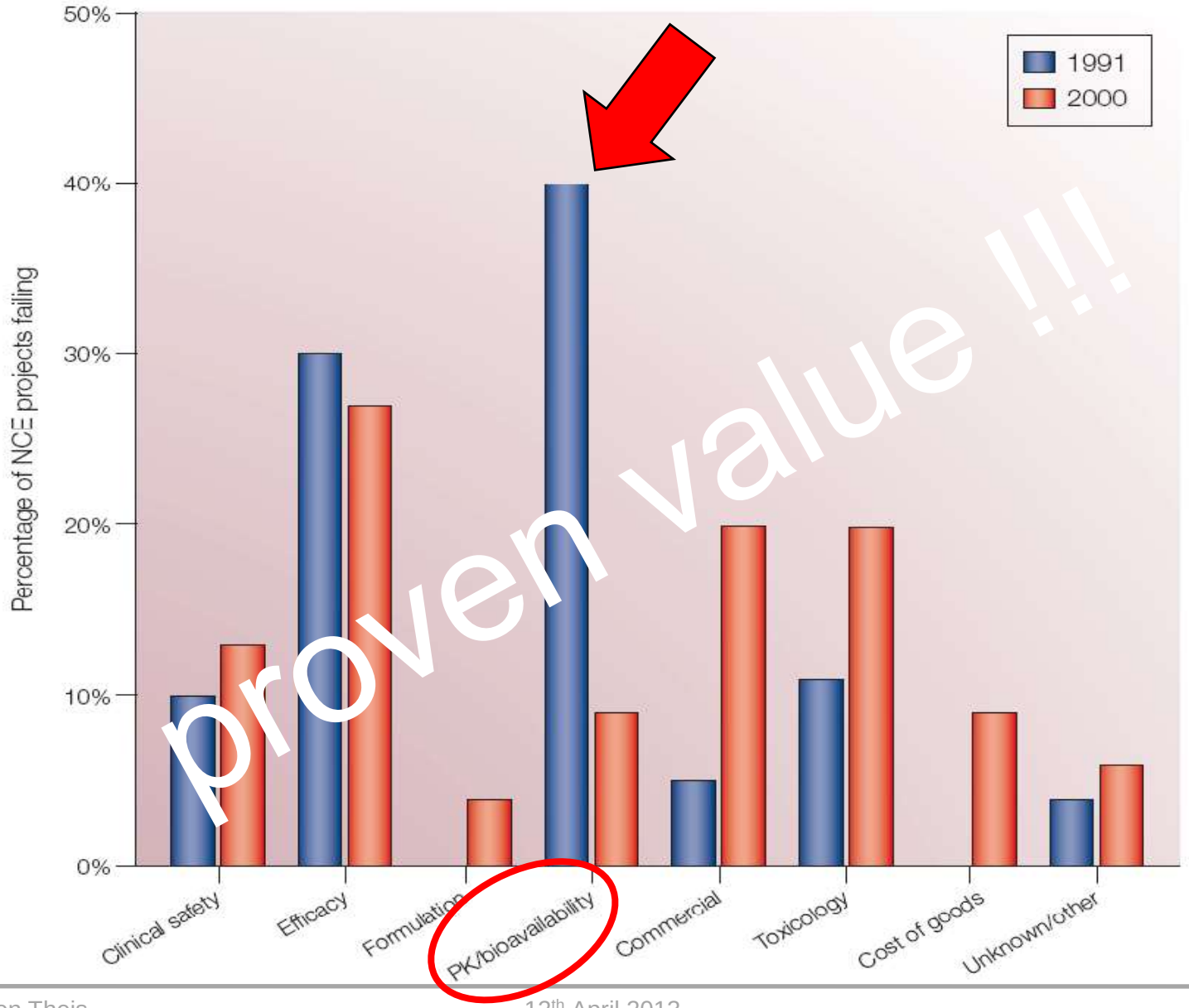
Phase II

- **Pathophysiological Response**

Mechanism-Based Pharmacokinetic-Pharmacodynamic Modeling - A New Classification of Biomarkers
Danhof et al., Pharm. Res. 22: 1432-7, 2005



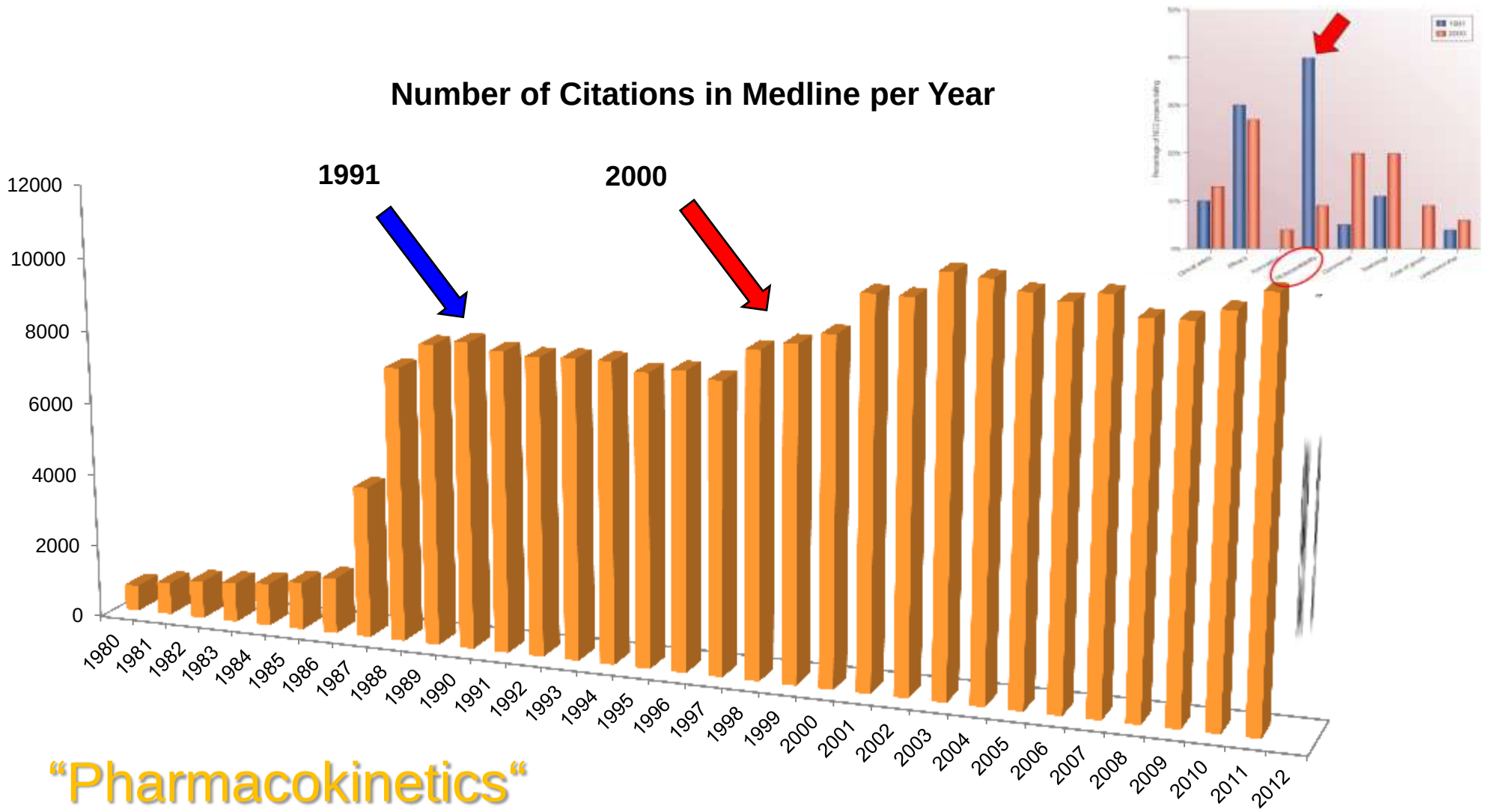
Reasons for Attrition During Clinical Development



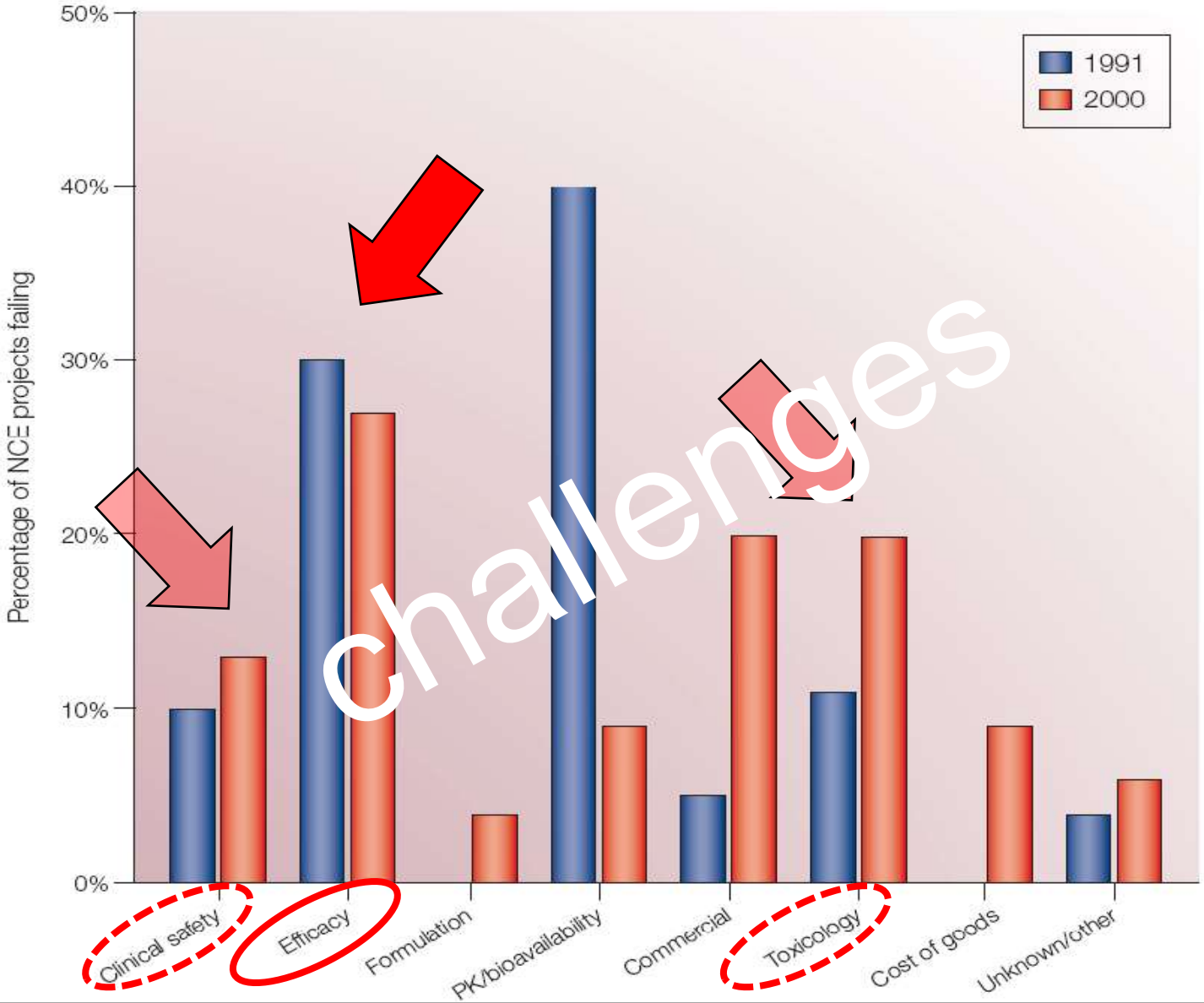
proven value !!!

Frank & Hargreaves, Nature Reviews Drug Discovery 2003

Systemic Pharmacokinetics – A Success Model !!!

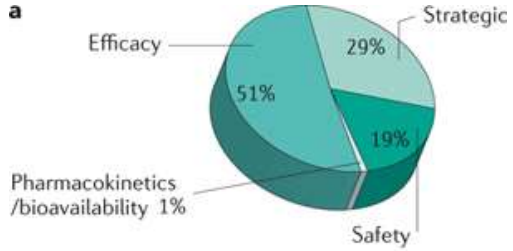


Reasons for Attrition During Clinical Development



Concentration – Effect Relationship:

Efficacy & Safety



Frank & Hargreaves, Nature Reviews Drug Discovery 2003

Pharmacokinetics & Pharmacodynamics

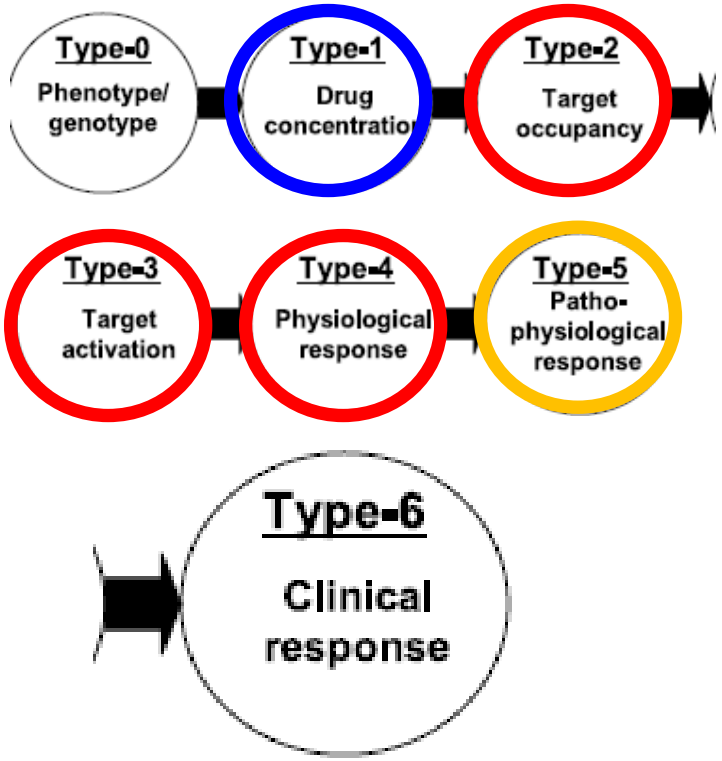
Phase I

- Systemic Pharmacokinetics
- Target Occupancy
- Target Activation
- Pharmacological Response

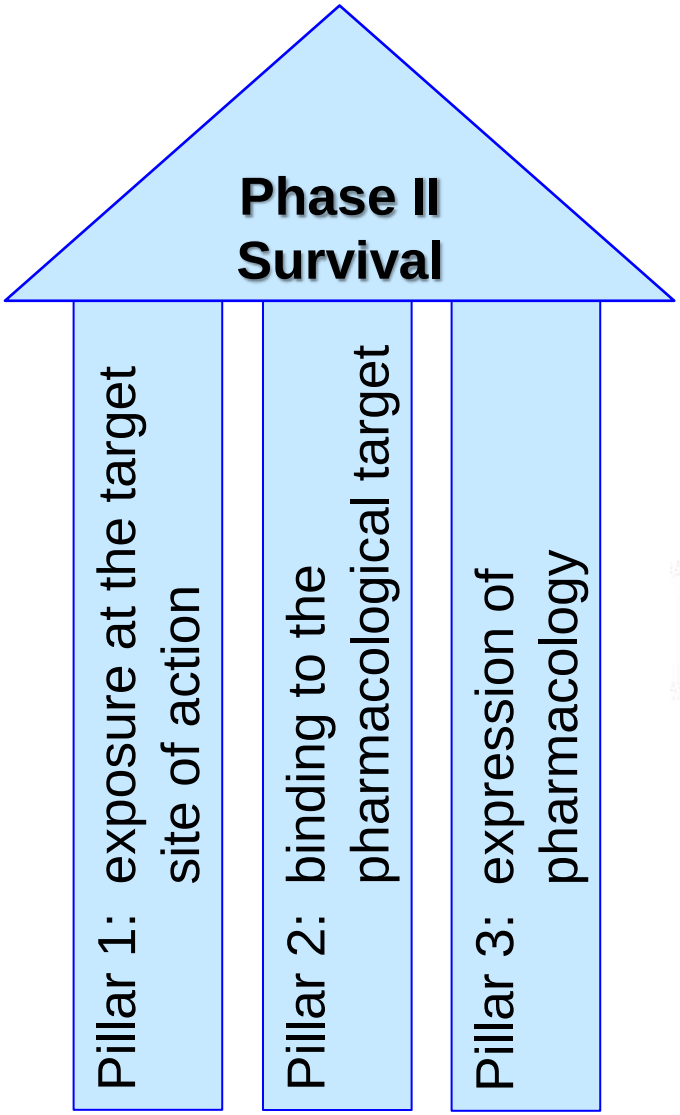
Phase II (or Challenge Models)

- Pathophysiological Response

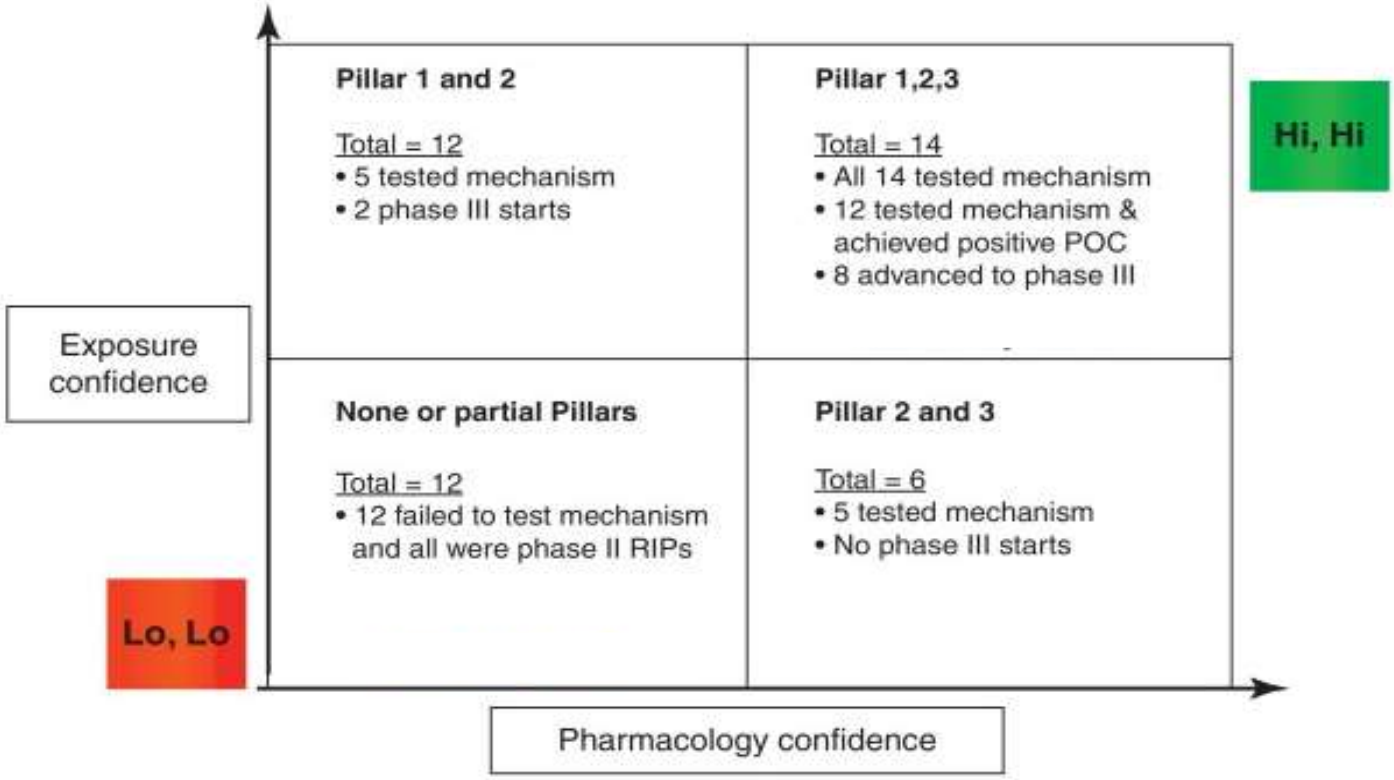
Mechanism-Based Pharmacokinetic-Pharmacodynamic Modeling - A New Classification of Biomarkers
Danhof et al., Pharm. Res. 22: 1432-7, 2005



Pharmacodynamics – A Success Model ???



Alignment with three Pillars of Survival for 44 Phase II programs between 2005 and 2009 in a Pfizer dataset



Paul Morgan et al.: Drug Discovery Today 17: 419 – 424 (2012)

Integrating R&D to enable better target selection, better phase I PD data, better early decision making

Clinical Focus on Target Selection and Validation

- Early target characterization utilising human epidemiology, genetics & other tools
- Drug development feasibility consideration (clinical endpoints, biomarkers, etc.)
- Early interaction within D & R to create meaningful data for early decision making
- Utilisation of all available know how (internal & external) to enable data acquisition

Translational Medicine

- the big picture
- what has proven its value
- what is new
- what are the latest trends
- rapid transition from the bench to the bedside
- your views

Focus on Understanding Variability

- Variability - not understood:
  - large sample sizes in clinical studies
  - high risk of subset of patients not receiving therapeutic benefit
  - high risk of subset of patients experiencing AEs or toxiticy

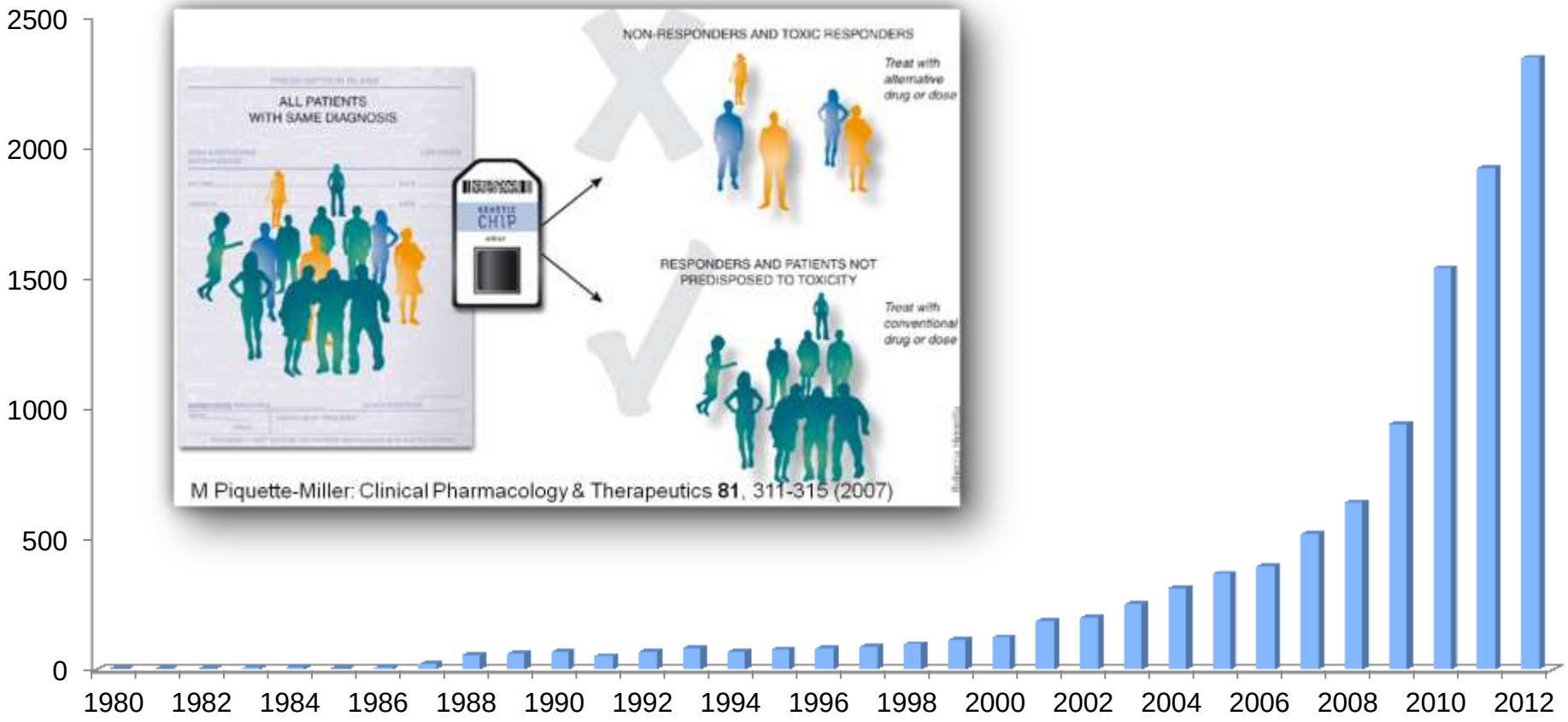
  ⇒ large investment with a high risk of failure

- Variability - well understood:
  - ability to perform small studies in patient subsets
  - high likelihood for each patient to receive therapeutic benefit
  - reduced risk of patients experiencing AEs or toxiticy
  - basis for “Personalized Medicine“

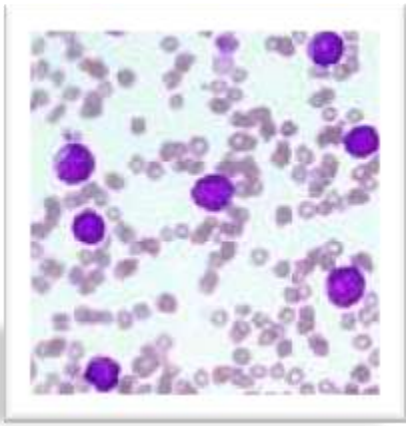
  ⇒ intelligent investment with an improved chance of success

Personalized Medicine

Number of Scitations in Medline per Year: “Personalized Medicine“

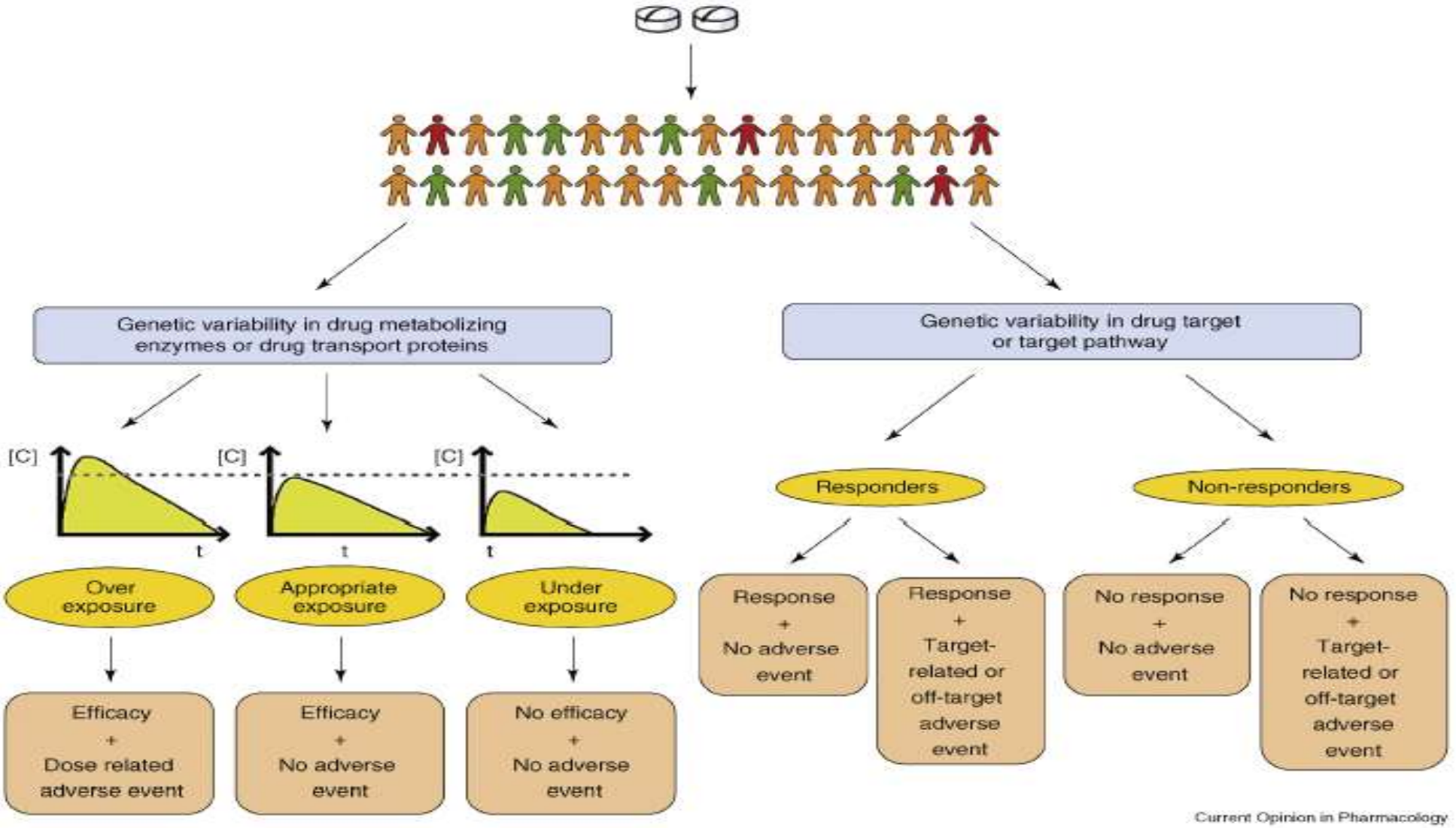


Evolution, not Revolution



Not a new concept .....

Variability in Drug Response – Key Factors



Personalised Medicine:
Predicting Variability in Drug Response

Variability in drug exposure

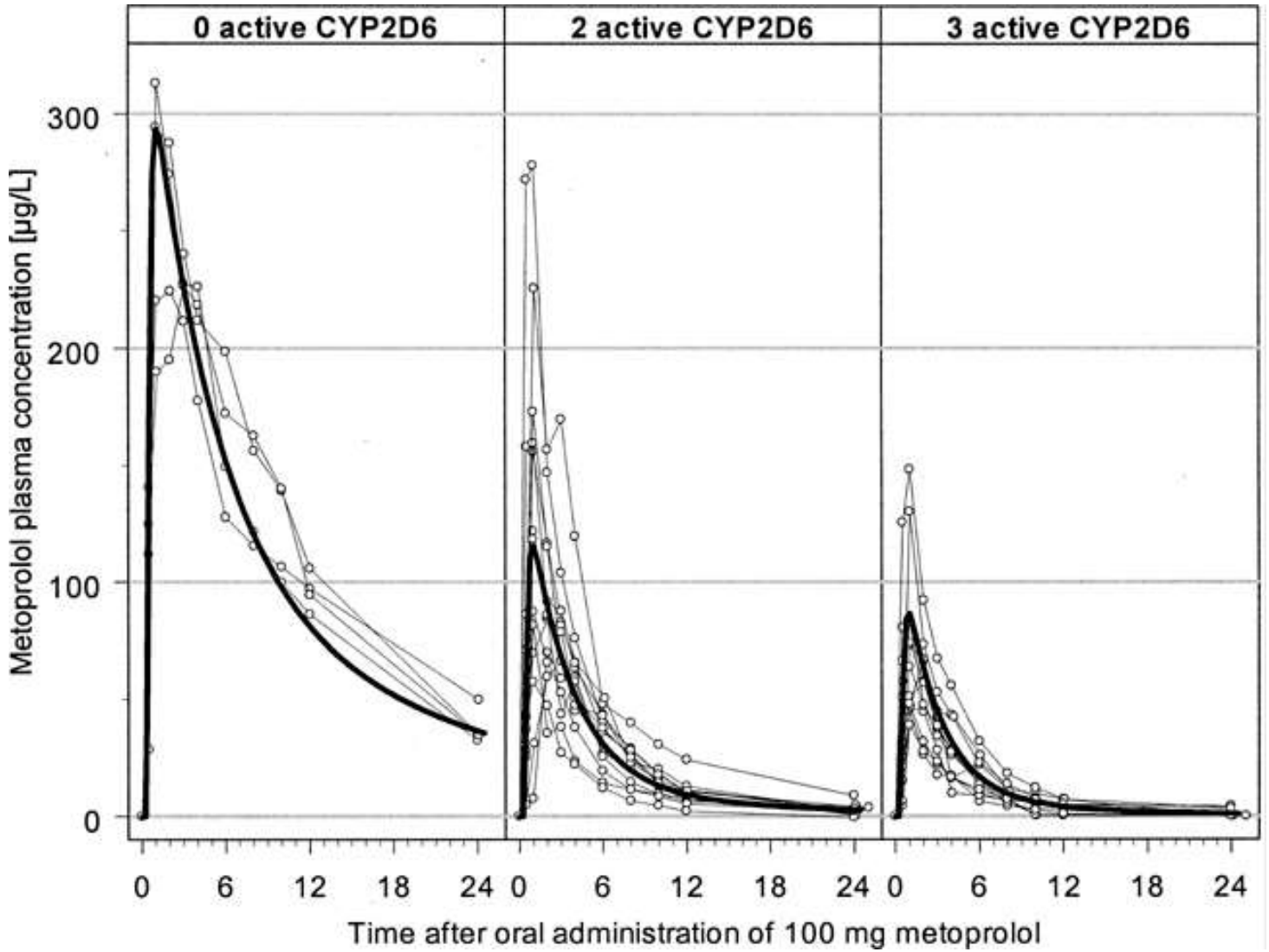
- Genetic polymorphisms of ADME enzymes and transporters
- Expression of ADME enzymes and transporters (reduced/increased)
- Inhibition of ADME enzymes and transporters

Variability in targets and pathways

- SNPs (B-RAF V600E/Vemurafenib)
- Gene Expression (Her2/trastuzumab)
- Immunology (HLA-B*5701/Abacavir)
- Viral characteristics (CCR5 Tropism/ Maraviroc)
- RNA “Footprint” (Oncotype DX/Adjuvant chemotherapy)

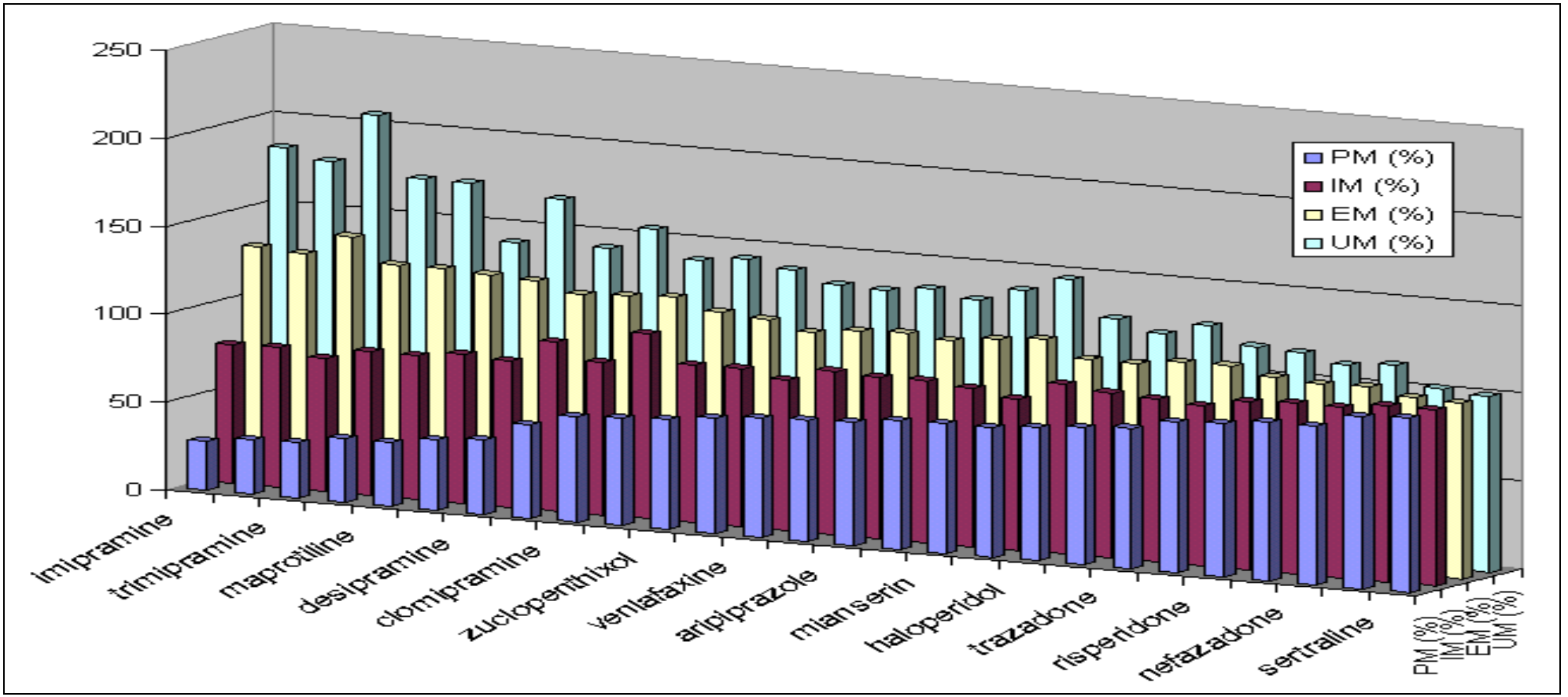
A **Predictive Marker** indicates the likelihood of a *specific* response to a *specific* therapy:
Pharmacodiagnostic Marker

Plasma concentration–time curves of 100 mg metoprolol orally in healthy volunteers



Kirchheiner J et al.: Clinical Pharmacology & Therapeutics (2004) **76**, 302–312

The Effect of CyP450 2D6 on Drug Concentrations of Psychoactive Drugs



Kirchheiner J et al, Molecular Psychiatry Feature Review 2004

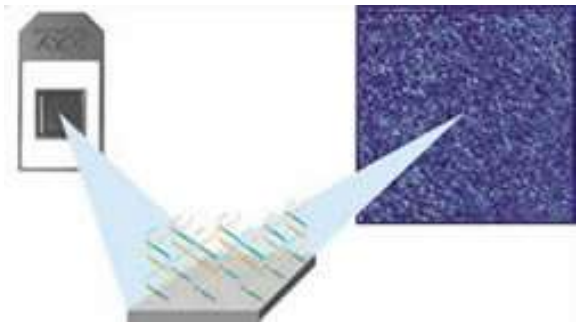
Genetic Variations of Drug ADME

Affymetrix® DMET™ Plus GeneChip® Key Features:

- 1,936 drug metabolism markers in 225 genes
- Markers in all FDA-validated genes
- More than 90 percent of the ADME Core markers as defined by the PharmaADME group
- Translation table for automated star allele analysis

Specifications:

- Average call rate ≥ 99%
- Average concordance to reference ≥ 99.5%
- Average reproducibility ≥ 99.8%



	BCGENOMICS_SAMPLE_ID	BATCH	WELL	CUSTOMER_SUBJECT_ID	GENE	VAR_COMMON_NAME	VAR_dbSNP_R
2	GR00003836	grcw	b09	10218	ABCG2	ABCG2_8900C>G(Q166E)	rs1061017
3	GR00003836	grcw	b09	10218	ABCG2	ABCG2_8184C>T(Y123Y)	rs2231139
4	GR00003836	grcw	b09	10218	ABCG2	ABCG2_26499G>T(E334*)	rs3201997
5	GR00003836	grcw	b09	10218	ABCG2	ABCG2_18295T>C(F208S)	rs1061018
6	GR00003836	grcw	b09	10218	ABCG2	ABCG2_21788T>C(S248P)	rs3116448
7	GR00003836	grcw	b09	10218	ABCG2	ABCG2_>(Q126X)	N/A
8	GR00003836	grcw	b09	10218	ABCG2	ABCG2_8825C>A(Q141K)	rs2231142
9	GR00003831	grcw	b04	10198	ABCG2	ABCG2_8900C>G(Q166E)	rs1061017
10	GR00003831	grcw	b04	10198	ABCG2	ABCG2_8184C>T(Y123Y)	rs2231139
11	GR00003831	grcw	b04	10198	ABCG2	ABCG2_26499G>T(E334*)	rs3201997
12	GR00003831	grcw	b04	10198	ABCG2	ABCG2_18295T>C(F208S)	rs1061018
13	GR00003831	grcw	b04	10198	ABCG2	ABCG2_21788T>C(S248P)	rs3116448
14	GR00003831	grcw	b04	10198	ABCG2	ABCG2_>(Q126X)	N/A
15	GR00003831	grcw	b04	10198	ABCG2	ABCG2_8825C>A(Q141K)	rs2231142

Personalised Medicine:
Predicting Variability in Drug Response

Variability in drug exposure

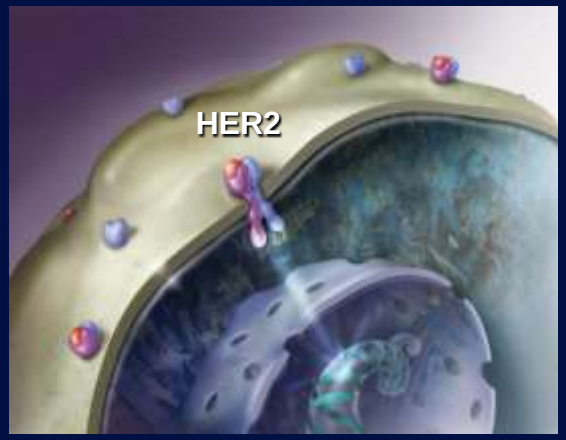
- Genetic polymorphisms of ADME enzymes and transporters
- Expression of ADME enzymes and transporters (reduced/increased)
- Inhibition of ADME enzymes and transporters

Variability in targets and pathways

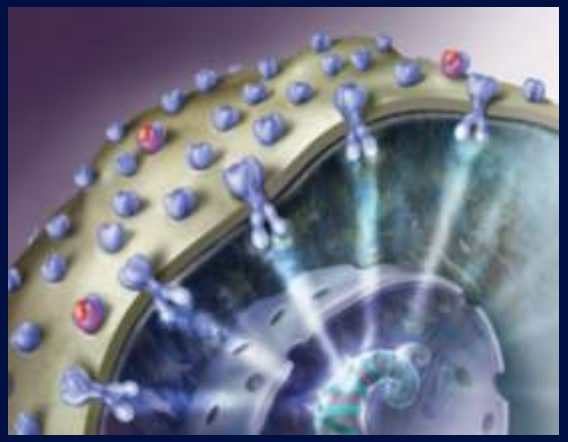
- SNPs (B-RAF V600E/Vemurafenib)
- Gene Expression (Her2/trastuzumab)
- Immunology (HLA-B*5701/Abacavir)
- Viral characteristics (CCR5 Tropism/ Maraviroc)
- RNA “Footprint” (Oncotype DX/Adjuvant chemotherapy)

A **Predictive Marker** indicates the likelihood of a *specific* response to a *specific* therapy:
Pharmacodiagnostic Marker

Stratified Therapy: The “Prototype” Herceptin



Normal Cell



Tumor Cell

Tumor Cell +

- **Response rates**
  (Mass R et al. Proc ASCO 2001)

Her2-Amplifizierung	Chemo	Chemo + Trastuzumab
FISH negative	38%	38%
FISH positive	31%	54%

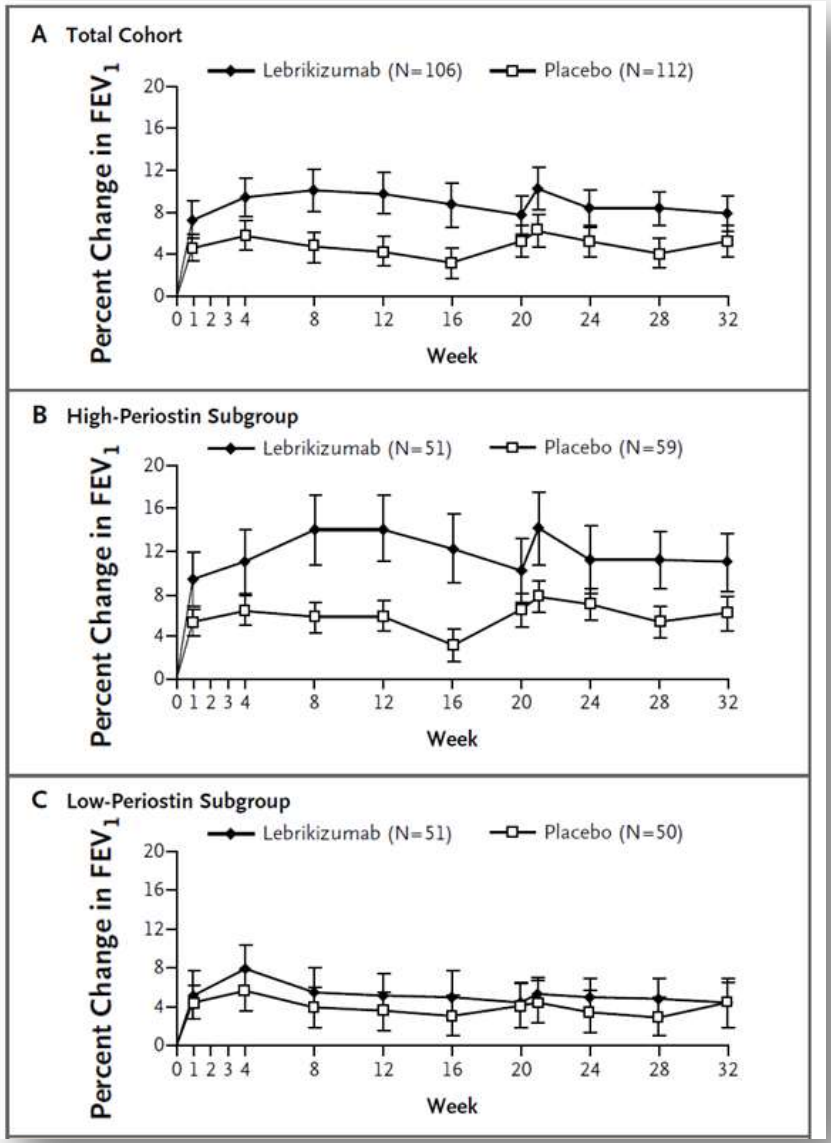
RRR FISH pos: 43% FISH neg: 0%

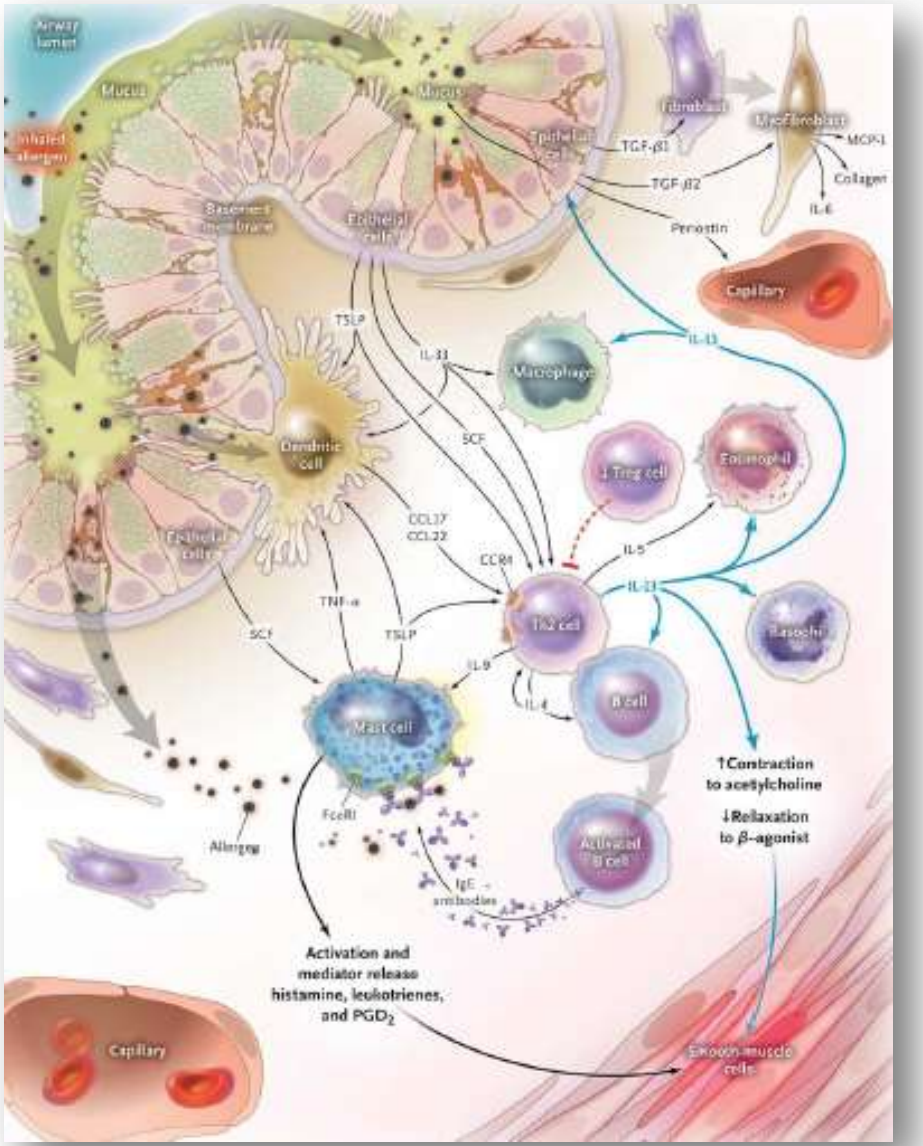
ARR FISH pos: 23% FISH neg: 0%

NNT FISH pos: 4 FISH neg: ∞ (all: 20)

⇒ **<u>Indication:</u> Pat. with metastatic breast cancer that overexpress HER2**

Lebrikizumab, IL-13, and Periostin



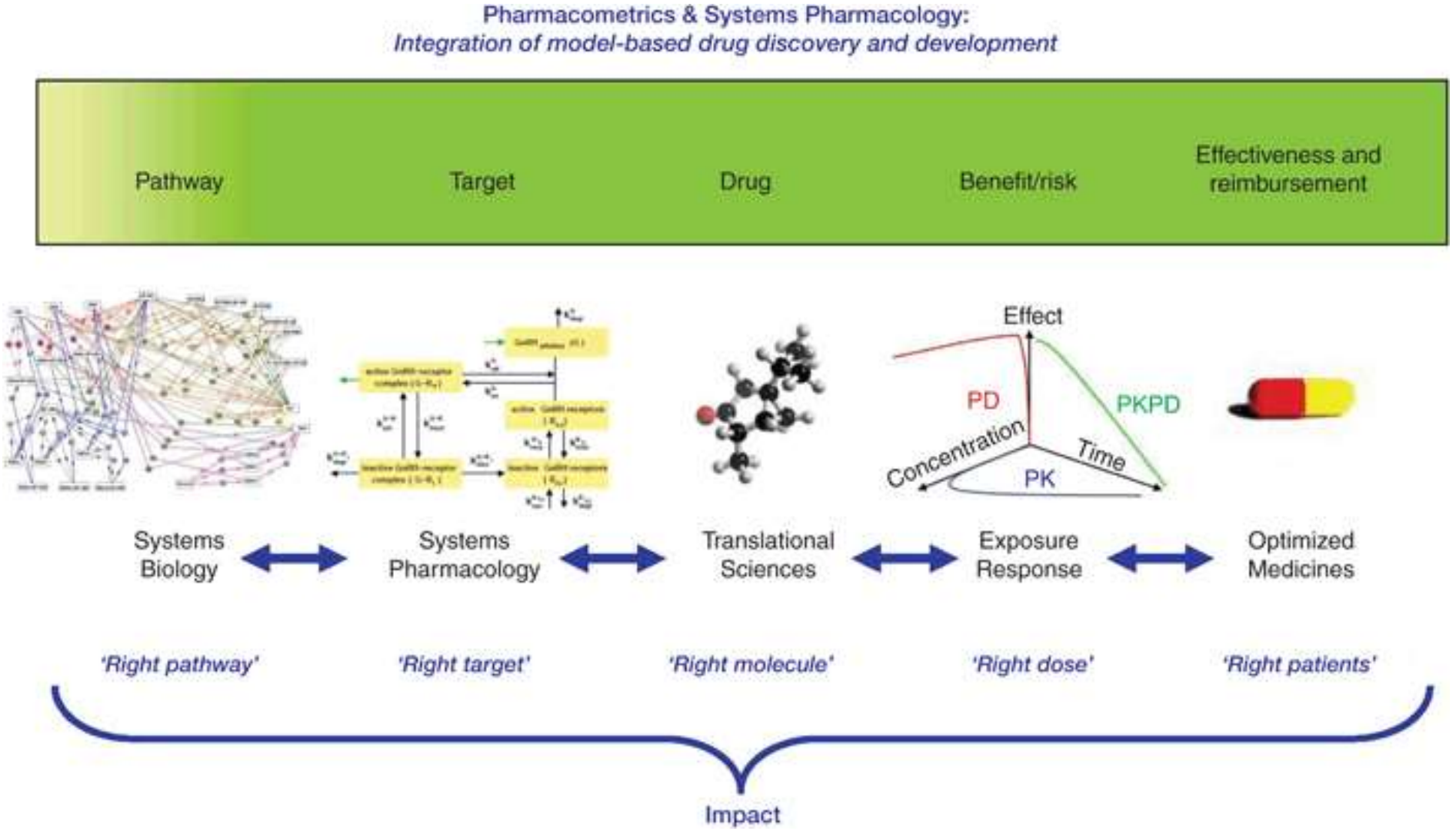


J Corren et al. N Engl J Med 2011

Translational Medicine

- the big picture
- what has proven its value
- what is new
- what are the latest trends
- rapid transition from the bench to the bedside
- your views

Integration of „what is new“



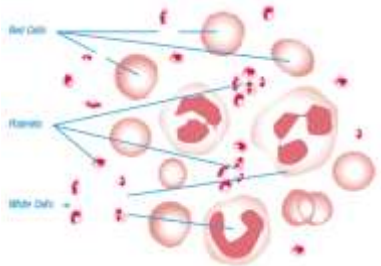
Van Der Graf, PH: CPT: Pharmacometrics & Systems Pharmacology (2012)

Translational Medicine

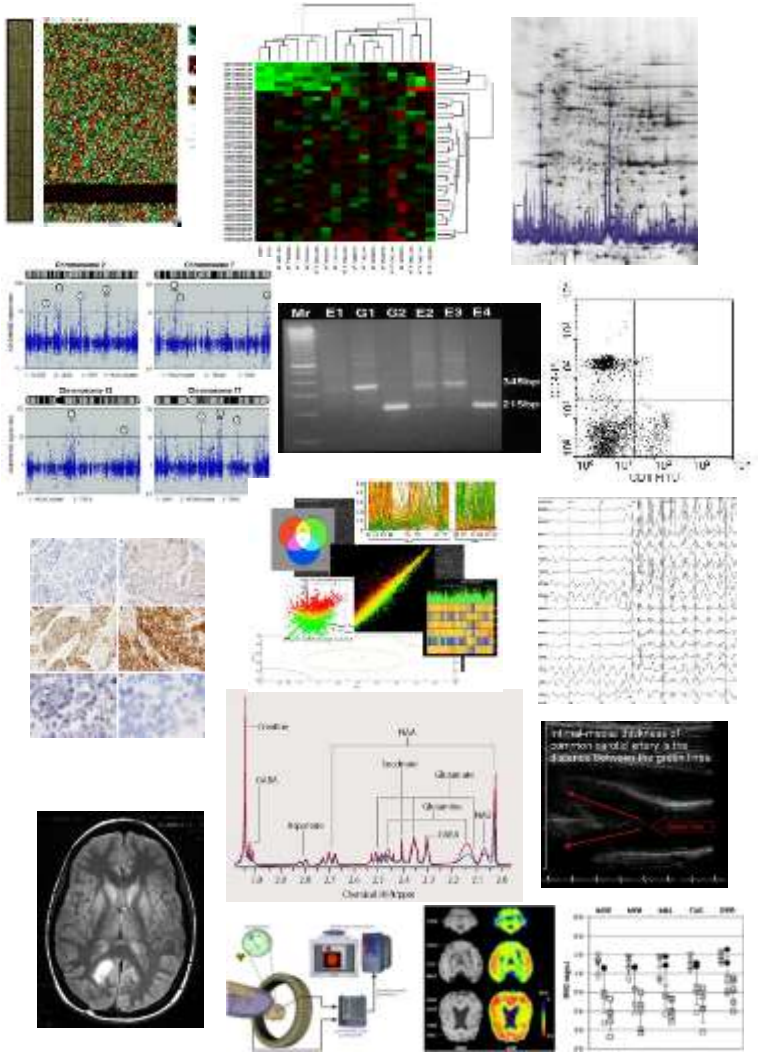
- the big picture
- what has proven its value
- what is new
- what are the latest trends
- rapid transition from the bench to the bedside
- your views

Assays as a Basis for Personalised Medicine

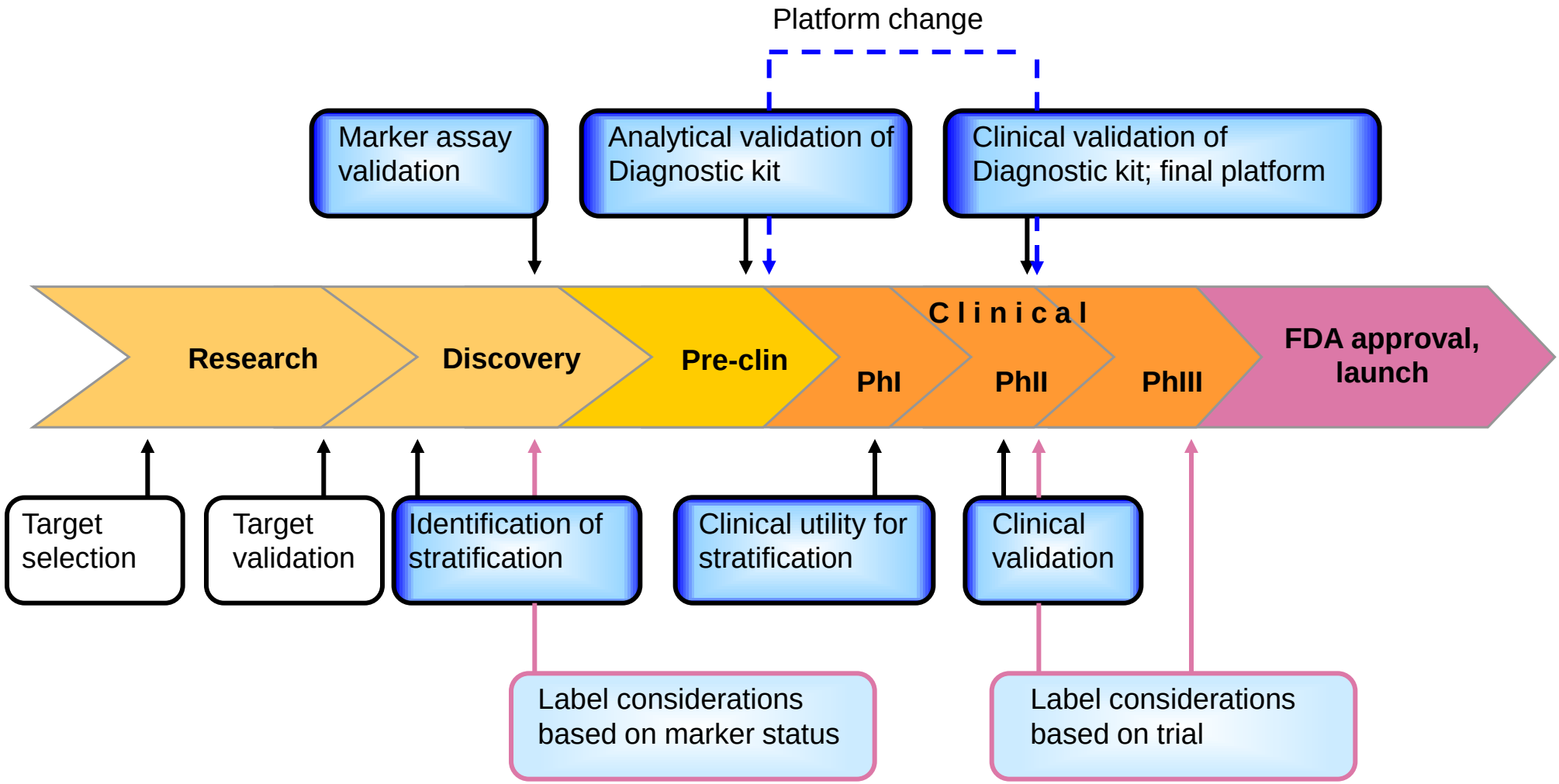
Biomarker Technologies "Yesterday"



Biomarker Technologies "Today"



Drug - Diagnostic Test Co-Development
The Regulatory Perspective Today

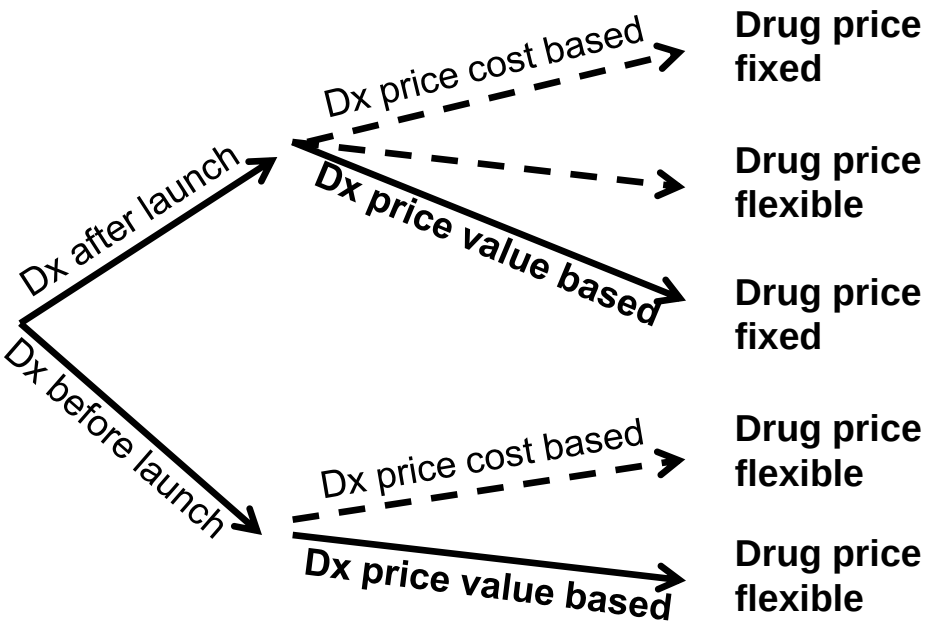


Adapted from FDA Drug-Diagnostic Co-Development Concept Paper

Personalized Medicine: Pricing Issues

Scenario: Pharmacodiagnostic test that will identify 20% responders, 80% nonresponders. USA based scenario.

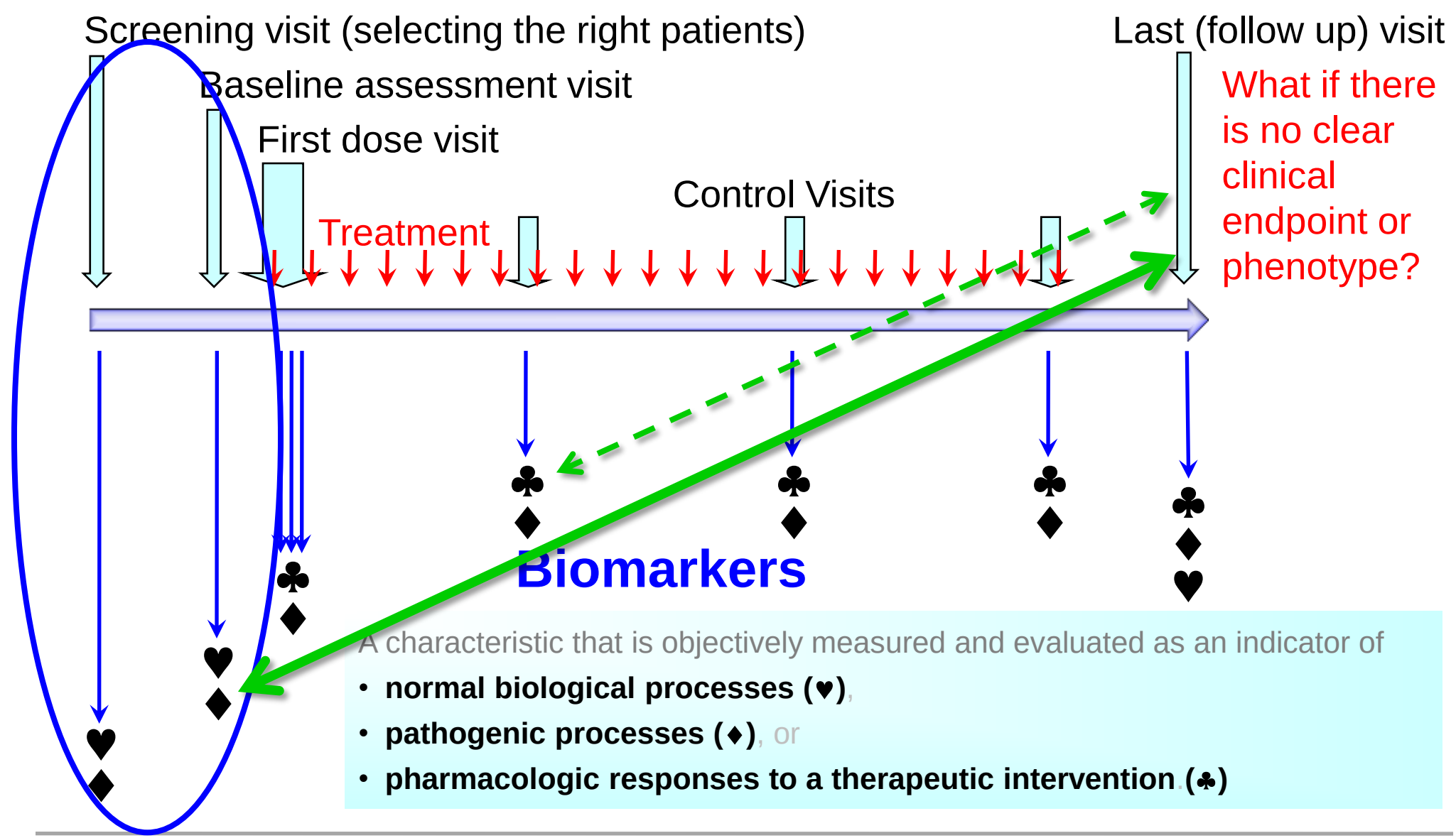
No Stratification based on a Diagnostic (Reference)



Patient	Insurer	Drug Company	Dx Company	Total Value Creation
0	0	100	0	100
20	70	20	10	120
20	0	90	10	120
20	0	20	80	120
0	0	110	10	120
0	0	60	60	120

Garrison LP & Austin MJF, Drug Information Journal, *2007*

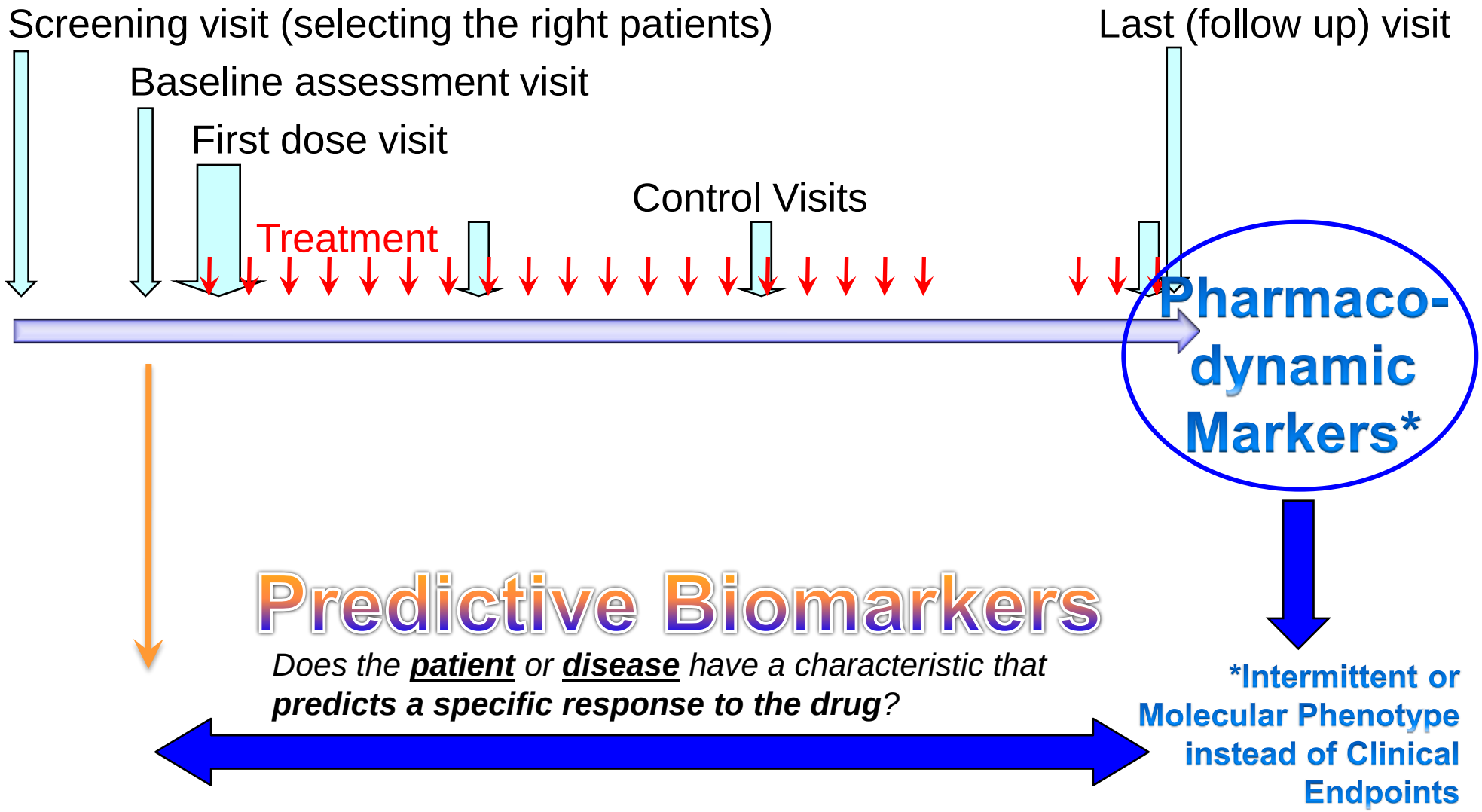
Correlation of Predictive Markers with Outcome



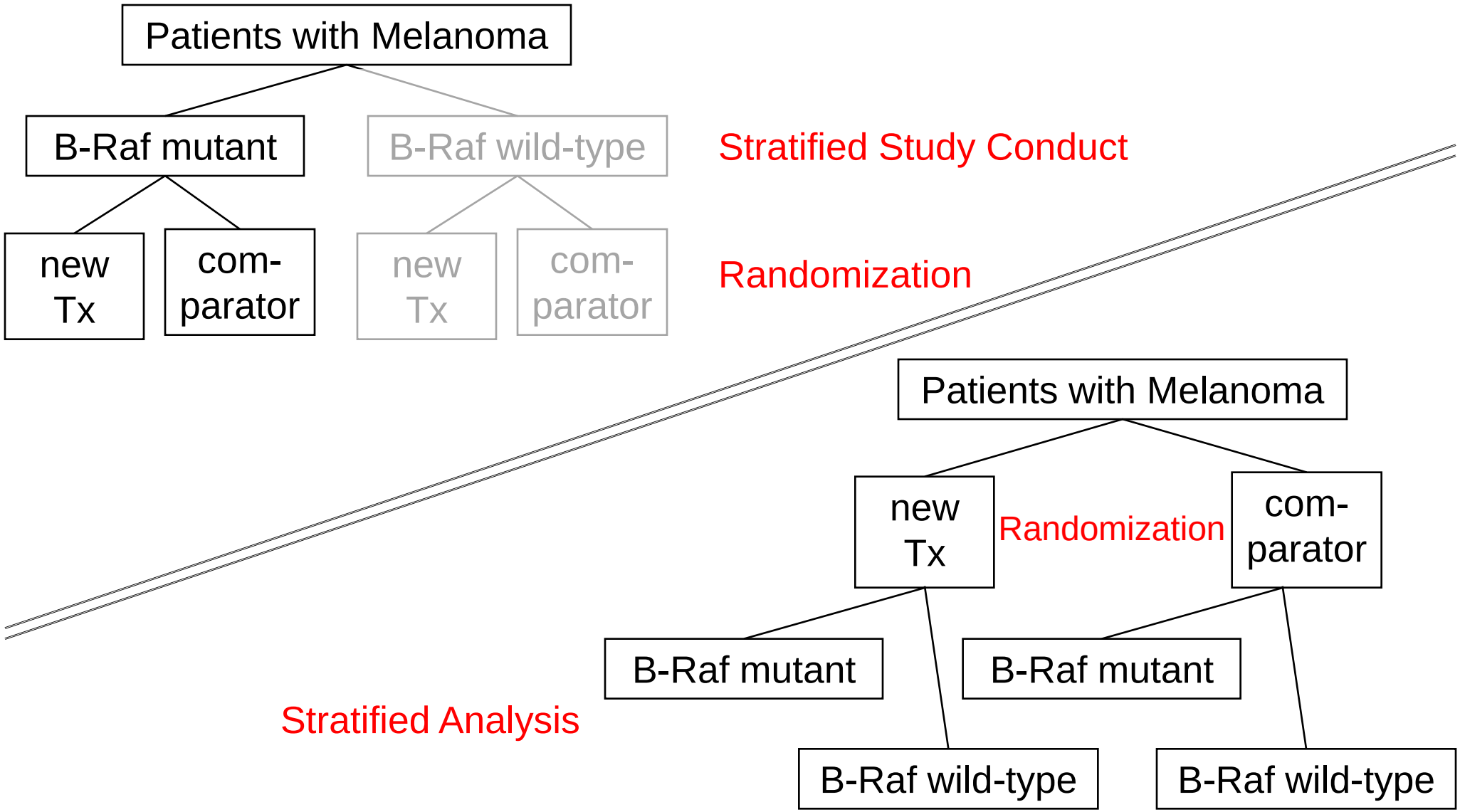
A characteristic that is objectively measured and evaluated as an indicator of

- **normal biological processes (♥)**,
- **pathogenic processes (♦)**, or
- **pharmacologic responses to a therapeutic intervention.(♣)**

Responders defined by Pharmacodynamic Markers



Appropriate Study Designs



Rapid transition from the bench to the bedside

1. Target Selection

BM discovery: Requirements: single BM point of contact (senior BM expert) to pull in overall BM expertise, medical biology/technology background, able to challenge; funds required

2. Clinical Lead Selection

BM qualification: Support to assist with CCS; test development; IVD development (possibly first Dx contact); facilitate the linking of BM data with biological activity for optimal decision making

3. Clinical Candidate Selection

Confirmatory BM phase: BM needs for early decision making should be understood, ideally integration into GLP tox, integration into clinical plan & clinical protocols

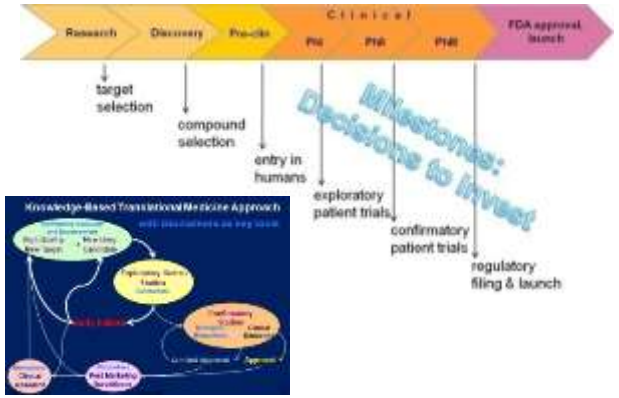
4. Entry in Human

Utilisation of BMs: Dose finding; HV or pat. heterogenicity; storage strategy; etc.

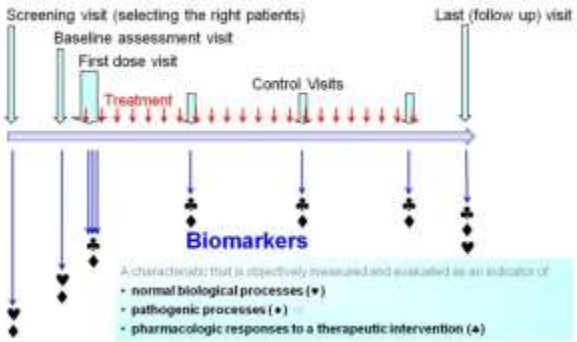
Flexibility

New Capabilities – New Challenges

Drug Development



Clinical Study Design

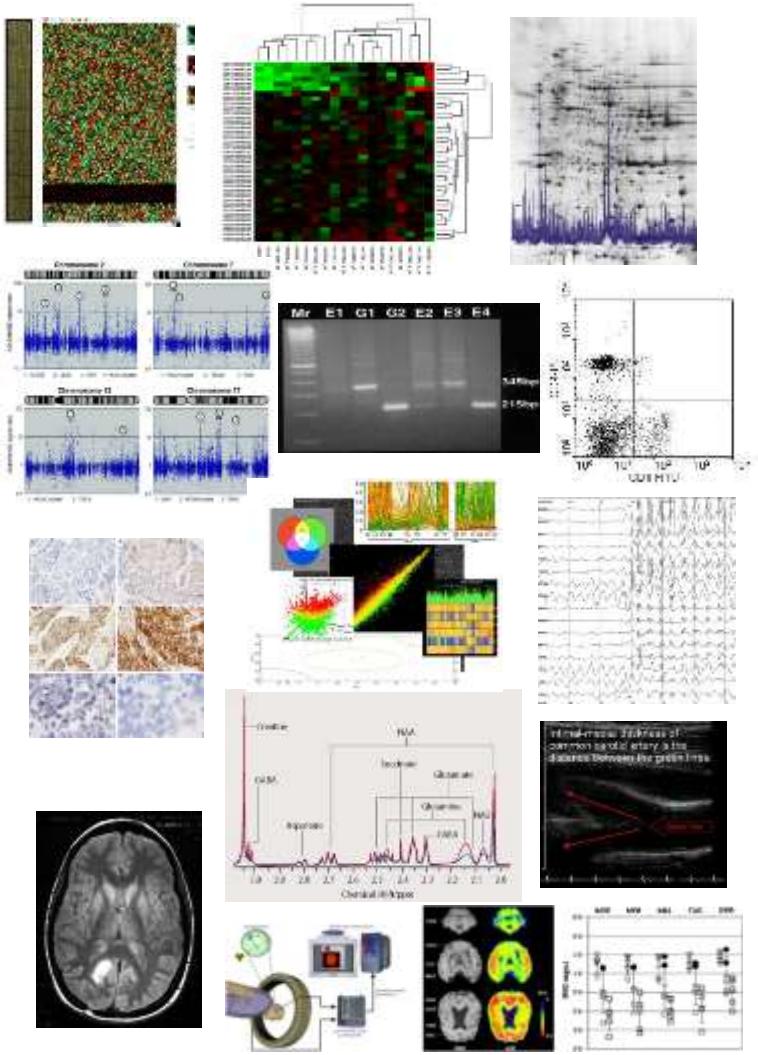


integrated data management & analysis

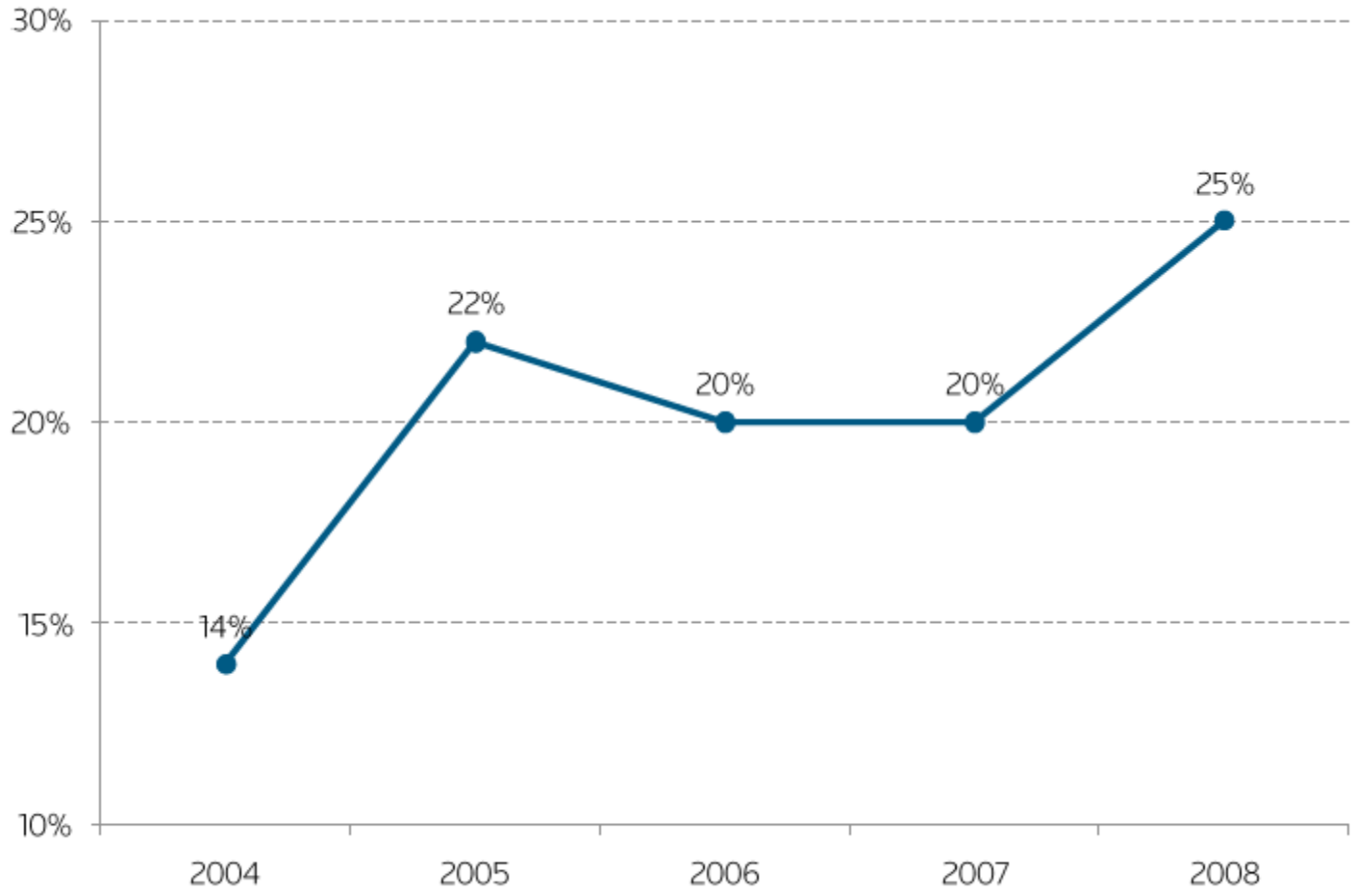
adaptive designs

Study Conduct & BM Logistics

Biomarker Technologies

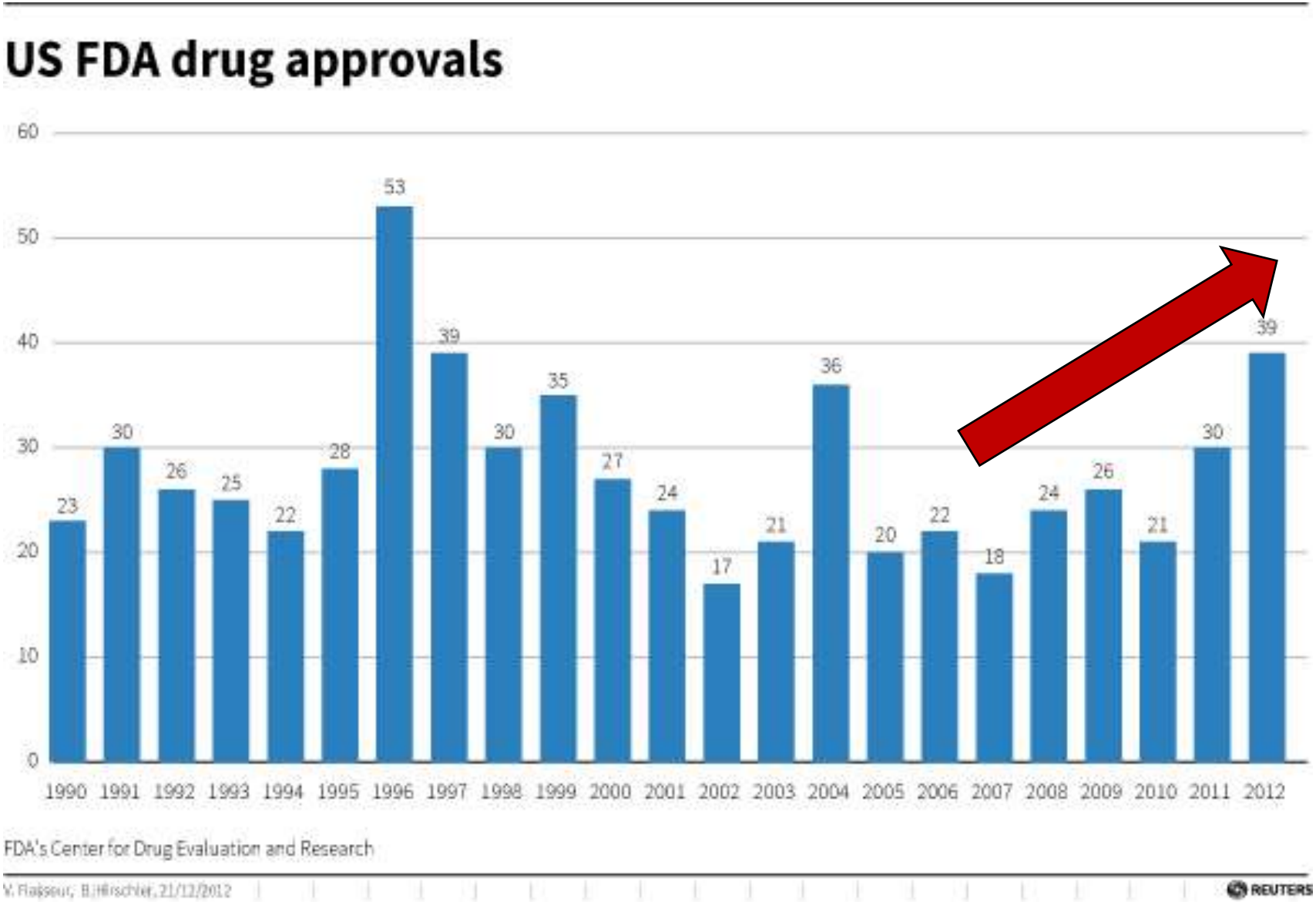


Early development spend as a proportion of total R&D spend (2004 – 2008)



Thomson Reuters. Whitepaper 2011

Reversing the Trend ?



Drug R&D remains a Gamble, but . . .

JT@inhecon.com

Deciding which technology to invest in . . .

Academia

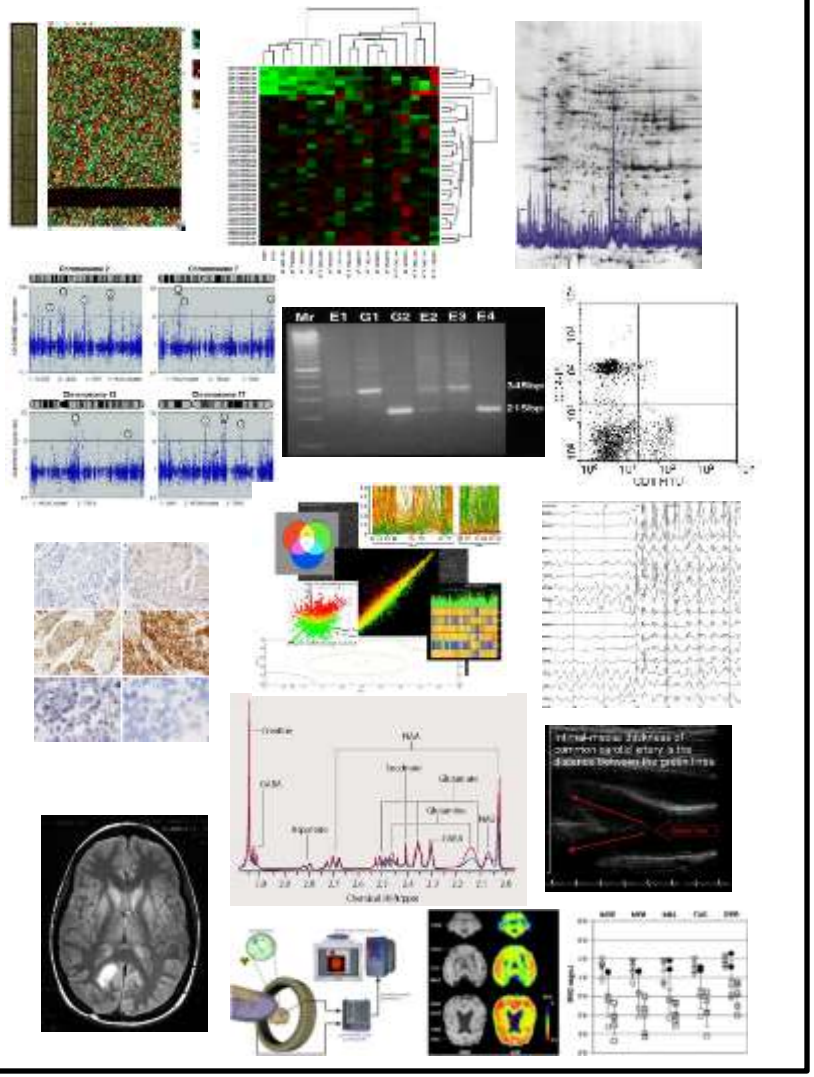
Biotech

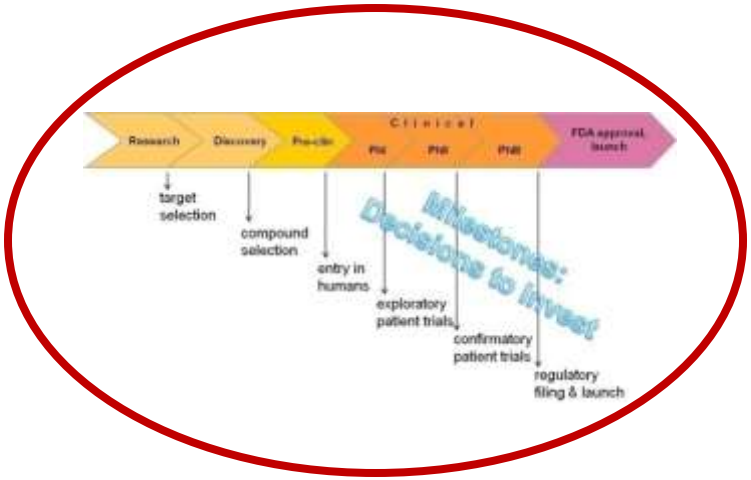
Engineering

Research Institutes

Pharma

Biomarker Technologies "Today"





Pharma

Adaptation and Utilisation in Drug Development

Technology Innovation – HARNESSED by Pharma