Biomarkers in clinical trials: Overview of roadmaps for PD/ prognostic/predictive biomarkers

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Newcastle Cancer Centre

Northern Institute for Cancer Research

Targeted Therapies – The Future of Cancer Treatment

Agents which exploit the molecular and cellular pathology of cancer:

- Oncogene antagonsists
- Tumour suppresor gene agonists
- Immortality gene inhibitors
- Anti-angiogenic agents
- Anti-invasive and anti-metastatic drugs

Biomarkers – Definition

A biomarker is:

“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or responses (pharmacologic or otherwise) to a therapeutic intervention”

Or

A test!

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The Cancer "Journey"

1:3 of us will get cancer

- Am I going to get cancer?
- Have I got cancer?
- What kind of cancer is it?
- How bad is my cancer?
- What is the best treatment?
- Is the treatment working?

The Cancer Patient Journey

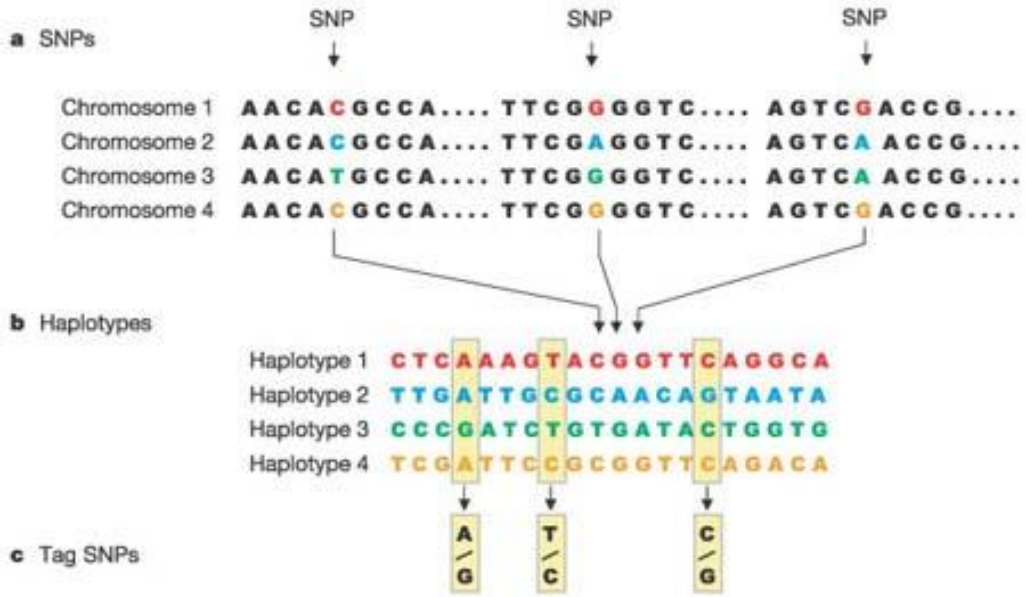
1:3 of us will get cancer

- Am I going to get cancer? **TESTS**
- Have I got cancer? **TESTS**
- What kind of cancer is it? **TESTS**
- How bad is my cancer? **TESTS**
- What is the best treatment? **TESTS**
- Is the treatment working? **TESTS**

Biomarkers in Cancer Management

Am I going to get cancer?

Predisposition biomarkers - Identification of individuals at risk of developing cancer



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Biomarkers in Cancer Management

Have I got cancer?

Screening biomarkers - Early detection of cancer in the general or at risk populations

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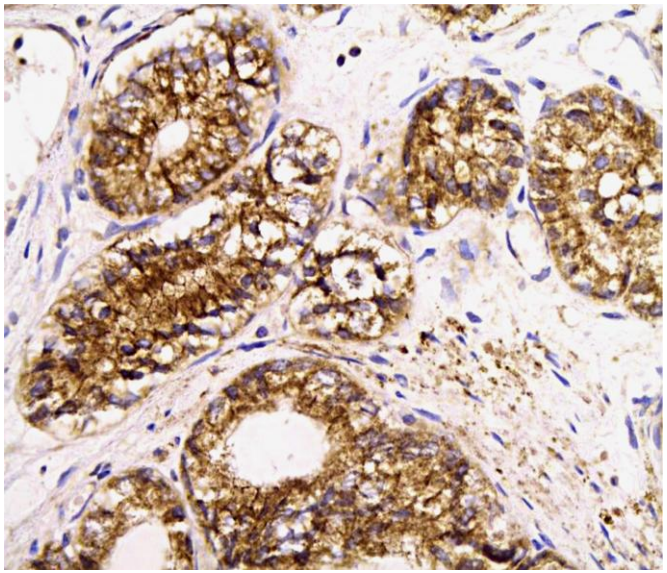
Biomarkers in Cancer Management

What kind of cancer is it?

Diagnostic biomarkers - Definition of tumour type, stage and grade



BTA stat® TEST

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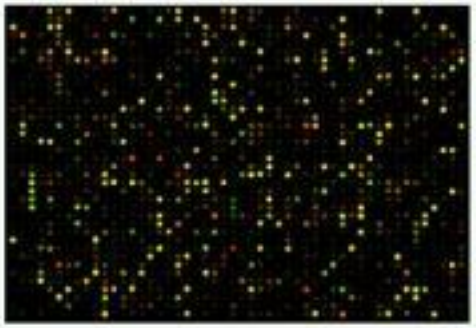
Biomarkers in Cancer Management

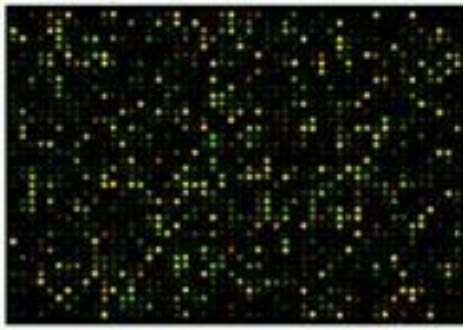
How bad is my cancer?

Prognostic biomarkers - Identification of the likely clinical disease course and hence appropriate therapeutic approach

MammaPrint®



Low risk



High risk

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Prognostic Biomarker-Driven Therapies for Medulloblastoma – Professor Steve Clifford

Disease biology:
Prognostic and predictive biomarkers

↓

Individualised therapy

↙ ↓ ↘

Favourable-risk:
Therapeutic reduction

High-risk:
Treatment intensification

Novel molecular agents:
Stratification

↘ ↓ ↙

Increased survival Reduced late-effects

↓

 Clinical trials 

Newcastle University

Validated medulloblastoma molecular and pathological prognostic biomarkers

- **>300 published prognostication studies**
- **Markers showing consistent findings in ≥2 clinical trials cohorts**

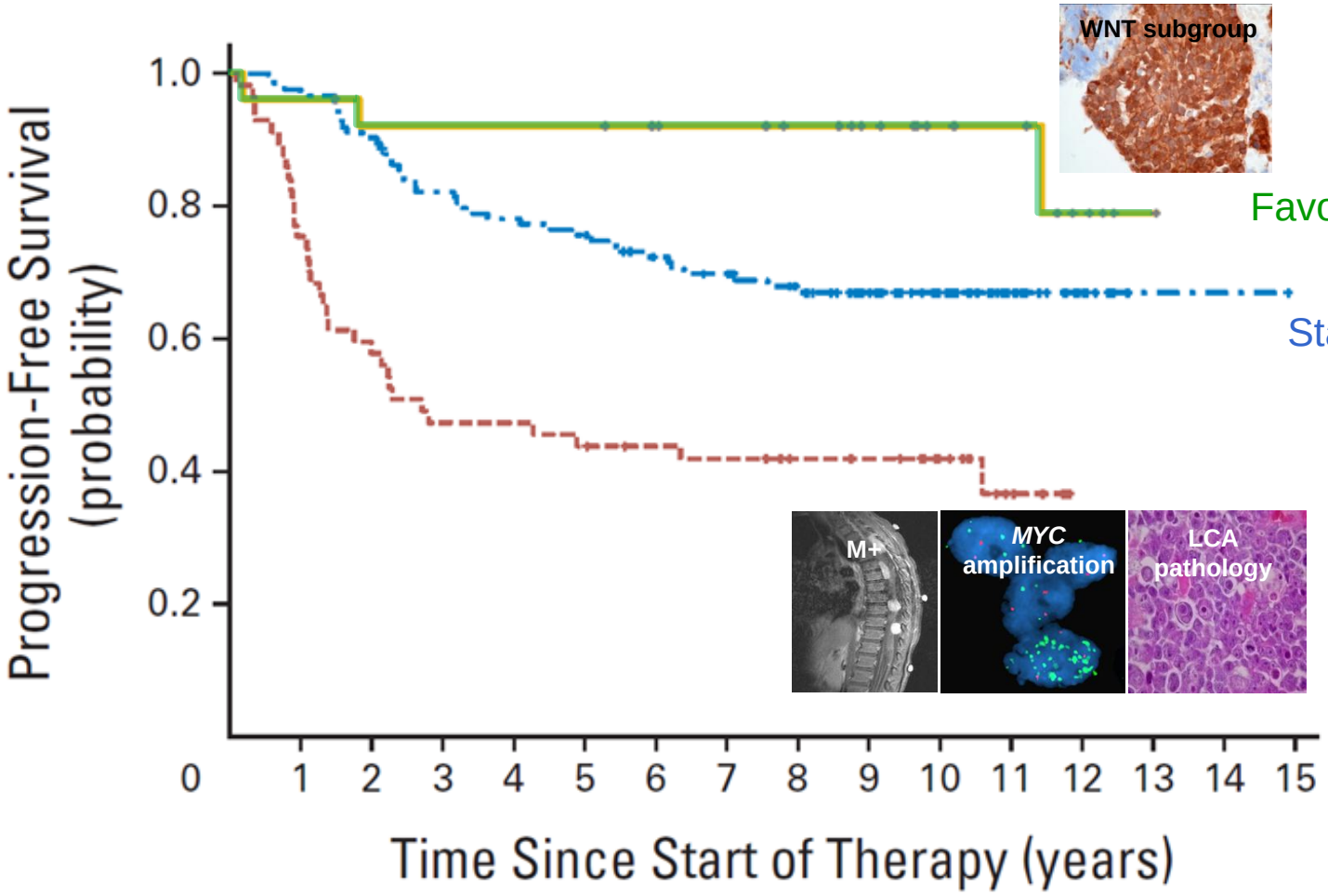
	Disease feature	Method of detection	Prevalence	Survival (risk-group vs. others)	Statistical analysis	Clinical trial	Cohort age range	References
Favourable risk	Wnt/Wg pathway activation (β-catenin nuclear stabilization)	IHC	27/109 (25%)	92% vs 65% (5 year OS)	*p=0.006* [m]	PNET3	3 - 16.8 yrs	Ellison et al, 2005
			10/69 (14%)	100% vs 68% (5 year EFS)	*p=0.03* [u]	SJMB96	3.1 – 20.2 yrs	Gajjar et al, 2006
	Desmoplasia (in infants ≤3yrs)	Histopathological assessment	20/43 (47%)	85% vs 34% (7 year PFS)	*p<0.001* [m]	HIT-SKK'92	<3 yrs	Rutkowski et al, 2005
			17/28 (61%)	53% vs 17% (5 year OS)	NR	CNS9204	<3 yrs	McManamy et al, 2007
Adverse risk	*MYC* gene amplification	FISH	5/84 (6%)	All dead at 5 yrs**	*p<0.001* [m]	PNET3	>3 yrs	Lamont et al, 2004
		qPCR	5/111 (4.5%)	40% vs 66% (7 year OS)	NS	HIT '91	3 - 18 yrs	Rutkowski et al, 2007
	Large-cell / anaplastic histology	Histopathological assessment	21/495 (4%)		*P<0.0001* [u]	COG trials		Brown et al, 2000
			23/116 (20%)	57% vs ~80% (5 year EFS)	*p=0.04* [u]	SJMB96	3.1 – 20.2 yrs	Gajjar et al, 2006
			52/315 (17%)	~55% vs ~75% (5 year OS)	*p=0.024* [m]	PNET3	2.7 – 16.4 yrs	McManamy et al, 2007

Newcastle University

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables

David W. Ellison, Mehmet Kocak, James Dalton, Hisham Megahed, Meryl E. Lusher, Sarra L. Ryan, Wei Zhao, Sarah Leigh Nicholson, Roger E. Taylor, Simon Bailey, and Steven C. Clifford



Favourable-risk (13%)

Standard-risk (60%)

High-risk (27%)

The PNET5 MB and PNET6 MB Clinical Trials (2012-2018)

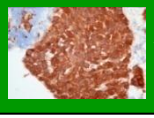
Surgery
Frozen tumour

Clinical staging

Molecular diagnostics and pathology review

Prospective biological studies

PNET5 MB
(5-10%)



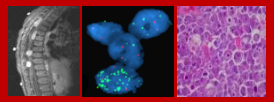
WNT

REDUCED

PNET6 MB
(40%)

STANDARD

HIGH-RISK
(30%)



M+ ***MYC*** **LCA**

INTENSIFIED

First molecularly-driven trial in paediatric CNS tumours

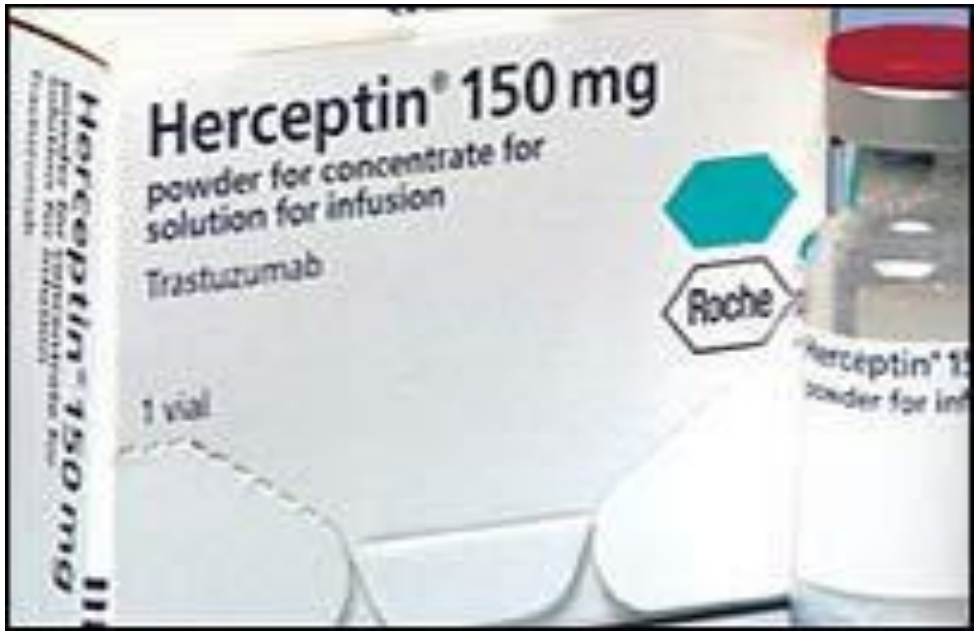
Biomarkers in Cancer Management

What is the best treatment?

Predictive biomarkers - Patient enrichment to maximize likely benefit from specific therapies:

Positive – Patients with the biomarker should receive therapy

Negative – Patients with the biomarker should not receive therapy



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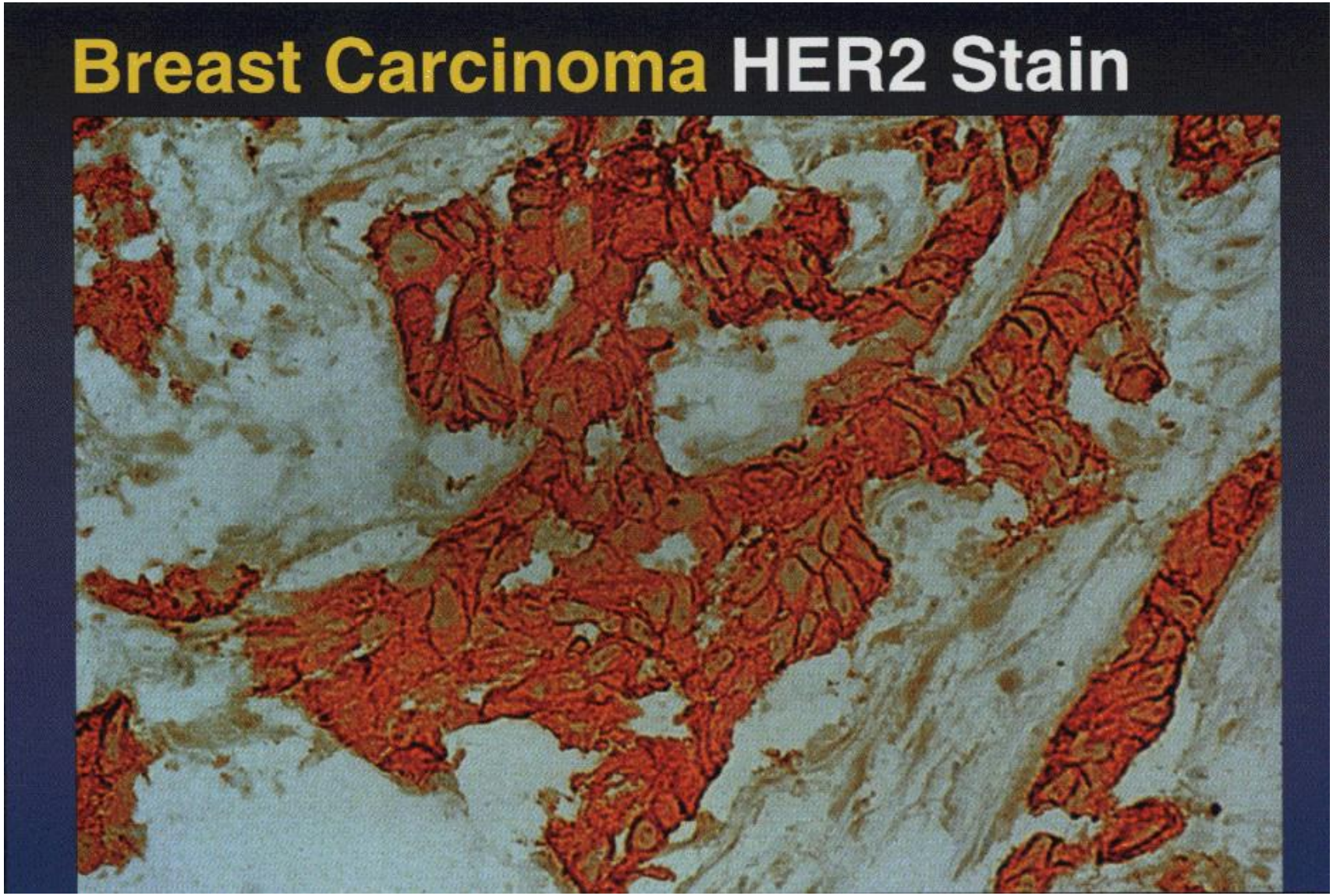
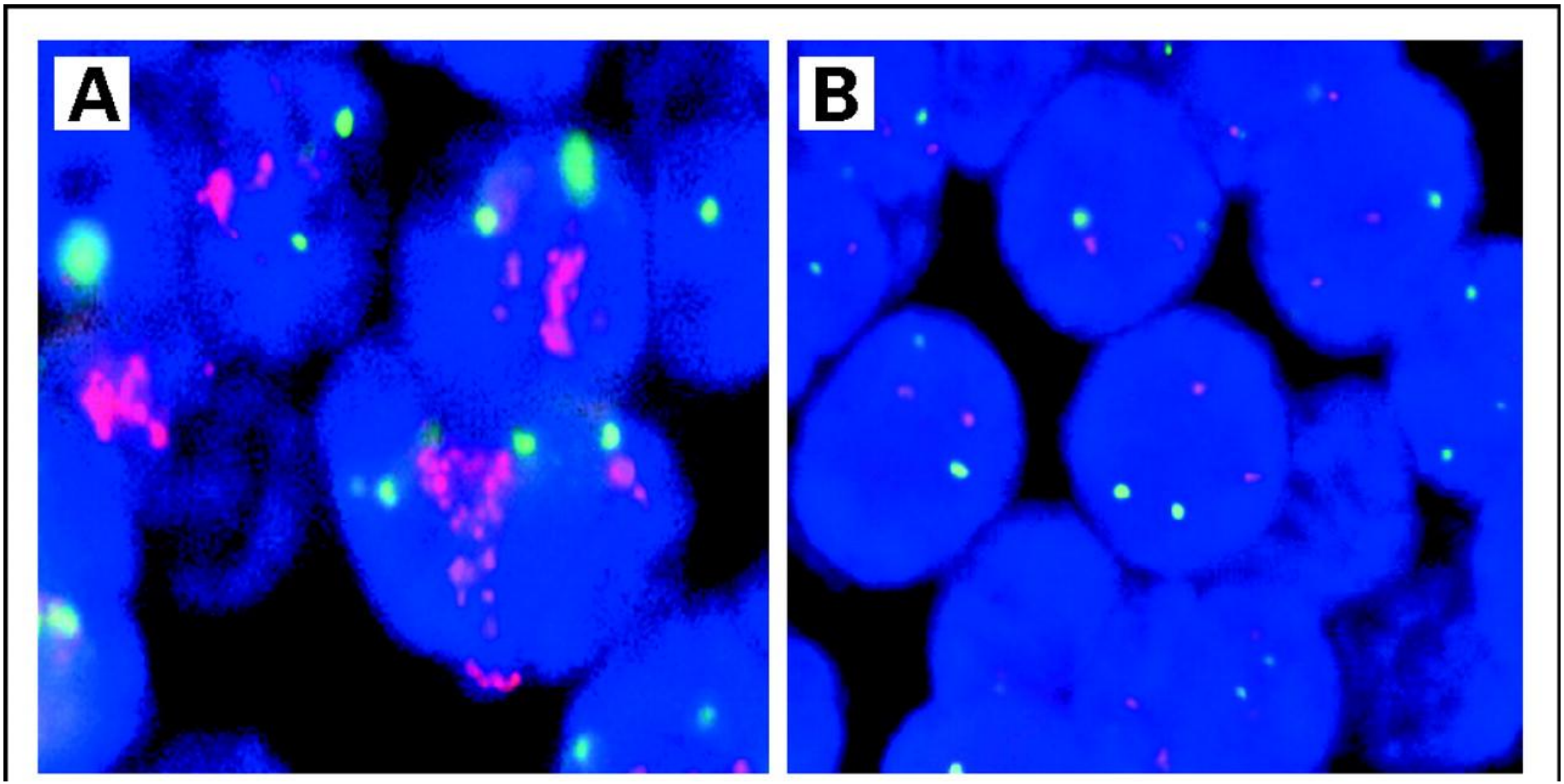
Positive Predictive Biomarker
- *HER2* expression in breast cancer



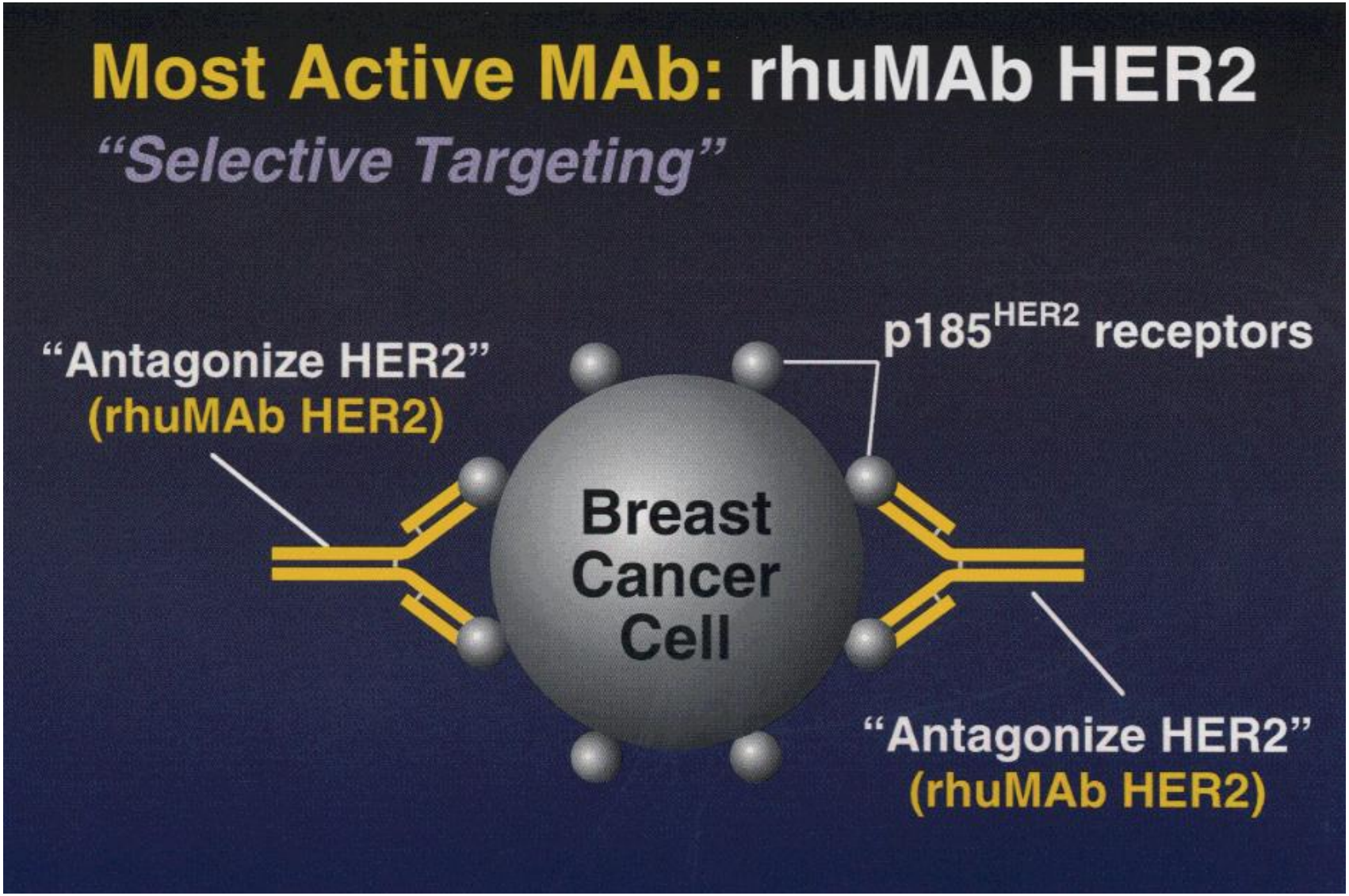
Positive Predictive Biomarker
- *HER2* amplification in breast cancer



Sauter, G. et al. J Clin Oncol; 27:1323-1333 2009

JOURNAL OF CLINICAL ONCOLOGY

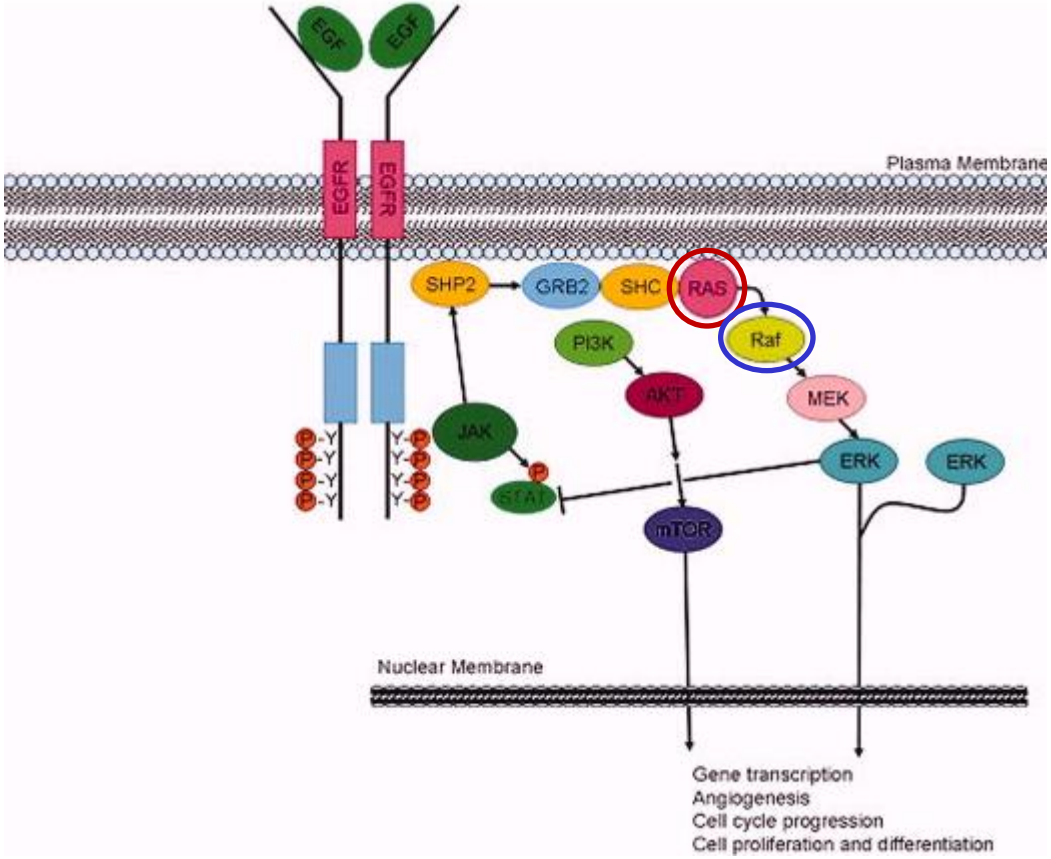
Positive Predictive Biomarker
- Trastuzumab therapy in breast cancer



Positive Predictive Biomarker
- *HER2* amplification and trastuzumab therapy in breast cancer

Study and *HER2* Amplification	No. of Assessable Patients	Objective Response (CR plus PR)	
		No.	%
H0649g			
FISH positive	173	33	19
FISH negative	36	0	0
H0650g			
FISH positive	82	28	34
FISH negative	29	1*	3.5

Negative Predictive Biomarker
- *K-Ras* and *B-Raf* Mutation in Colorectal Cancer



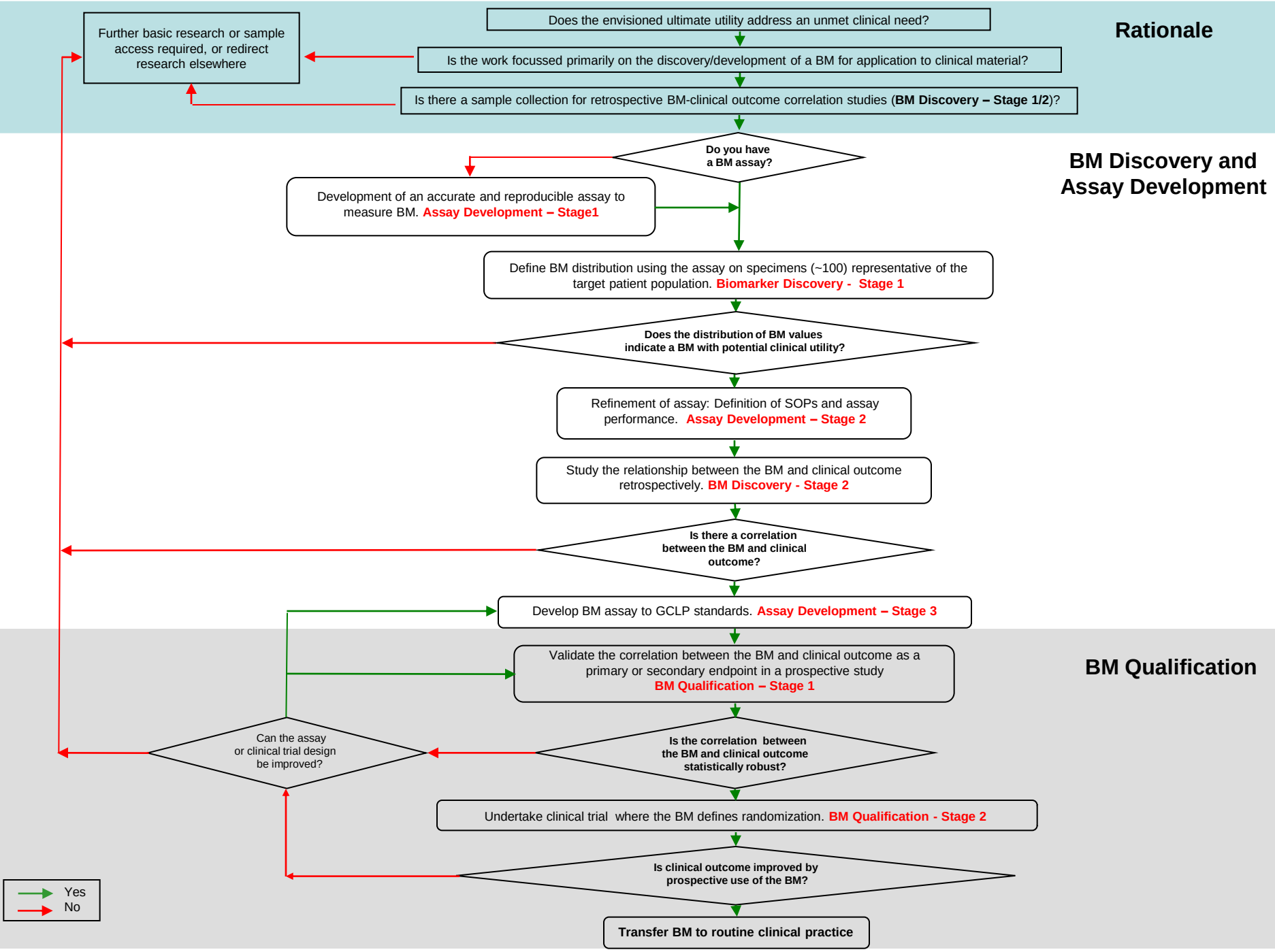
- ***K-Ras*** is mutated in 30-50% of colon cancer
- ***B-Raf*** is mutated ca. 10% of colorectal cancers
- Mutant *K-Ras* is a negative prognostic biomarker in colorectal cancer

Negative Predictive Biomarker
- *K-ras* mutation and EGFr-targeted antibody therapy in colorectal cancer

Study	Drugs	Size	WT K-*ras*	Mut K-*ras*	p =
Personeni	C +/- irinotecan	54	22%*	0%	0.05
Finocchiaro	C	81	27%	6%	0.02
De Rook	C +/- irinotecan	37	22%	0%	<0.01
Viret	C+irinotecan	32	22%	6%	NS
Stoehlmacher	C + irinotecan or +FOLFOX/FIRI	30	56%	0%	<0.01
Amado	Panitumumab	427	17%	0%	-
Van Cutsem	C + FOLFIRI	540	59%	36%	-
Bokeneyer	C + FOLFOX	233	61%	33%	-
Tejpar	C + irinotecan	148	46%	0%	-

C = Cetuximab, NS = not significant, ND = not determined, * % = response rate

PROGNOSTIC/PREDICTIVE BIOMARKER (BM) ROADMAP



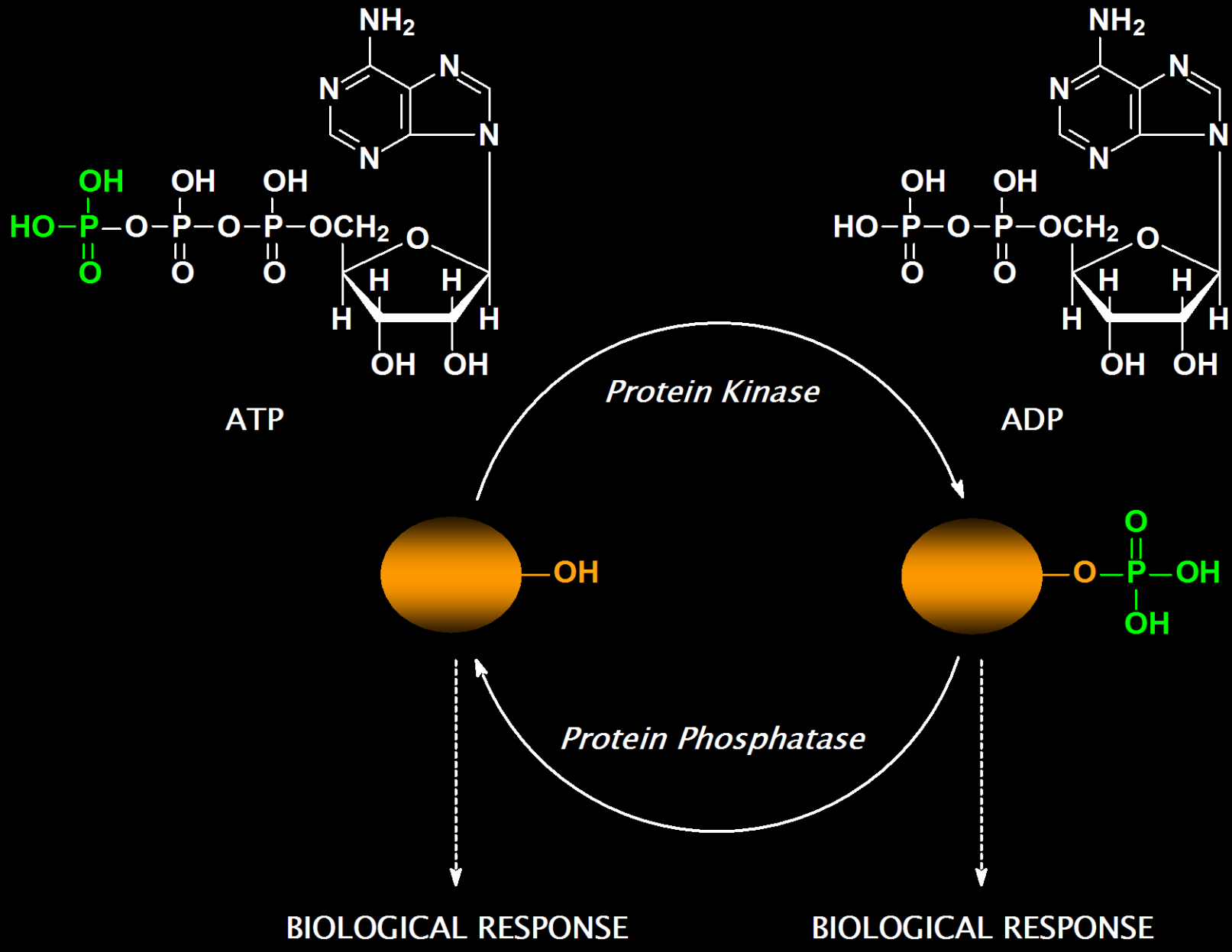
Clinically Established Predictive Biomarkers for Targeted Therapies

- **Positive Predictive Biomarkers**
  - *Her2/c-ErbB2* amplification: Trastizumab, lapatinib in breast cancer
  - *EGFr* mutation: Gefitinib, erlotinib in non-small cell lung cancer
  - *c-Kit* mutation: Imatinib in GIST
  - *Alk* amplification/translocation: Crizotinib in lymphoma/lung cancer
  - *B-Raf* mutation: Vemurafenib in melanoma
  - *Bcr-Abl* translocation: Imantinib, dasatinib, nilotinib in CML/ALL
  - Oestrogen receptor expression: Anti-oestrogens in breast cancer
  - *RAR* translocation: All-*trans*-retinoic acid in PML
- **Negative Predictive Biomarkers**
  - *K-Ras/B-Raf* mutation: Cetuximab, panitumumab in colorectal cancer

Biomarkers in Early Phase Trials with Targeted Therapies in Cancer

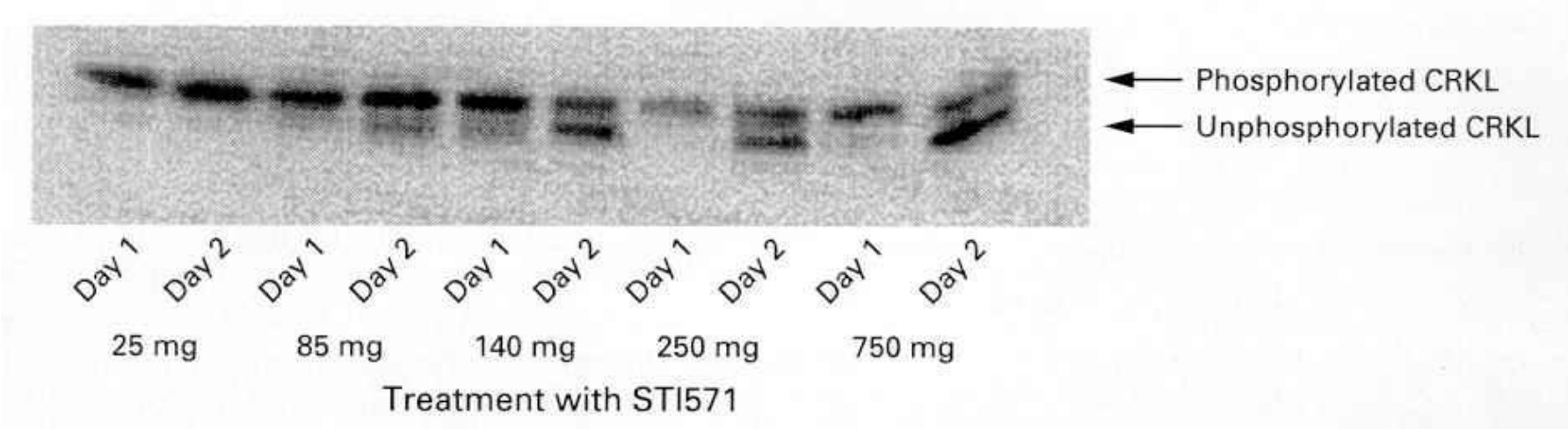
- Predictive biomarkers
  - Does the tumour have the target and is it functional?
- Pharmacokinetic biomarkers
  - Are active drug levels achieved?
- Pharmacodynamic biomarkers
  - Proof of mechanism (POM)
    - Does the drug hit its target?
  - Proof of concept (POC)
    - Is the required effect on tumour biology produced?
- Surrogate response biomarkers
  - Is the patient going to benefit?

Mechanism of Action of Protein Kinases

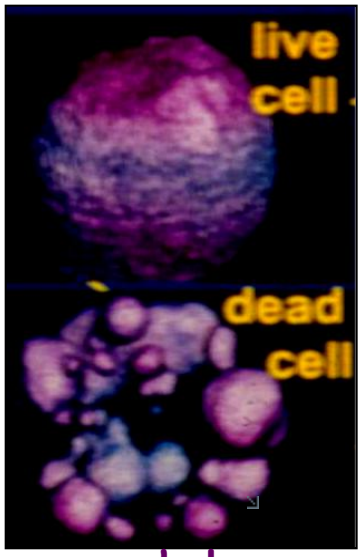


Imatinib - POM PD Biomarker

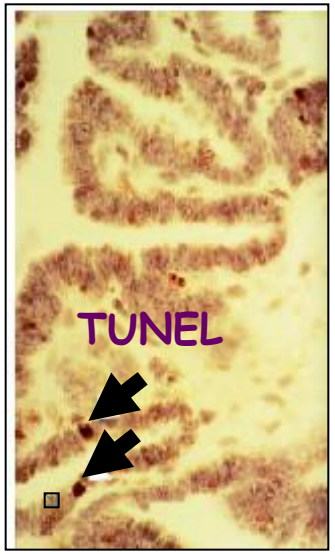
Proof-of-mechanism (POM) pharmacodynamic biomarker - inhibition of CRKL phosphorylation

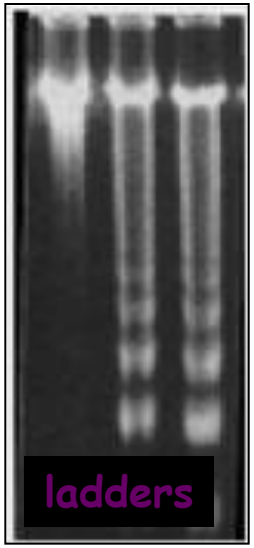


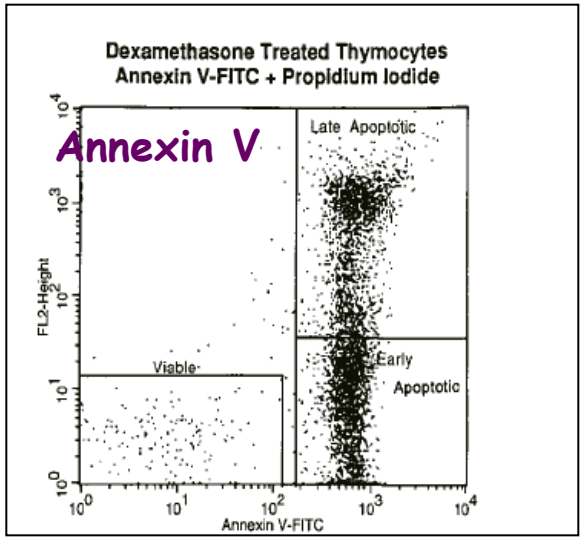
POC PD Assays for Apoptosis Induction by Targeted Agents

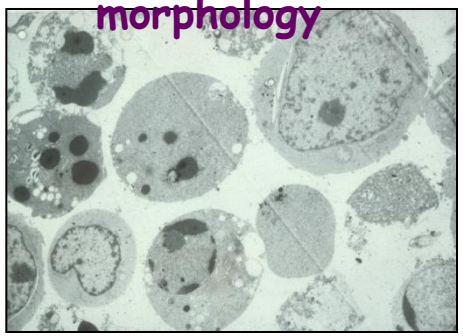


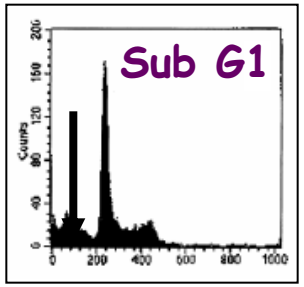
morphology

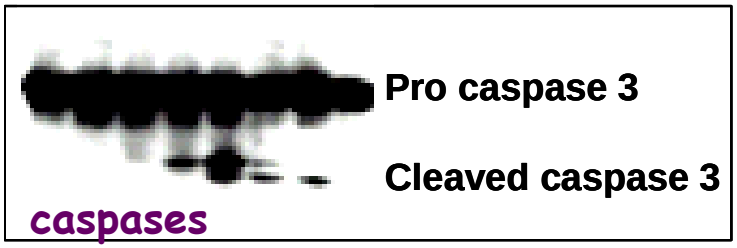






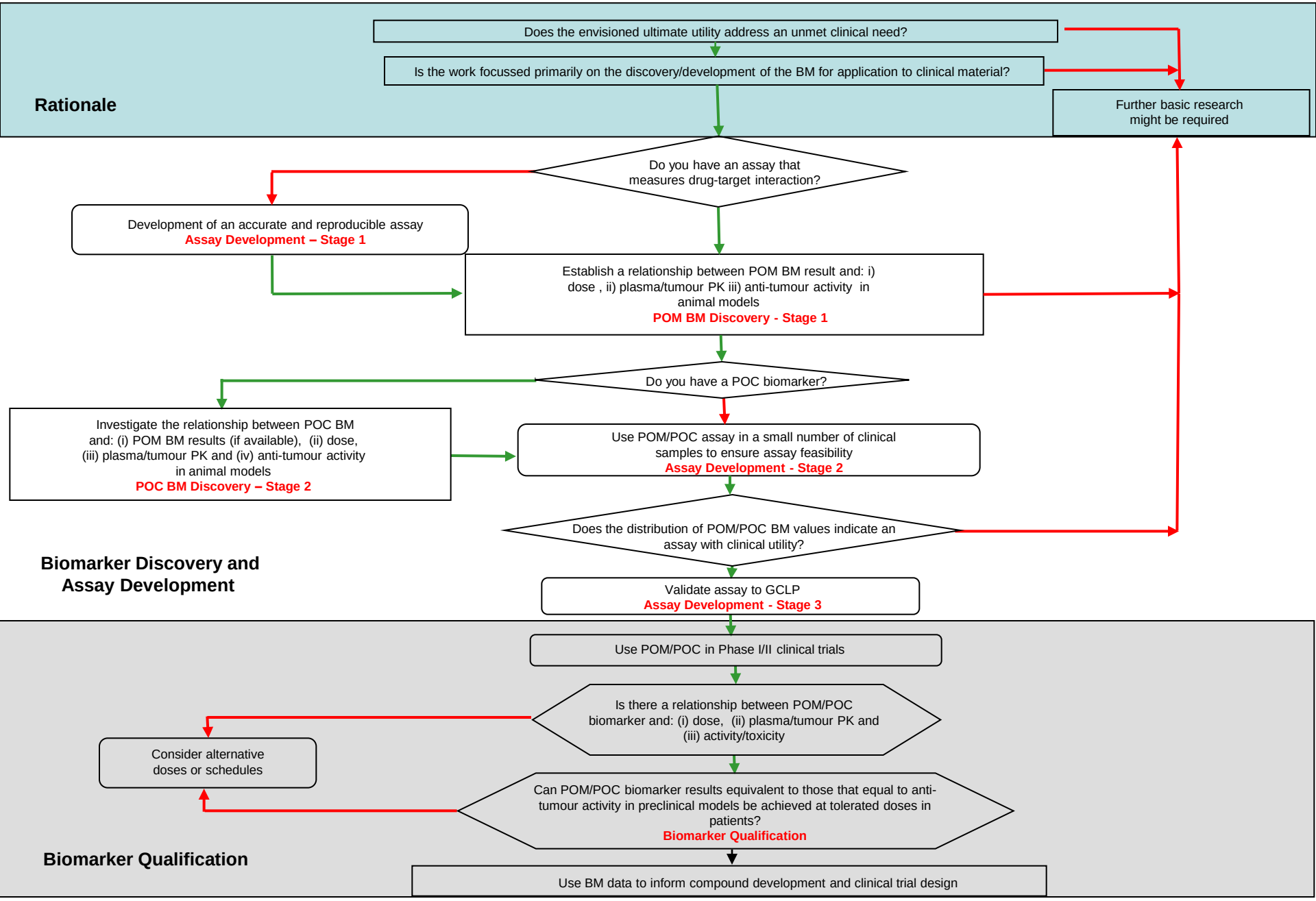






Courtesy of Professor Caroline Dive, Paterson Institute, Manchester

PHARMACOLOGICAL BIOMARKER (BM) ROADMAP



Biomarkers in Cancer Management

Is the treatment working?

Surrogate response biomarkers - Early prediction of ultimate clinical efficacy

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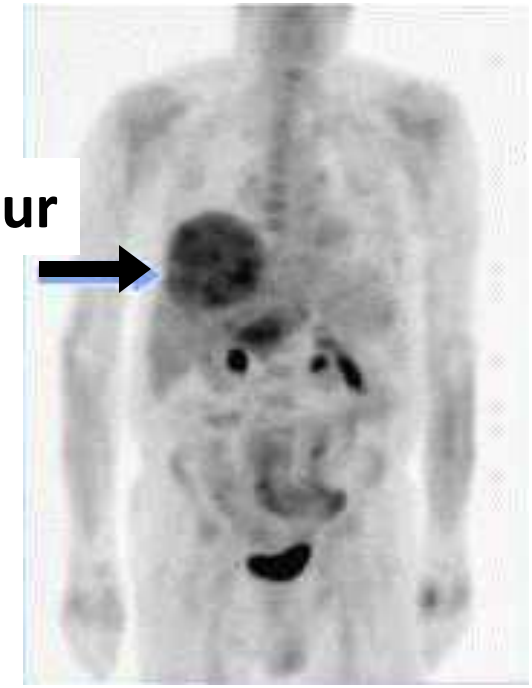
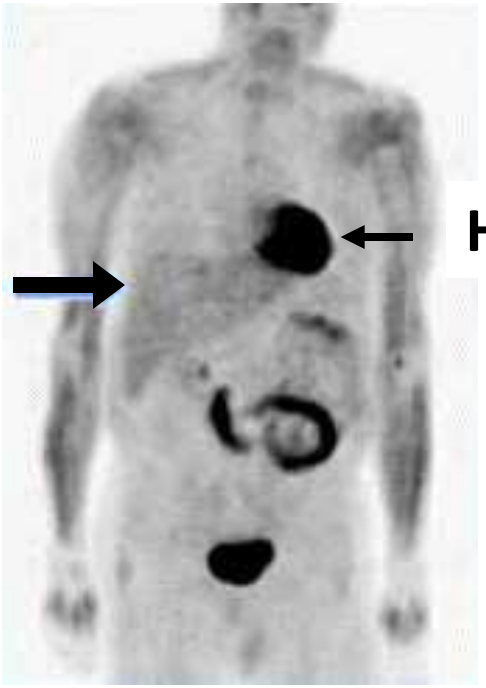
^{18}F-Fluorodeoxyglucose PET Scanning in GIST as a Surrogate Response Biomarker – Imatinib Therapy

PET Scans **Tumour**

1 month apart

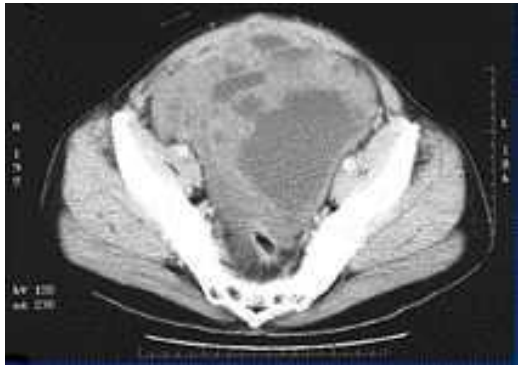


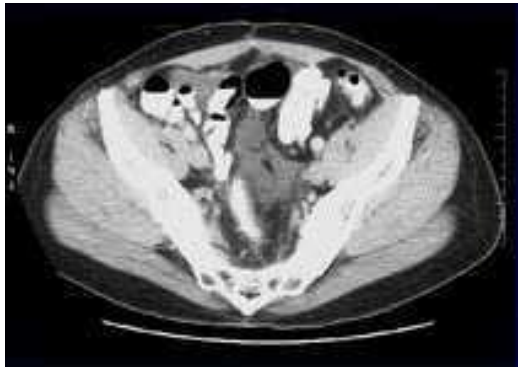


Heart

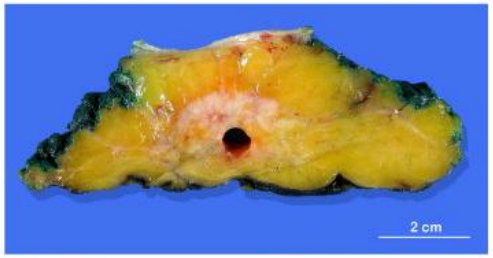
CT Scans

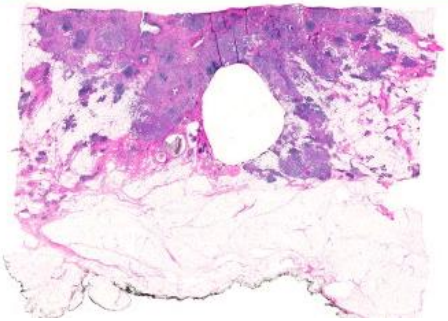
6 months apart





Biomarker Approaches



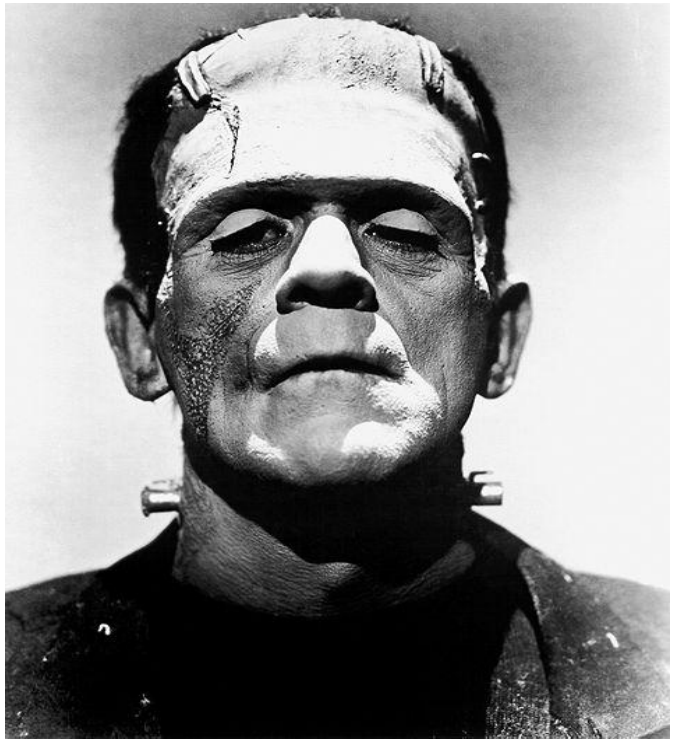


- **Invasive**
  - Tumour biopsy
  - Normal tissue biopsy
  - Blood borne

- **Non-Invasive (Imaging)**
  - MR
  - PET
  - Others (SPECT, ultrasound, etc)

Targeted Therapies and Stratified Medicine - Science fact *NOT* science fiction

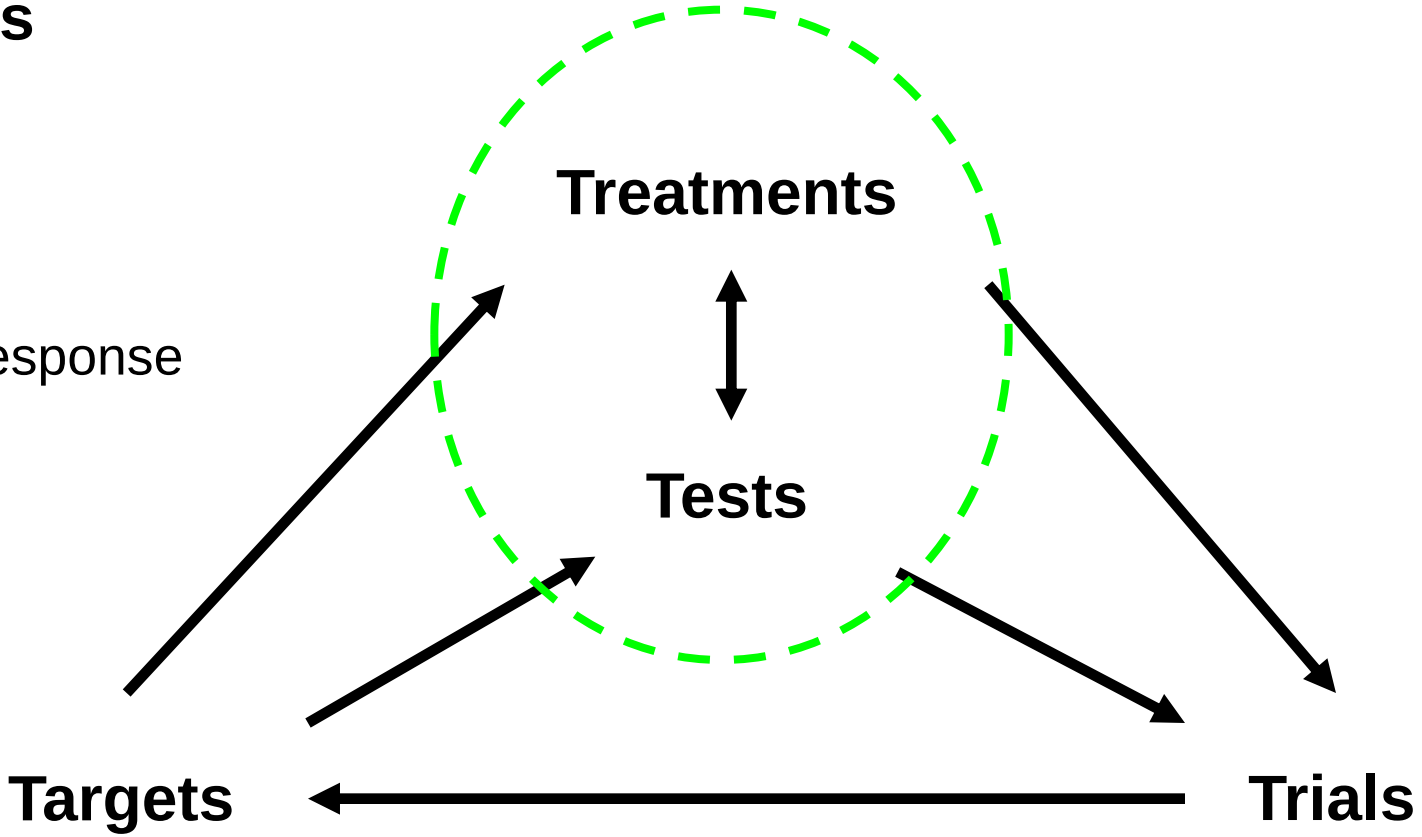
- **Growth factor and receptor antagonists**
  - Bevacizumab, cetuximab, crizotinib, gefitinib, erlotinib, rituximab, sorafinib, sunitinib, trastuzumab
- **Second messenger or signal transduction inhibitors**
  - Imatinib, dasatinib, nilotinib, sorafinib, vemurafenib
- **Regulators of gene expression**
  - All-*trans* retinoic acid
  - SAHA
  - Anti-estrogens and anti-androgens



Predictive, Pharmacological and Surrogate Response Biomarkers for Stratified Medicine with Targeted Therapies in Cancer

Biomarkers

- Predictive
- PK
- PD – POM
- PD - POC
- Surrogate response



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