Personalized Medicine
A new challenge for applied human pharmacology?

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Leipzig
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Personalized Medicine:
Predicting Variability in Drug Response

Variability in drug exposure

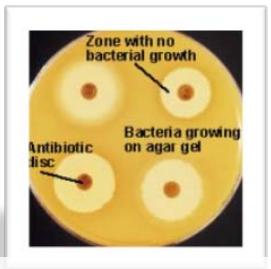
- Genetic polymorphisms of ADME enzymes and transporters
- Expression of ADME enzymes and transporters (reduced/increased)
- Inhibition of ADME enzymes and transporters

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

Personalized Medicine: Past, Present, Future



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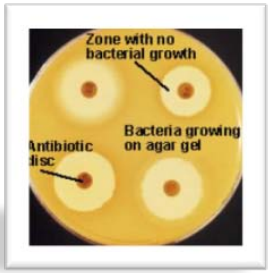
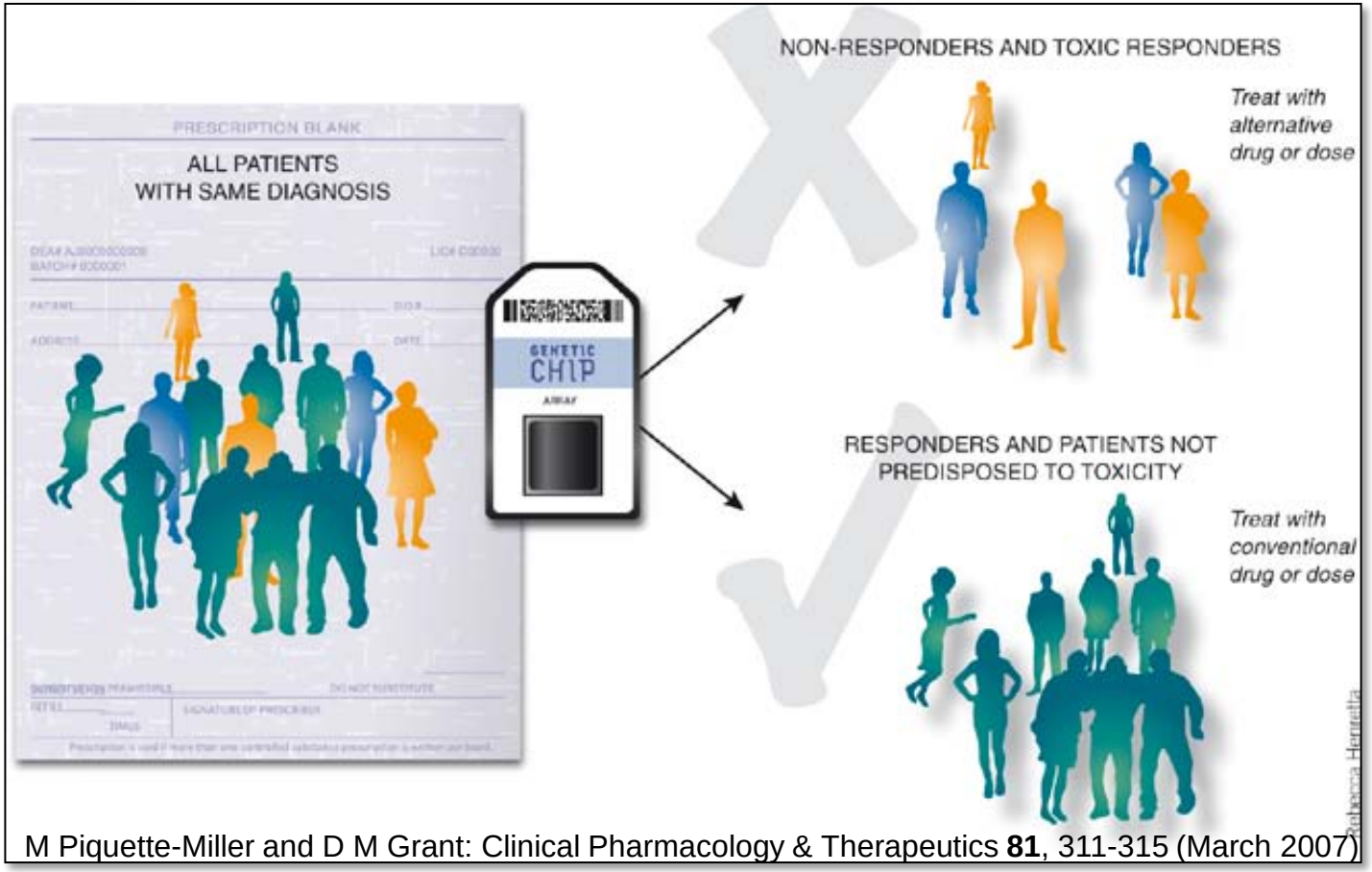
Data from CMAJ. 2008 Jan 29;178(3):296-305. Percentages used from data on improving depression scores

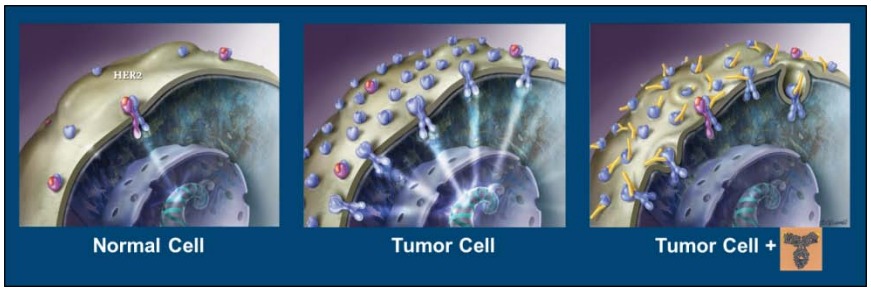
1950s-1960s: Antibiotic Resistance Testing





M Piquette-Miller and D M Grant: Clinical Pharmacology & Therapeutics **81**, 311-315 (March 2007)

Personalized Medicine: Past, Present, Future



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1998: Herceptin (trastuzumab)

Clinical Trials Assay (CTA) vs HercepTest®

- Her2 is the molecular target for trastuzumab
- Standardized immunohistochemistry (IHC) assay developed at Genentech for phase I-III clinical trials; 2+ or 3+ protein overexpression required for study entry
- All testing performed at a central core laboratory (LabCorp)
- CTA establishes a de facto standard – but CTA was not commercially viable => Requirement for commercially available HER2 test for marketing of Herceptin
- Genentech partners with DAKO to develop a commercially available IHC kit

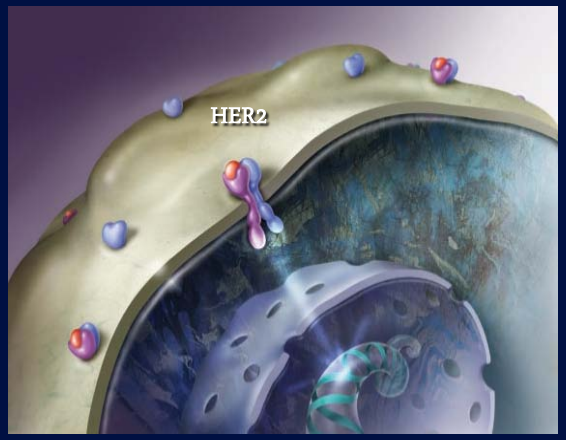
		Clinical Trial Assay		
		+	–	Total
HercepTest	+	216	59	275
	–	58	215	273
	Total	274	274	548

Concordance = **79%** (76%-82%)

Applications received simultaneous approval by CBER and CDRH on September 25, 1998

From: Cheryl A. Madsen, July 29, 2004

1998: Stratified Therapy: The “Prototype” Herceptin



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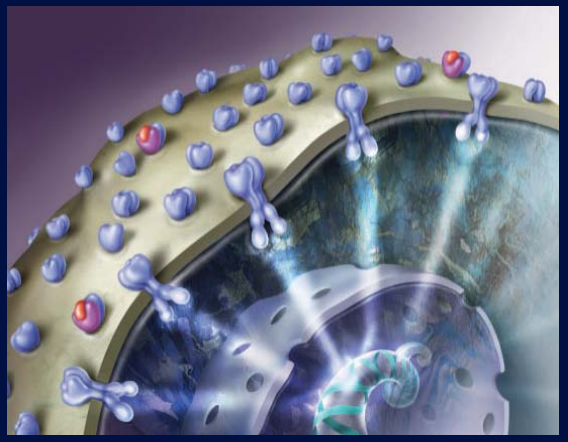


Tumor Cell

Tumor Cell +

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

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

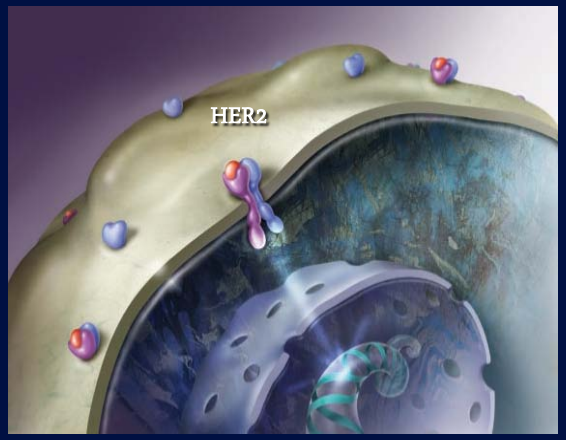
RRR FISH pos: 43% FISH neg: 0%

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**

Today: Personalized Medicine – Increased Complexity



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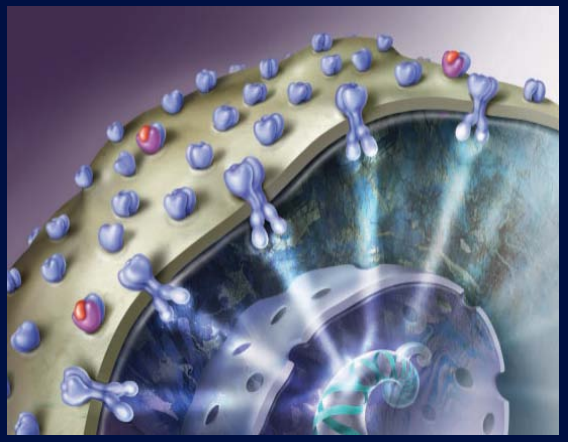
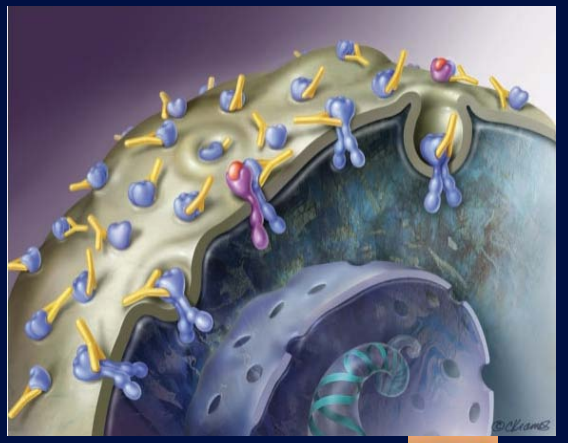


Tumor Cell



Tumor Cell +

At launch:

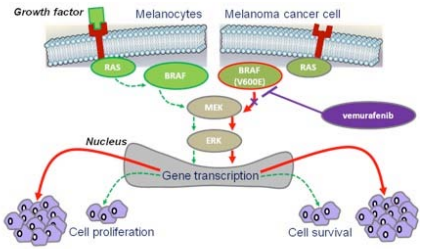
Dako IHC test → Roche/Genetech Herceptin

Today:

Dako IHC test / other IHC tests / FISH / . . . → Roche/Genetech Herceptin; GSK Lapatinib

Tomorrow?

Personalized Medicine: Past, Present, Future



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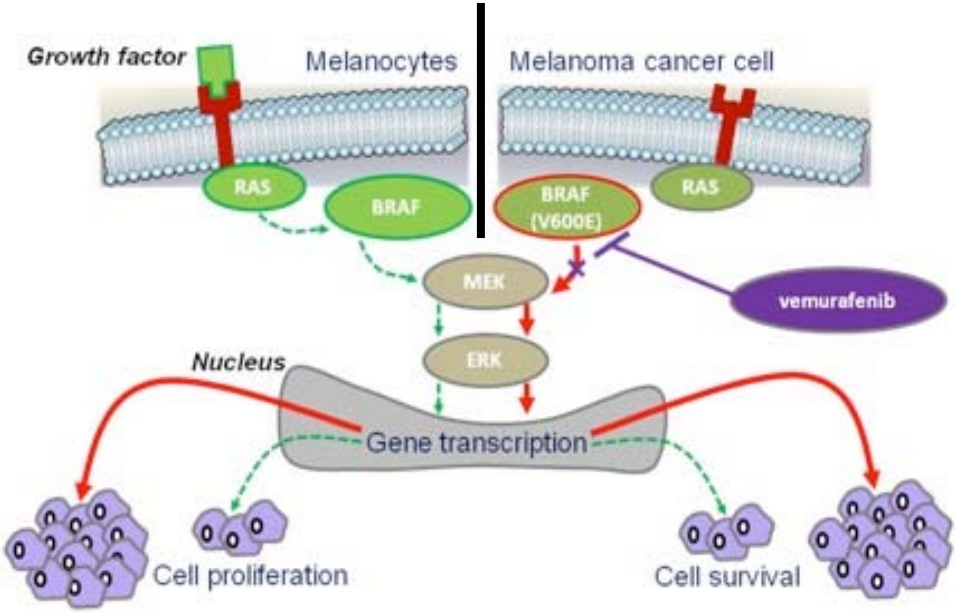
October 4, 2006: Press Release on PLX4032



Plexxikon Inc. and Roche .. announced …to develop and commercialize PLX4032, (**Vemurafenib**), which **selectively inhibits B-Raf^{V600E}, a mutated form of the BRAF kinase gene**.

The BRAF^{V600E} gene has been associated with increased tumor aggressiveness and decreased survival in … approximately 70% of malignant melanomas … PLX4032 may offer a new treatment modality for the … cancer patients … who carry the BRAF^{V600E} gene. Plexxikon … **plans to initiate a Phase 1 clinical trial by the end of this year**.

Separately, Roche Molecular Diagnostics … and Plexxikon announced they will collaborate on **development of an in vitro assay to screen for the presence of the BRAF^{V600E} mutation in biological samples taken from patient tumors**.

Predictive/Pharmacodiagnostic Markers in Phase I

Safety Study of PLX4032 in Patients With Solid Tumors (Phase 1)
Information provided by: Plexxikon ClinicalTrials.gov Identifier: NCT00405587

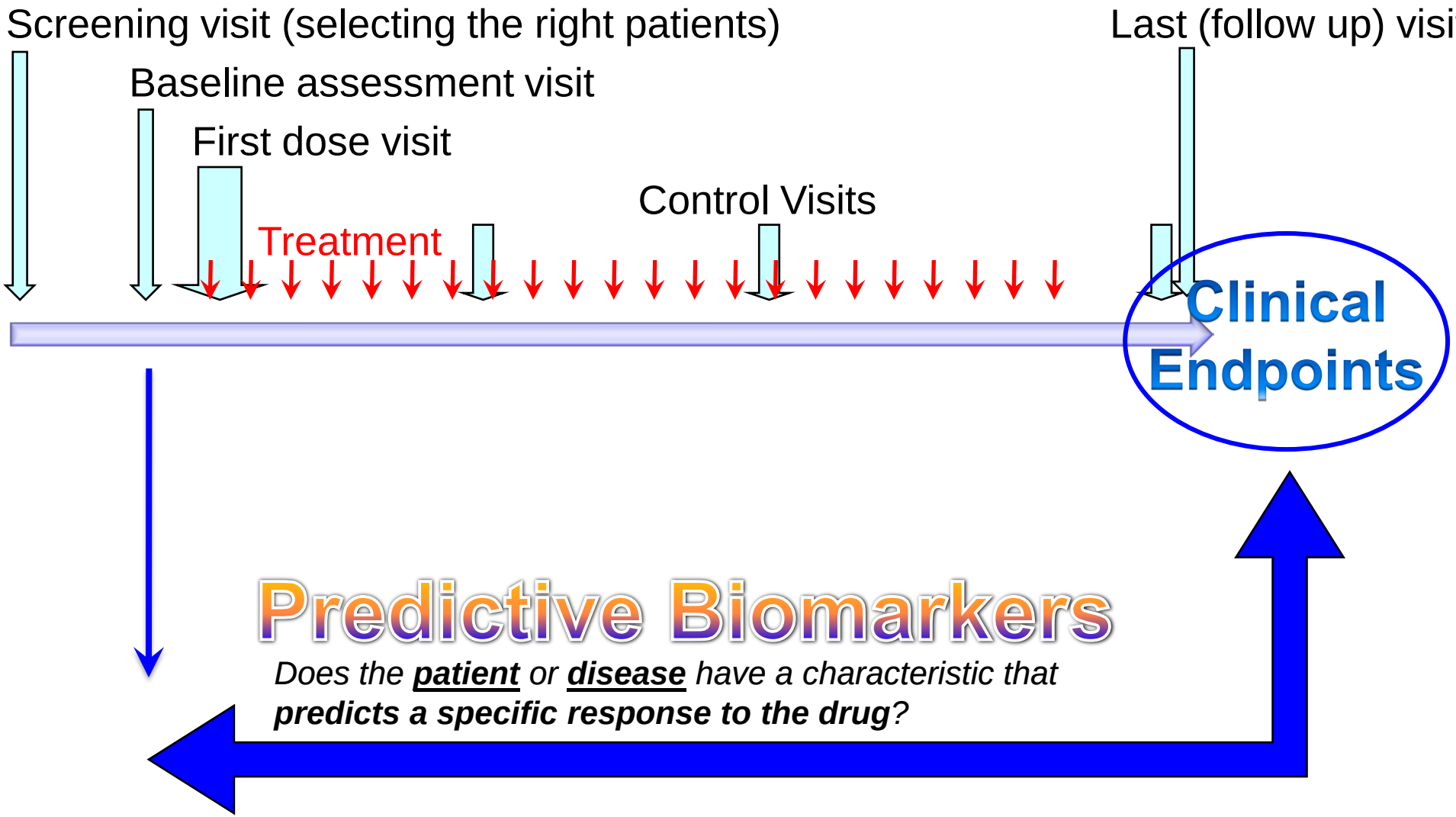
Primary Outcome Measures:
Maximum tolerated dose, Dose-limiting toxicities, Safety

Secondary Outcome Measures:
Pharmacodynamic activity in tumor biopsy tissue

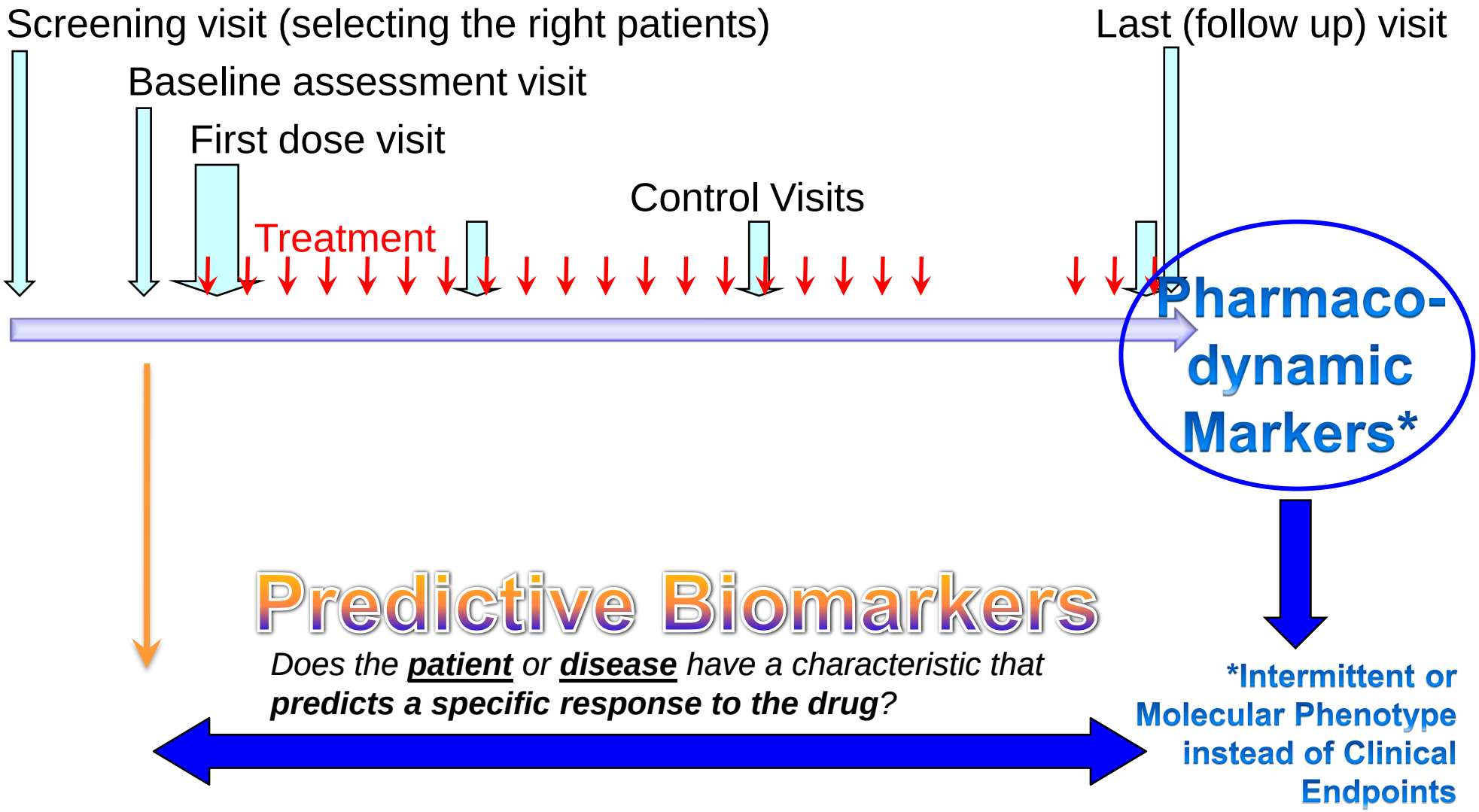
Inclusion Criteria:

- Solid tumors confirmed histologically whose tumors are refractory to standard therapy, or for whom standard or curative therapy does not exist.
- Patients from whom paired melanoma biopsies are planned **must have a V600E+ BRAF mutation confirmed prior to the administration of PLX4032**
- Patients in the Extension cohorts (melanoma or adenocarcinoma of the colon or rectum) must have both a V600E+ BRAF mutation
- .....

Predictive BMs in a Typical Clinical Study



Responders defined by Pharmacodynamic Markers



Pharmacodynamic Response Markers

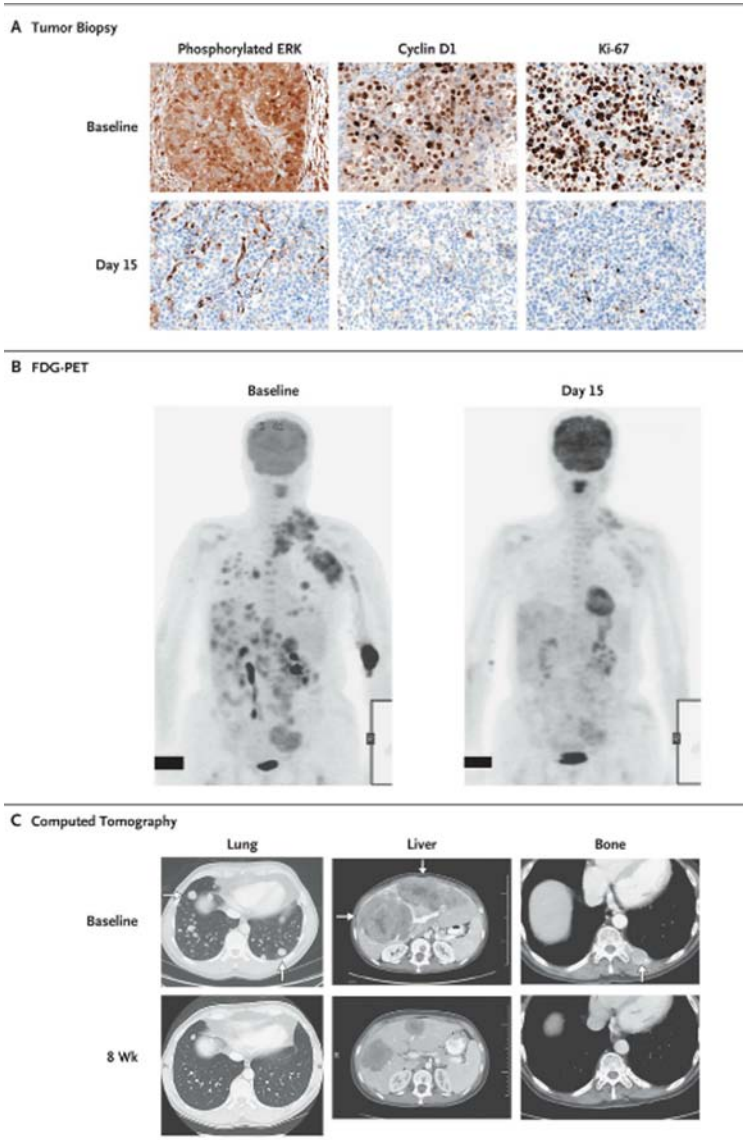


Figure 2. Representative Findings of the Effect of PLX4032 at the Recommended Phase 2 Dose in Study Patients with Melanoma That Carried the V600E Mutation.

The recommended phase 2 dose was 960 mg twice daily. Panel A (hematoxylin and eosin) shows immunohistochemical analyses of the expression of phosphorylated extracellular signal-regulated kinase (ERK), cyclin D1, and Ki-67 in tumor-biopsy specimens obtained at baseline and on day 15 of treatment. Panel B shows the uptake of ^{18}F-fluorodeoxyglucose (FDG) at baseline and on day 15 of treatment, as assessed by means of positron-emission tomography (PET). Panel C shows computed tomographic images of lesions (arrows) in lung, liver, and bone (with each pair of images shown for a different patient) at baseline and at 8 weeks.

Flaherty et al., NEJM 2010

Personalized Medicine: Past, Presence, Future

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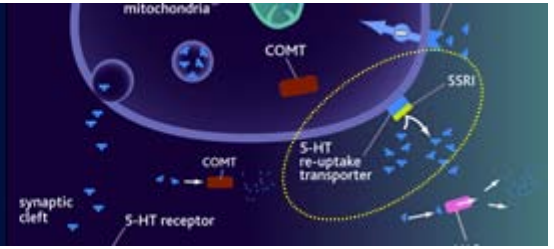

Future Challenges: Responder Identification

PAROXETINE

- **Indication: Major Depression, ...**
- **Dos.: 20 mg/day, increase in 10mg steps to max 50 mg/day**

- **"Symptomatic improvement in about 50% of treated patients"**

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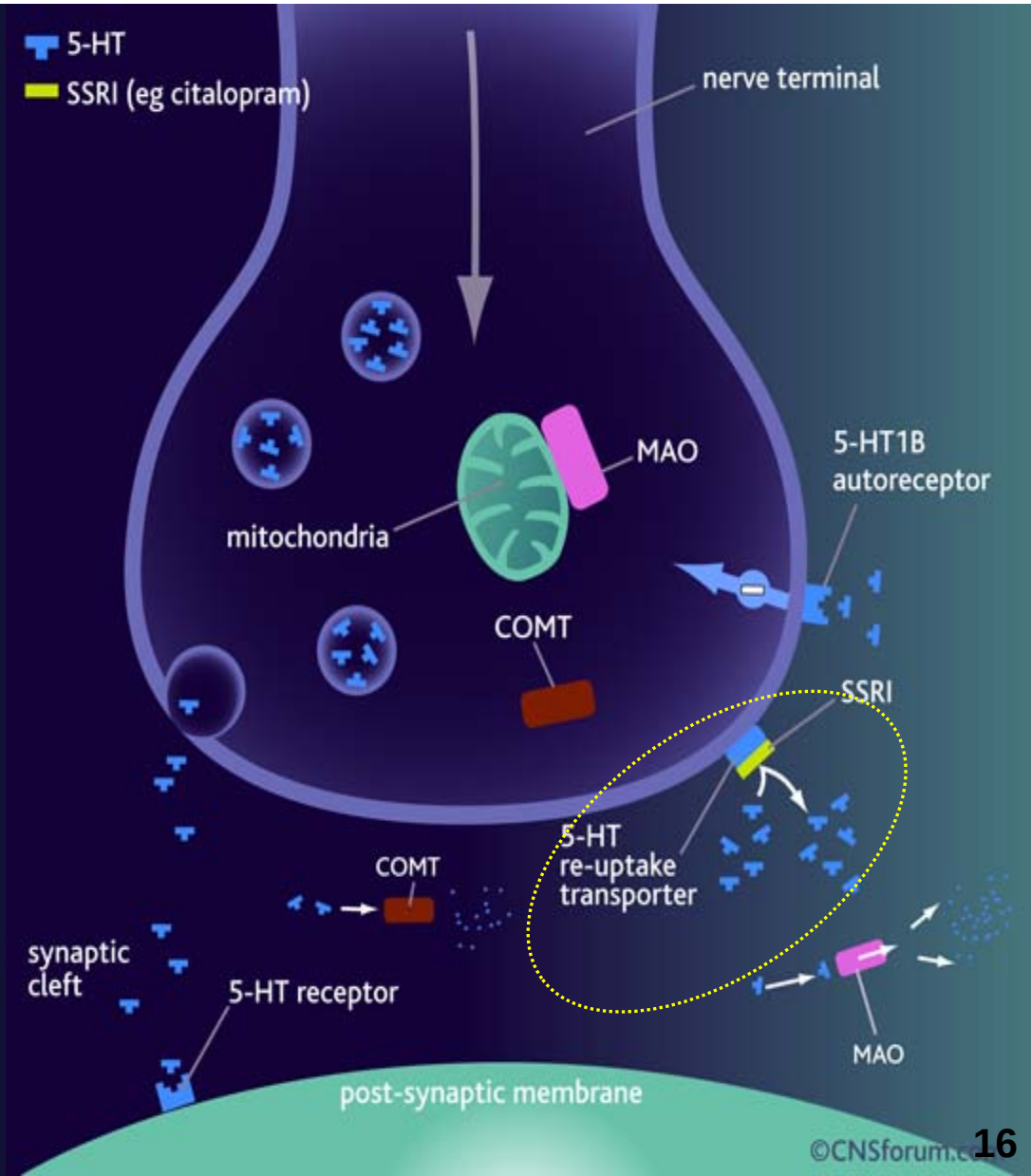


Drug Development with a Focus on Personalized / Stratified Medicine

what are the key challenges?

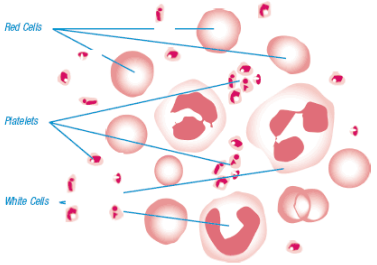
how can these challenges best be met?

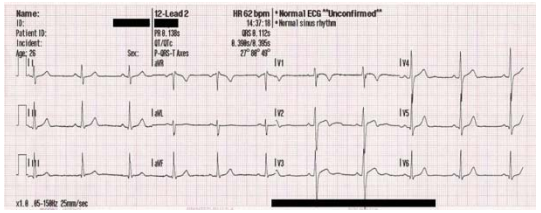
is there a role for applied human pharmacologists?

The Basis for Personalized Medicine: Innovation

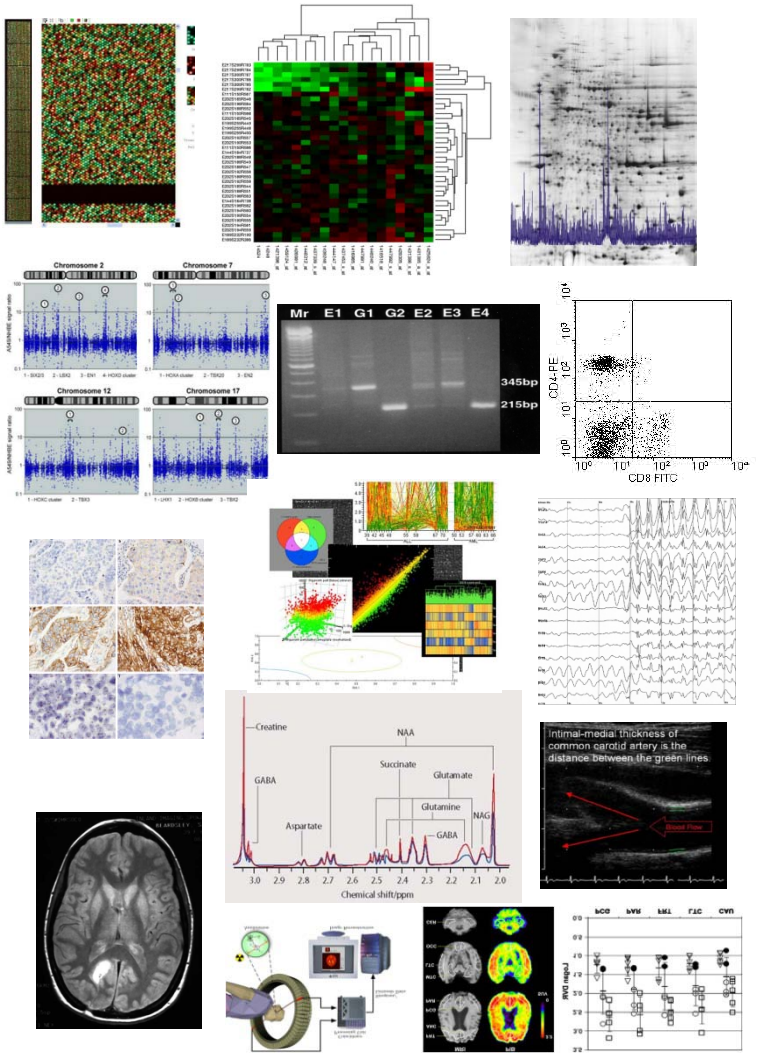
Biomarker Technologies "Yesterday"

			Ref. Range
White Blood Cell Count	3.4	$10^3/mm^3$	(5 – 13)
Hemoglobin	10.7	g/dL	(11 – 16)
Hematocrit	31.7	%	(33 – 48)
Platelet Count	118	$10^3/mm^3$	(140 – 450)
Sodium	140	mmol/L	(135 – 145)
Potassium	5.3	mmol/L	(3.5 – 5.0)
Chloride	111	mmol/L	(98 – 107)
Carbon Dioxide	19	mmol/L	(18 – 27)
BUN	27	mg/dL	(6 – 20)
Creatinine	2.0	mg/dL	(0 – 0.9)
Glucose	88	mg/dL	(60 – 115)
Calcium	8.7	mg/dL	(8.6 – 11.0)
Total Protein	6.2	g/dL	(6.3 – 8.6)
Albumin	3.2	g/dL	(3.7 – 5.6)
Total Bilirubin	0.2	mg/dL	(0.2 – 1.0)
AST	36	IU/L	(15 – 40)
ALT	27	IU/L	(2 – 15)
Alkaline Phosphatase	125	IU/L	(96 – 437)
C-reactive Protein	9.0	mg/dL	(0.3 – 0.9)
Tacrolimus Level	12.2	ng/ml	
Influenza A & B Antibody	negative		
Cytomegalovirus Culture	negative		
Blood Viral Culture	negative		
Blood Culture	negative		
Urine Culture	negative		
Stool Culture	No bacterial pathogen Positive *Enterovirus*		
Marrow *Mycobacterium* Culture	negative		
Bartonella henselae IgG	1:64		
Bartonella henselae IgM	<1:16		
Bartonella quintana IgG	<1:64		
Bartonella quintana IgM	<1:16		
Histoplasma Yeast Titer	<1:8		
Histoplasma Mycelial Titer	<1:8		
Blastomyces Titer	<1:8		
Coccidioides Antibody Titer	<1:2		



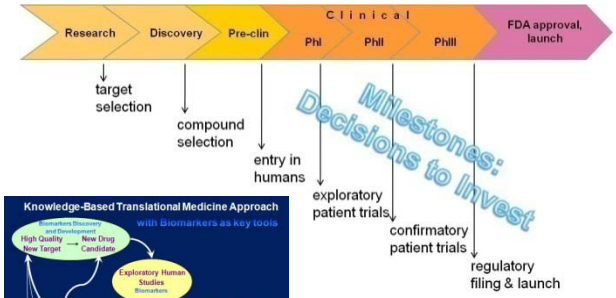


Biomarker Technologies "Today"

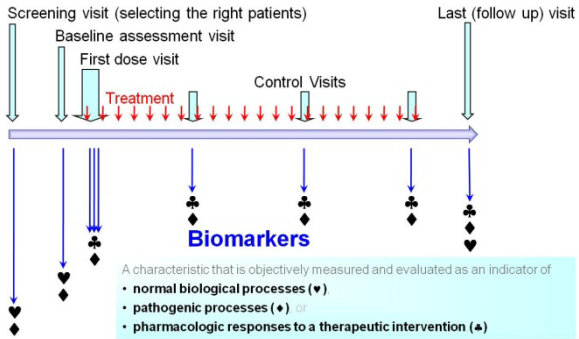


New capabilities → New complexities

Drug Development



Clinical Study Design

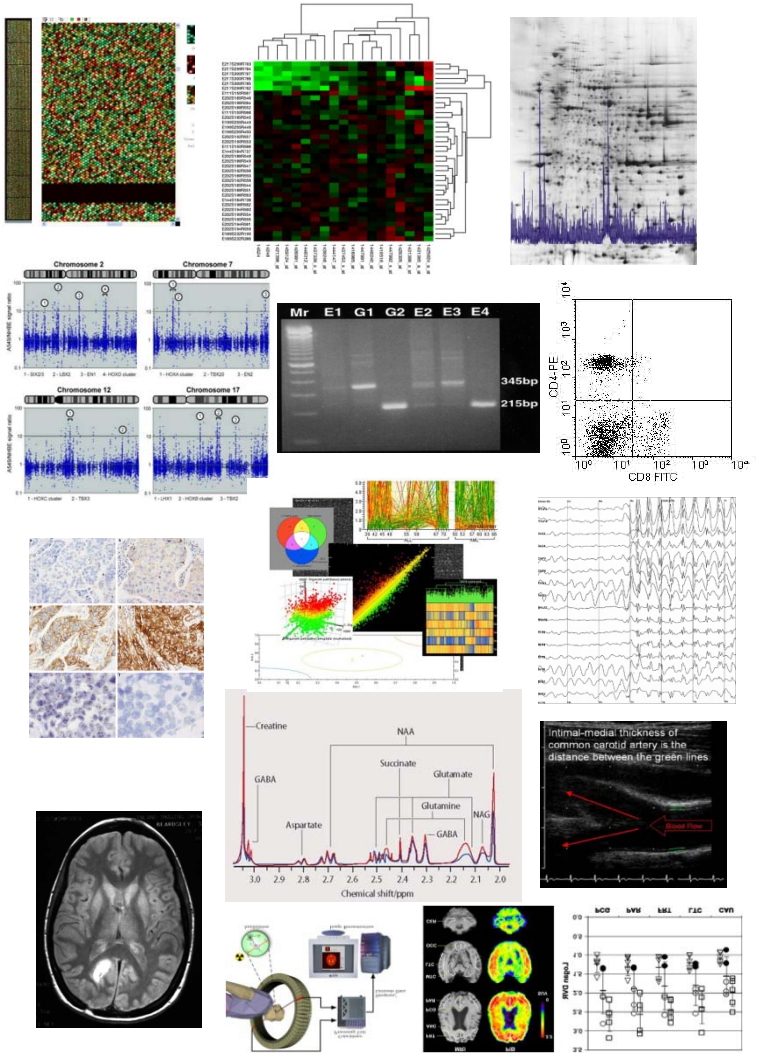


integrated data management & analysis

adaptive designs

Study Conduct & BM Logistics

Biomarker Technologies



What Biomarkers/Diagnostics do we Need?

Academia

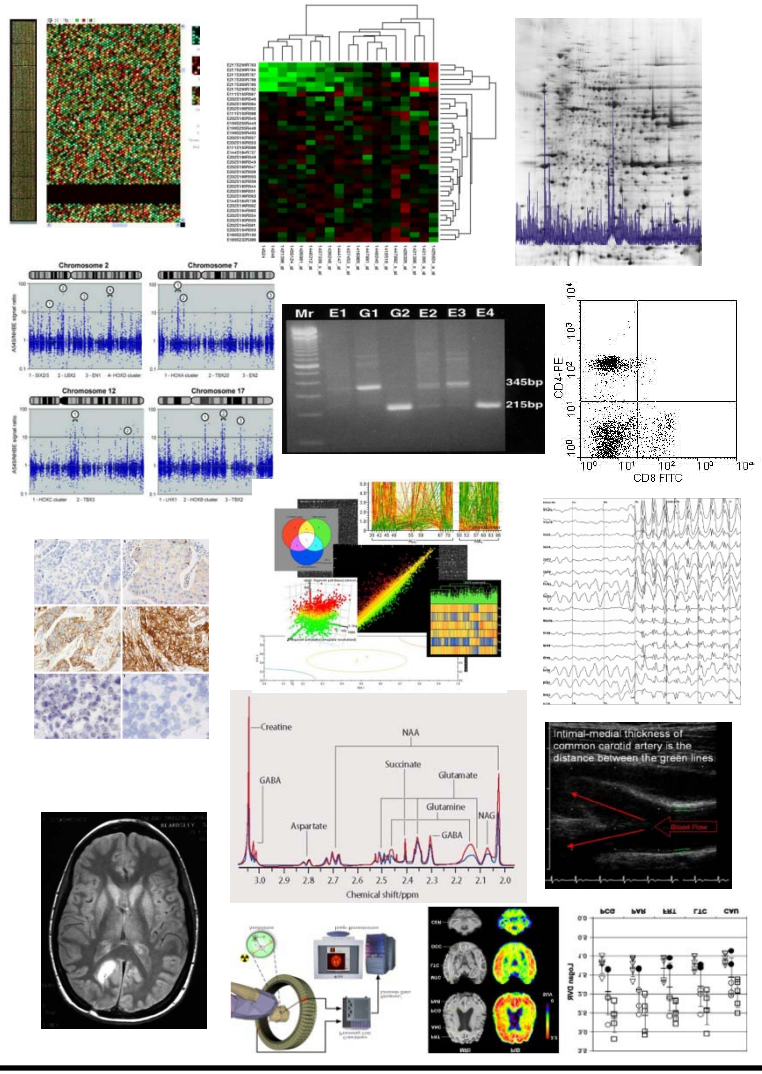
Biotech

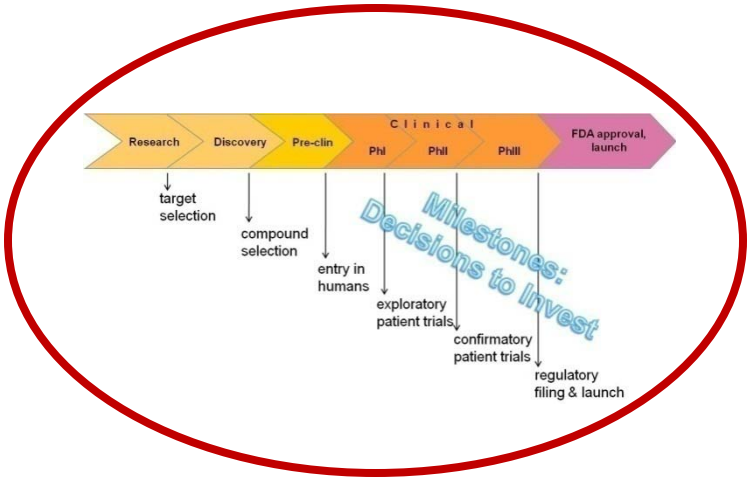
Engineering

Research Institutes

Pharma

Biomarker Technologies "Today"





Pharma

Adaptation and Utilisation in Drug Development

Technology Innovation – HARNESSED by Pharma

Biomarkers in Early R&D Projects – when?

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

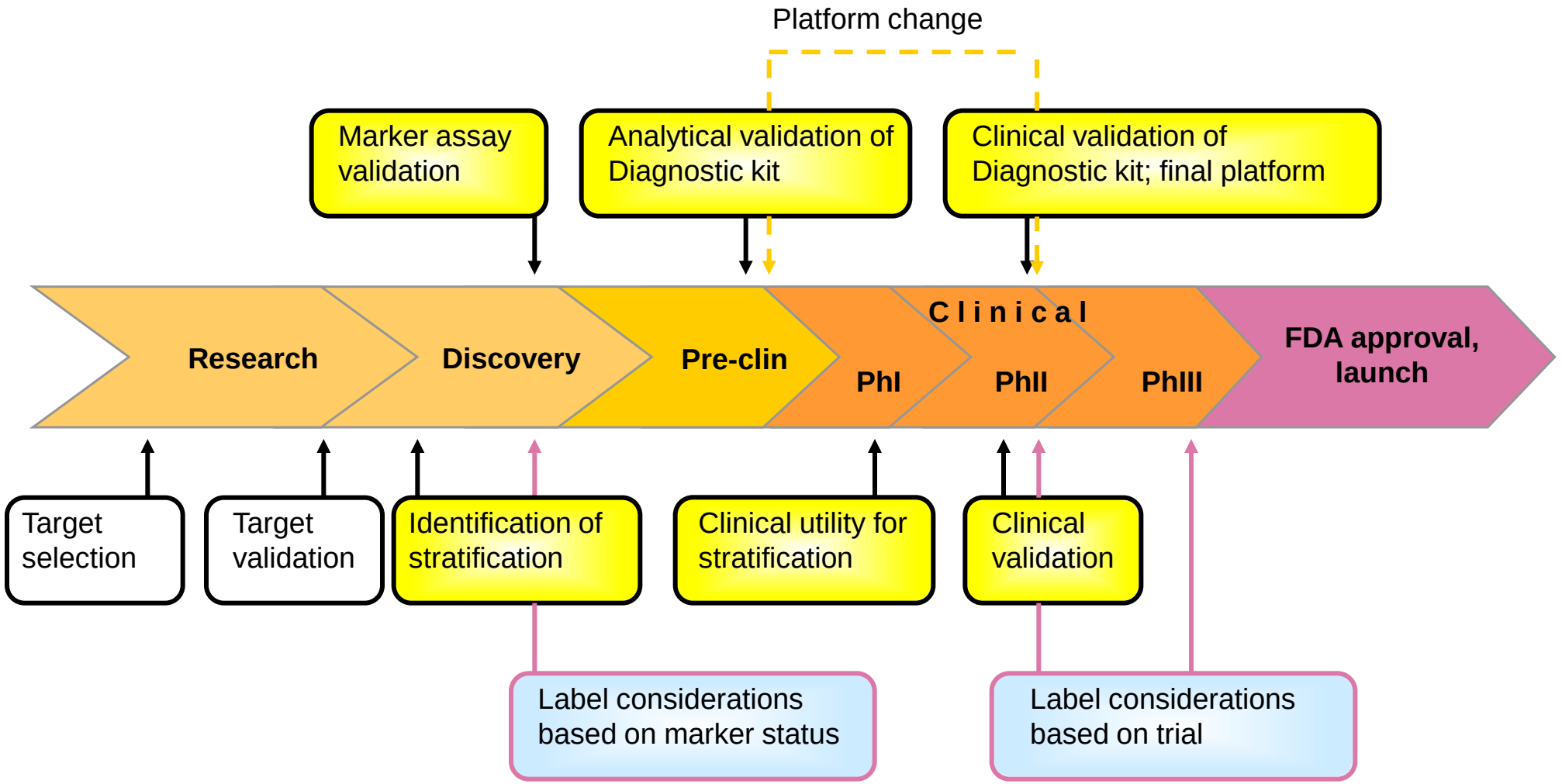
Confirmatory BM phase: BM needs for early decision making should be understood, ideally integration into GLP tox, integration into clinical plan & clinical protocols

4. Entry in Human

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

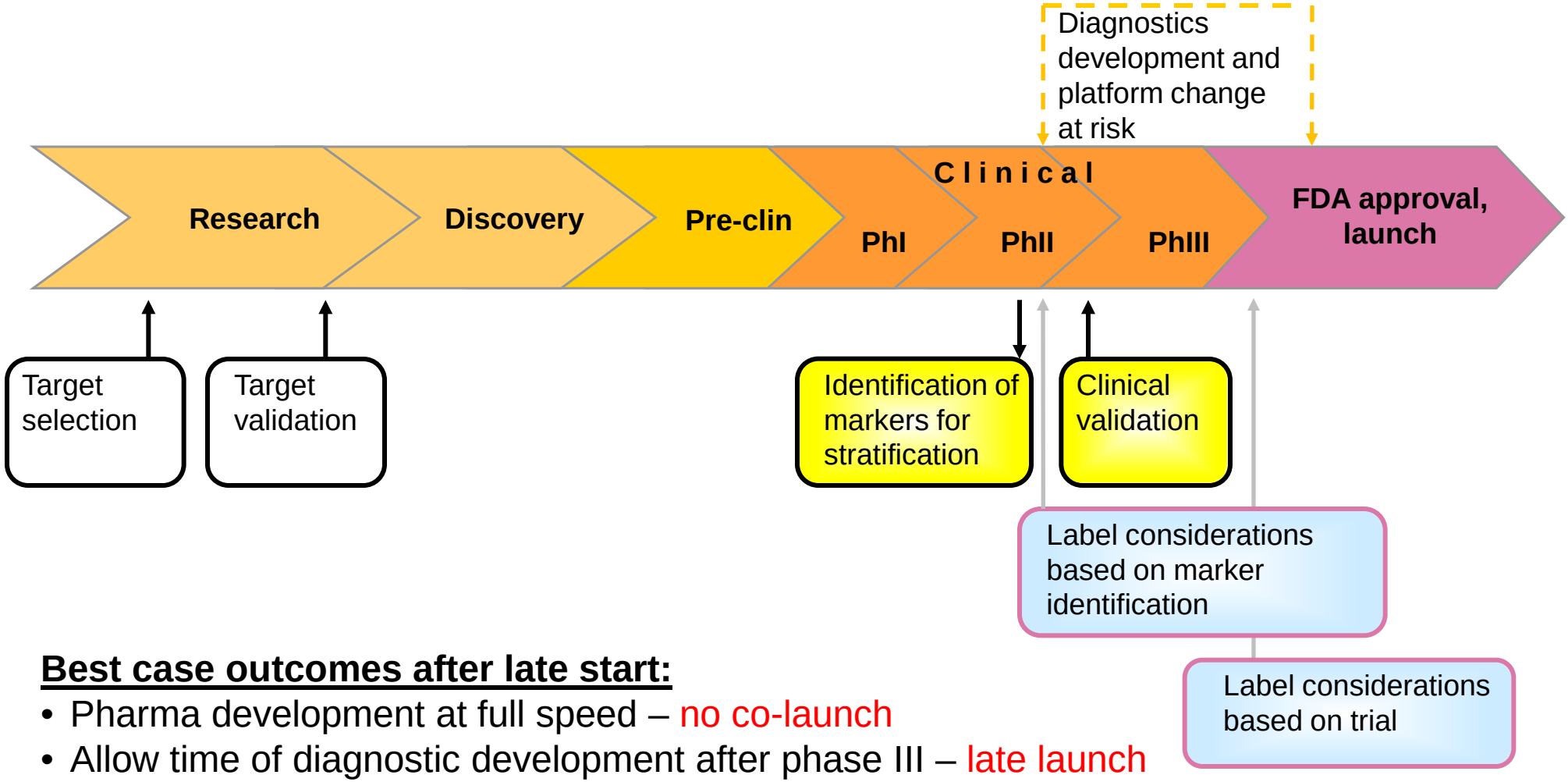
Flexibility

Drug - Diagnostic Test Co-Development
The Regulatory Perspective



Adapted from FDA Drug-Diagnostic Co-Development Concept Paper

Drug - Diagnostic Test Co-Development
Late scenario (end of Ph II or later)



Best case outcomes after late start:

- Pharma development at full speed – no co-launch
- Allow time of diagnostic development after phase III – late launch
- Allow time for platform development prior to phase III – pharmacodiagnostic delay
- Very high risk of delays in any case – nightmare for commercial (pricing etc.)

Enabling Personalized/Stratified Medicine

- **Biomarker "discovery"**
  - early identification of BMs, understanding the related science (ideally at target selection!)
  - assessment of utility in human experimentation
- **Biomarker "development" (Fit for Purpose !)**
  - BM characterisation & validation (technical, biological, clinical)
  - design of BM kit suitable for clinical studies (multicentre !)
- **Clinical trial design and conduct**
  - selection of suitable population (healthy subjects/challenge?, patients?, which patients?)
  - obtaining suitable phenotypic data for responder / non-responder identification
  - acceptance of biomarkers by investigators and patients
  - BM logistics
  - BM data management and statistics
  - agreed decision making criteria (supporting go/no go decision?)
- **Clinical utility of pharmacodiagnostic markers**
  - ensuring that pharmacodiagnostic markers do not become bottleneck or controlling
  - commercial aspects on market size and accessibility
- **Timing**
  - Completion of all required activities prior to clinical study start, to decision making, to launch

applied human pharmacology expertise essential

Rheinisch-Bergisches TechnologieZentrum

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