Institute of Clinical Pharmacology

The gap between biomarkers and surrogate endpoints

Oncology

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The Promises of Biomarkers

- In 2004 more that 30,000 papers dealing with biomarkers have been published
- Biomarkers are a child of the genomics technologies
  - reduce risk in drug development (pharma)
  - improve patient outcomes (healthcare providers)
- Activities
  - earlier diagnosis
  - patient stratification
  - assessment of drug toxicity and efficacy
  - disease staging
  - disease prognosis

Definitions
(NIH Definitions Working Group)

- **Biomarker**
  A characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic processes to a therapeutic intervention.

- **Clinical endpoint**
  A characteristic or variable that measures how a patient feels, functions, or survives.

- **Surrogate endpoint**
  A biomarker intended as a substitute for a clinical endpoint.

Types of Biomarkers

- **Translation Biomarker:** a biomarker that can be applied in both a preclinical and clinical setting.
- **Disease Biomarker:** a biomarker that relates to a clinical outcome or measure of disease.
- **Efficacy Biomarker:** a biomarker that reflects beneficial effect of a given treatment.
- **Staging Biomarker:** a biomarker that distinguishes between different stages of a chronic disorder.
- **Surrogate Biomarker:** a biomarker that is regarded as a valid substitute for a clinical outcomes measure.
- **Toxicity Biomarker:** a biomarker that reports a toxicological effect of a drug on an *in vitro* or *in vivo* system.
- **Mechanism Biomarker:** a biomarker that reports a downstream effect of a drug.
- **Target Biomarker:** a biomarker that reports interaction of the drug with its target.

Prognostic biomarkers used in oncology drug development

Name	Definition	Examples
Biological progression markers	Measurements of cellular proteins associated with tumour appearance or progression Measures of tumour burden	CEA, FP, CA-125 (Rustin response criteria), hCG, PSA (e.g., PSA-DT)
Risk markers	Risk markers Describe risks of cancer occurrence or cancer progression	Somatic mutation, amplification and overexpression of oncogenes and tumour suppressor genes (e.g., PTEN, BCR-ABL, HER-2/neu, RAS, AKT) Aneuploidy Genetic predisposition (e.g., APC, BRCA1/2, MLH1, MSH2, Li-Fraumeni syndrome, ataxia telangiectasia) Genetic polymorphisms (e.g., CYP1A1, GSTM1, GSTP1, SRD5A2) DNA methylation Environmental and lifestyle (e.g., HPV or HBV infection, tobacco use) Multifactorial risk model (e.g., Gail model for breast cancer risk)

Kelloff, 2005

Predictive biomarkers used in oncology drug development

Name	Definition	Examples
Drug effect/ pharmacodynamic markers	Biological effects produced by a drug that may or not be directly related to neoplastic process	Effect on molecular target (e.g., EGFR inhibition, RAS farnesylation inhibition)
		Induction of enzyme activity relevant to drug toxicity (e.g., CYP1A1, CYP1A2)
		Functional (and molecular) imaging of drug interaction at target tissue
Cellular, histopathological, and imaging biomarkers	Biological effects occurring during neoplastic progression (causally related to cancer)	Quantitative pathology or cytology of cancers, precancers, high-risk tissue
		Anatomical imaging (e.g., MRI, CT)
		Functional imaging (e.g., FDG-PET)
		Genomic and proteomic expression profiles
		Proliferation biomarkers (e.g., PCNA, Ki-67)
		Apoptosis biomarkers (e.g., BCL-2 expression, TUNEL)
		Differentiation biomarkers (e.g., cytokeratins)

Kelloff, 2005

Clinical correlates: surrogate endpoint biomarkers used for evaluation of oncologic drugs and biological products

- Objective Response/ Response Rate
- Time to Progression
- Disease free survival or time to recurrence
- Progression-free survival
- Quality of life, symptom improvement, composite endpoints
- Intraephithelial neoplasia

  IEN are precancers that are treated by drug therapy or surgical removal. Regression of existing or preventiion of new IEN have been considered for supporting approval of drugs to prevent cancers or to treat precancers

Kelloff, 2005

There are already several tumor associated Markers with (proven?) predictive value

- ß-HCG (Choriocarcinoma)
- ß-HCG (Testicular Tumors)
- AFP (Testicular Tumors)
- AFP (Hepatocellular Carcinoma)
- Calcitonin (Medullary Thyroid Carcinoma)
- Thyroglobulin (Differentiated Thyroid Cancer)
- PSA (Prostate Cancer)
- .....

What' s to learn from Prostate Specific Antigen (PSA) Vicini 2004

- Purpose: Metaanalysis of more than 30 published studies monitoring serum prostate specific antigen (PSA) after treatment with surgery or radiation therapy (RT) for nonmetastatic prostate cancer.
- In spite of a high number of studies no cutoff value for prediction of therapy failures (within a 5 year period) can be given
  - Up to 25% failures
  - Biochemical failures do not correlate with clinical failures
- Conclusions: The overall benefit of monitoring serum PSA after treatment for prostate cancer remains controversial.

  … additional studies must be done to determine the appropriate use of this marker in properly treating patients after therapy.

Actually the expectation from Biomarkers / Predictive Medicine are different

Pharma

- Rational identification and validation of novel targets
  - Early POC/P
  - Modeling simulation
- Identification of real target population
- Identify drug candidates which can be developed **early**
  - Reduce attrition rates in late phases
- Theranostics?

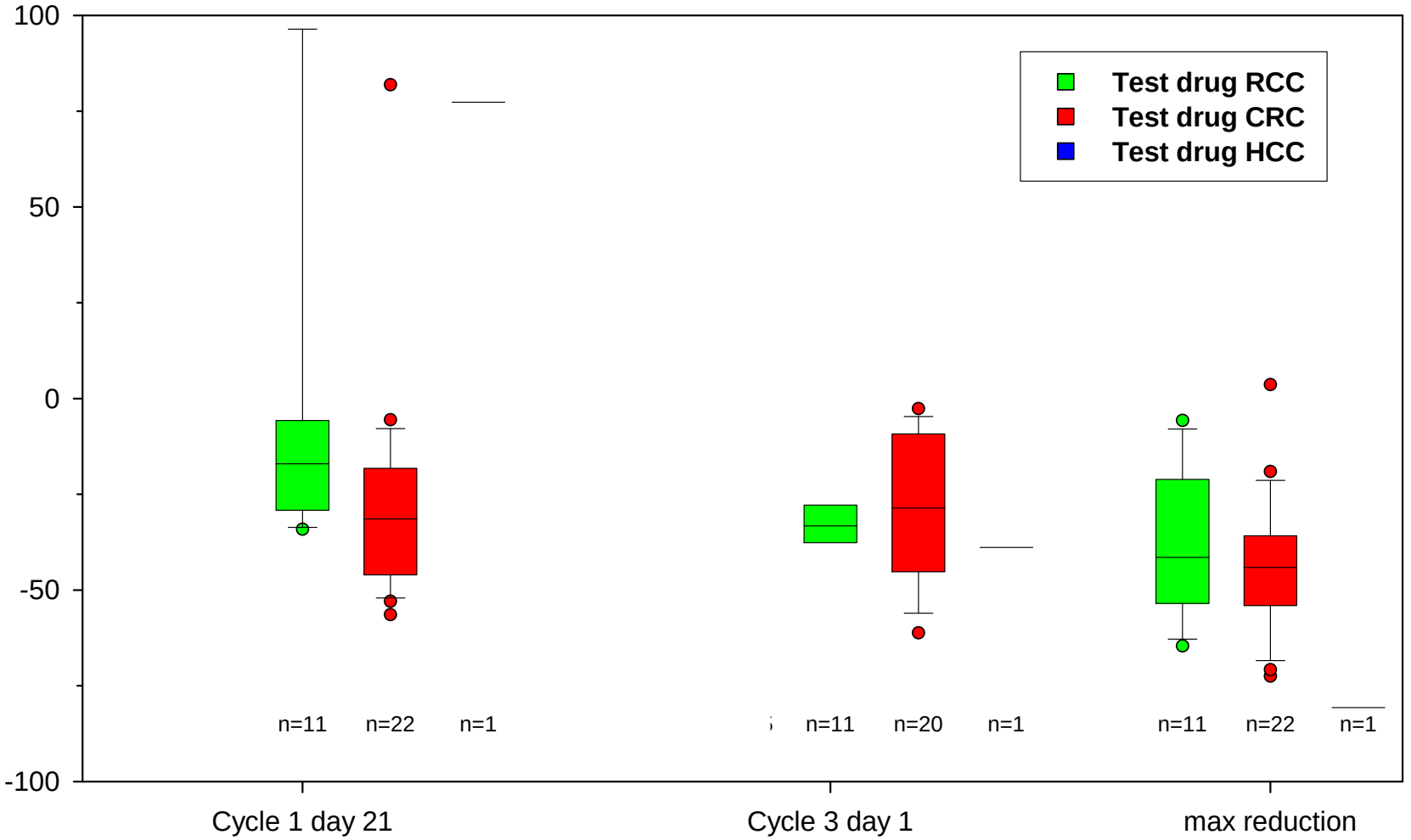
Clinics

- Identification of real target population
  - Treat responders
  - Prohibit treatments at risk
- High response rates from start of therapy
- Rational use of rationed therapies
- Theranostics

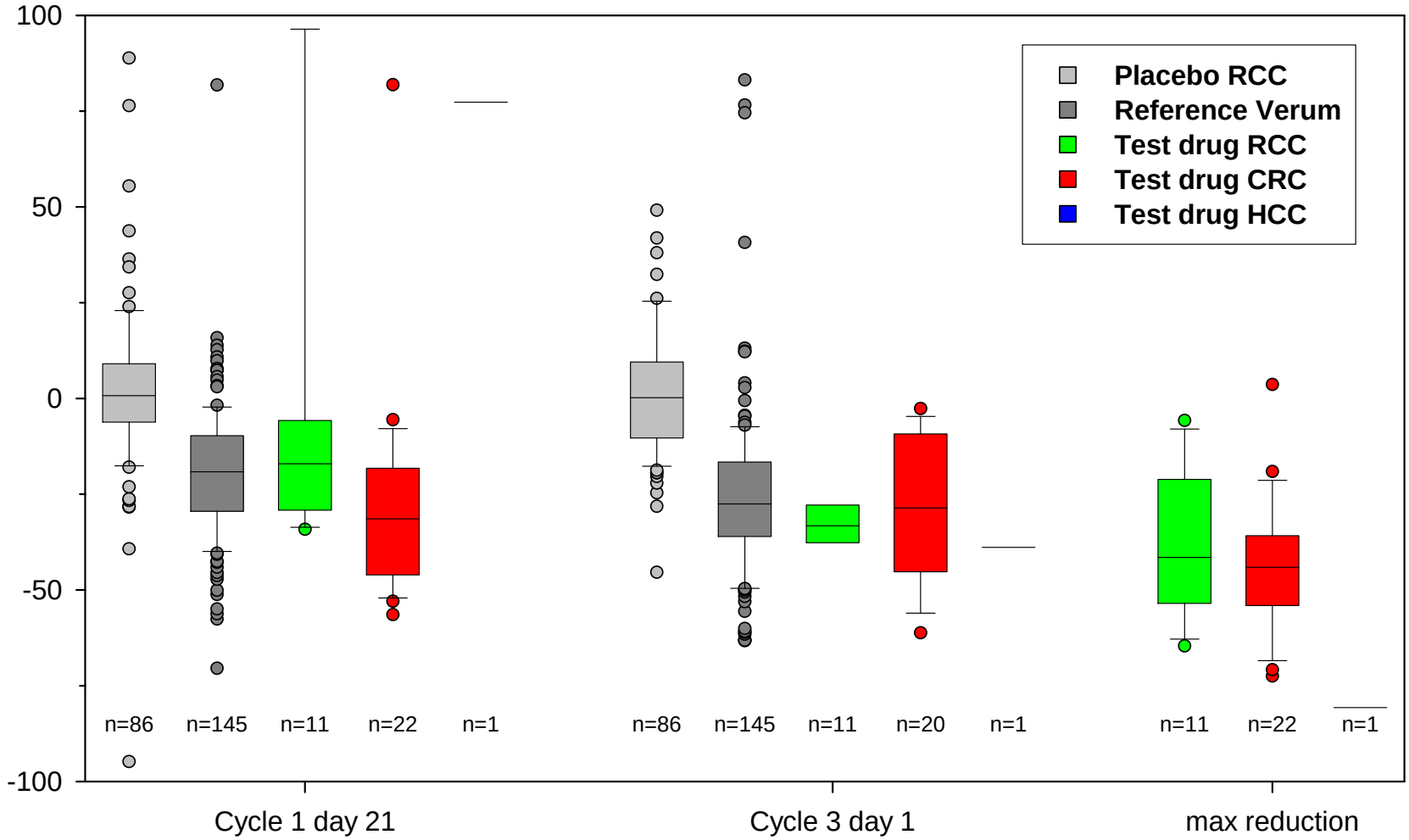
Biomarker

Surrogate

Development of a new Biomarker to enable drug comparison / therapy monitoring?



Development of a new Biomarker to enable drug comparison / therapy monitoring?



Validity

- A biomarker is valid(ated) if
  - It can be measured in a test system with well established performance characteristics
  - Evidence for its clinical significance has been established
- Or is a biomarker already validated when he is useful?

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Recommendations for a genetic test to enter clinical practice

- Technology must have final approval from appropriate governmental regulatory bodies.
- The scientific evidence must permit conclusi… effect of the technology on health outc…
  - Evidence is evaluated on quali… …s.
  - Technology can measu… …se.
  - Evidence must d… …rements affect outcomes…
- The t… …net health outcome.
- … …beneficial as any established c…
- Th… …ent must be attainable outside the investigational setti…s.

Or is a biomarker already validated when he is useful?

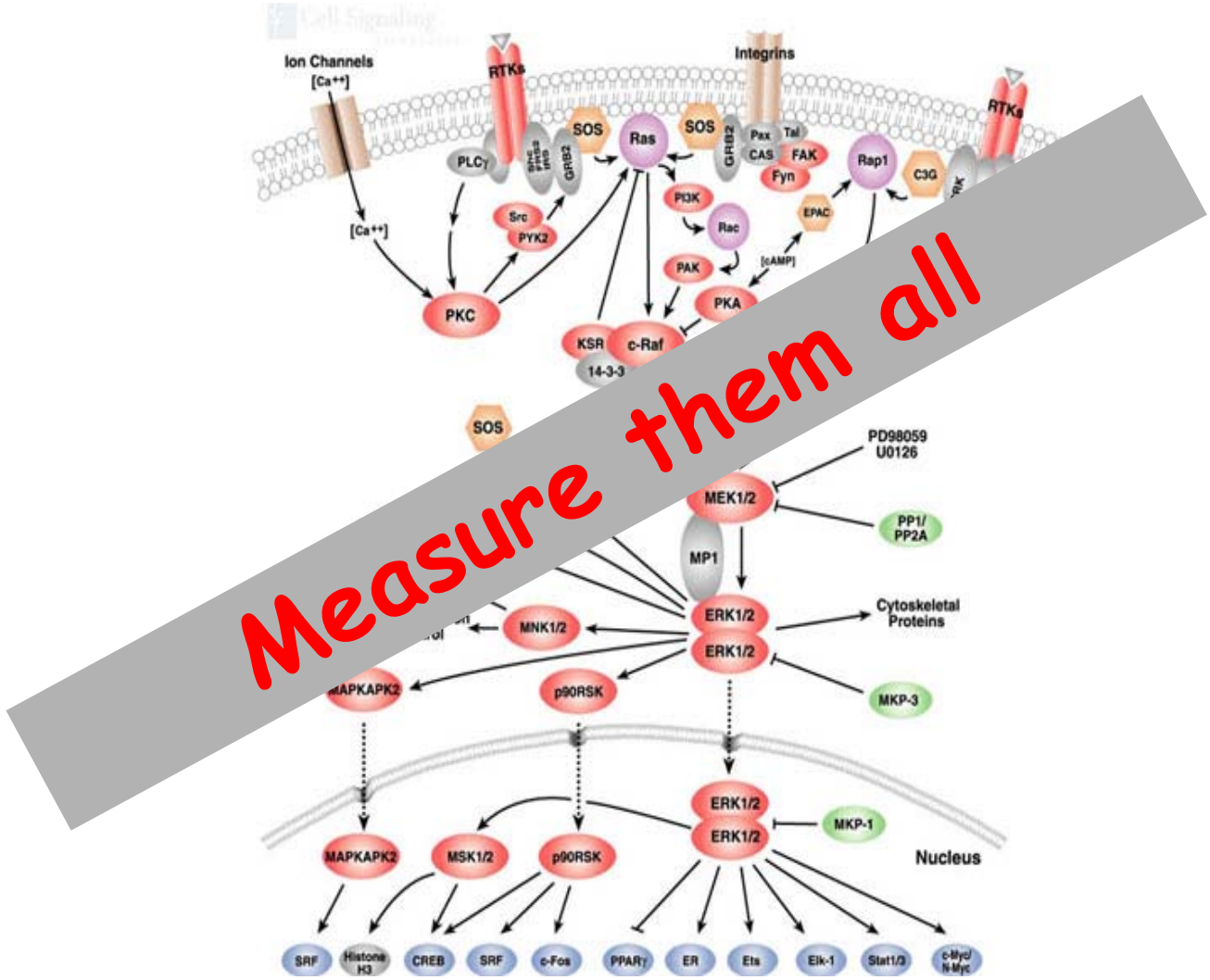
Confounding factors and bias why biomarker studies fail

- Accuracy of phenotype (disease) is critical
  - All patients must have same disease
  - Several causes lead to the same phenotype
- Inappropriate Dx method
- Inappropriate sample sizes / control groups
- Most diseases are multifactorial by nature (phenotype is affected by variants in numerous genes)
- The same biomarker signature can result in different phenotypes due to the effects of age, sex, environment, concomitant diseases, nutrition, comedication….

Cancer is a multifactorial disease and biomarker analysis has to reflect this

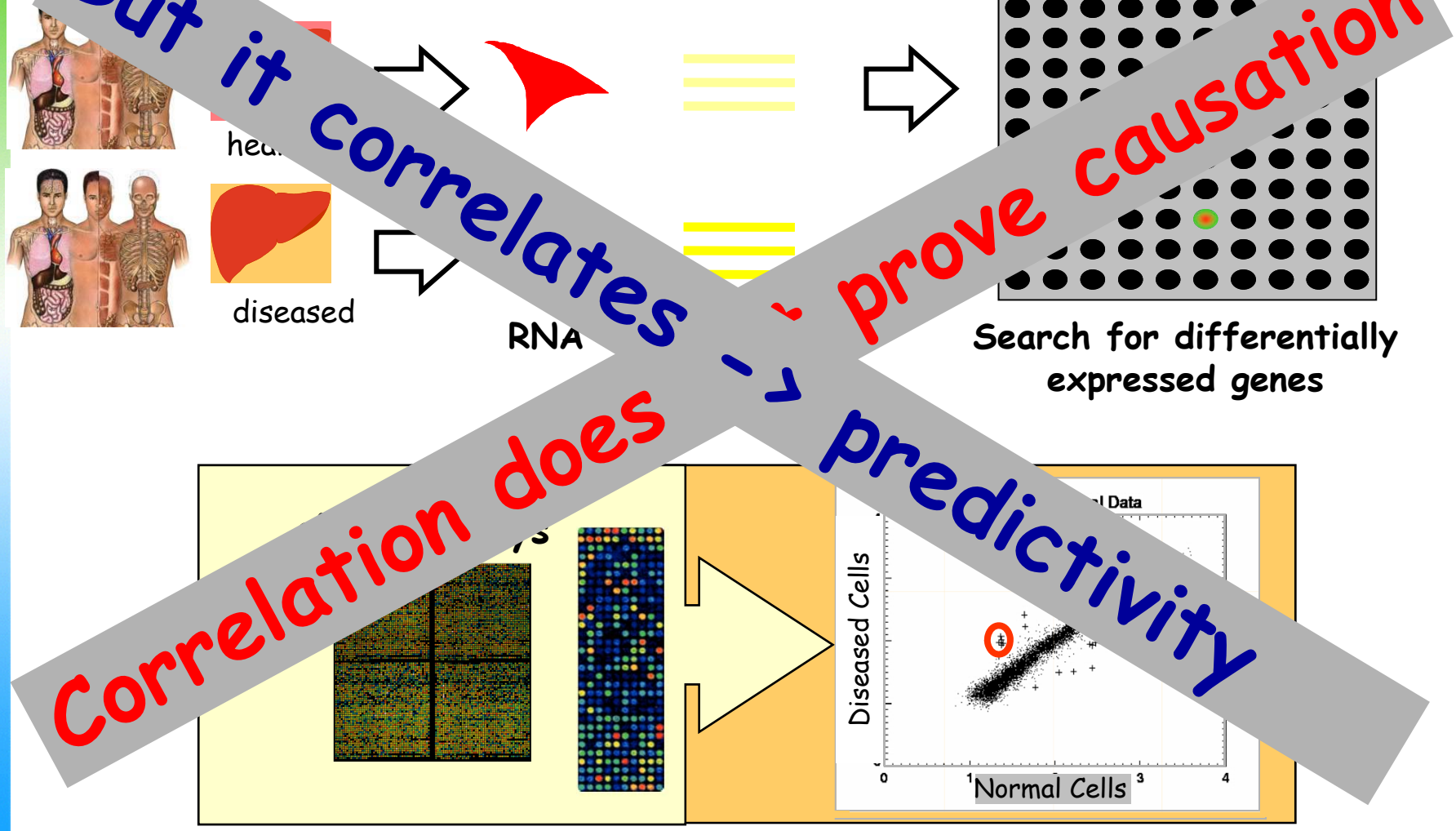
- DNA adducts
- DNA damage
- DNA replication
- Angiogenesis
- Apoptosis
- Behavior
- Cell cycle
- Cell signaling
- Development
- Gene regulation
- Immunology
- Metabolism
- Metastasis
- Miscellaneous
- Pharmacology
- Signal transduction
- Transcription
- Tumor Suppressor/ Oncogenes

Biomarkers may be organized in Regulatory Pathways



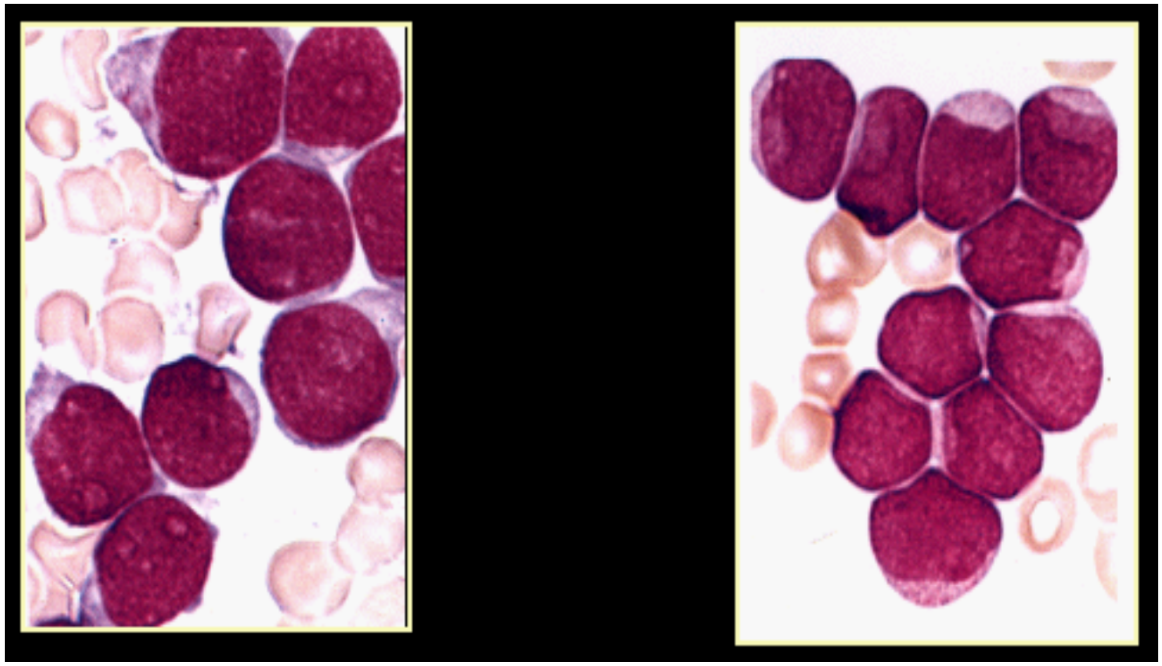
Measure them all

Actual Target Identification using Genomic Technologies



Proof of Concept: Acute Leukemia Diagnosis

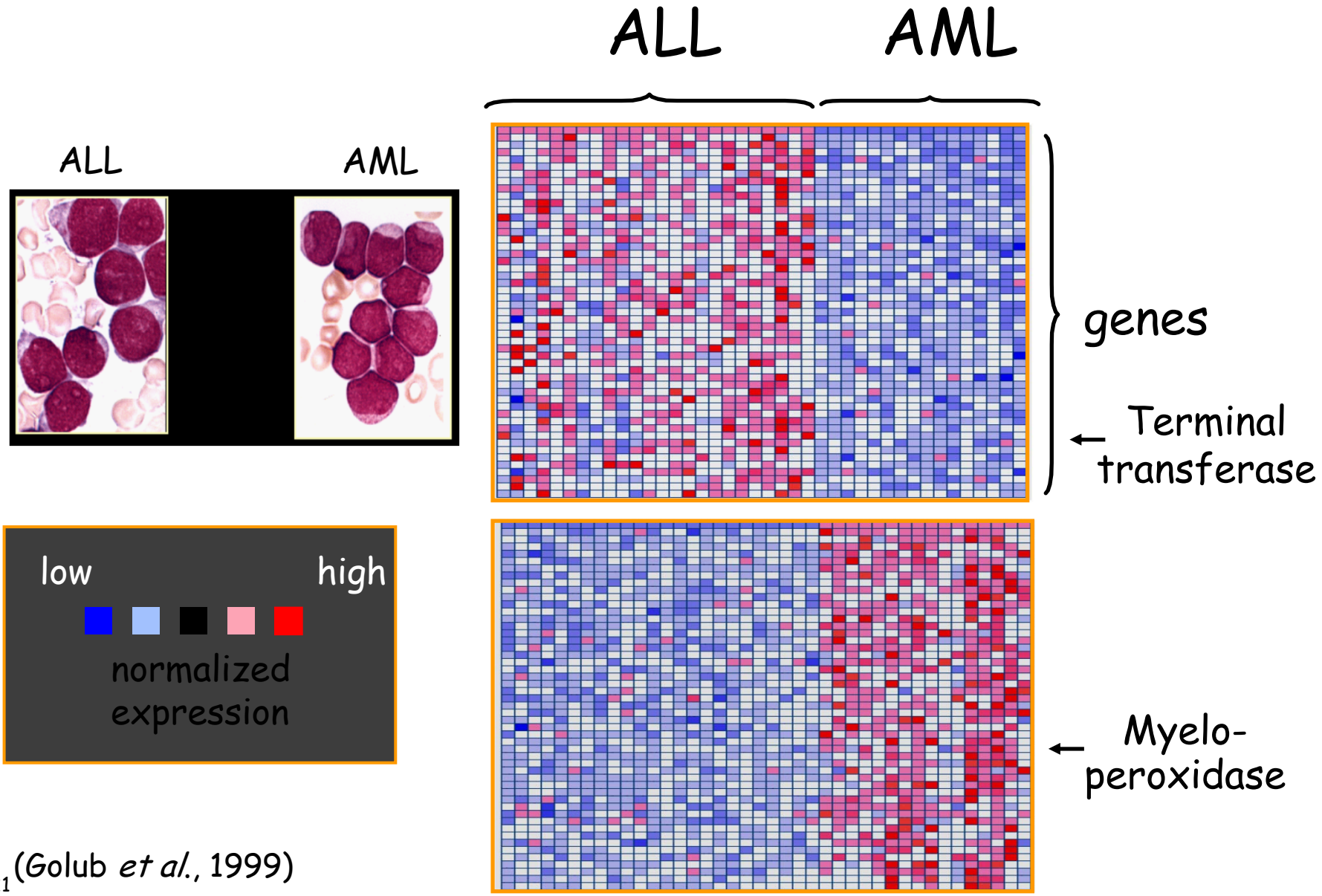
ALL AML



Molecularly distinct tumors are morphologically similar

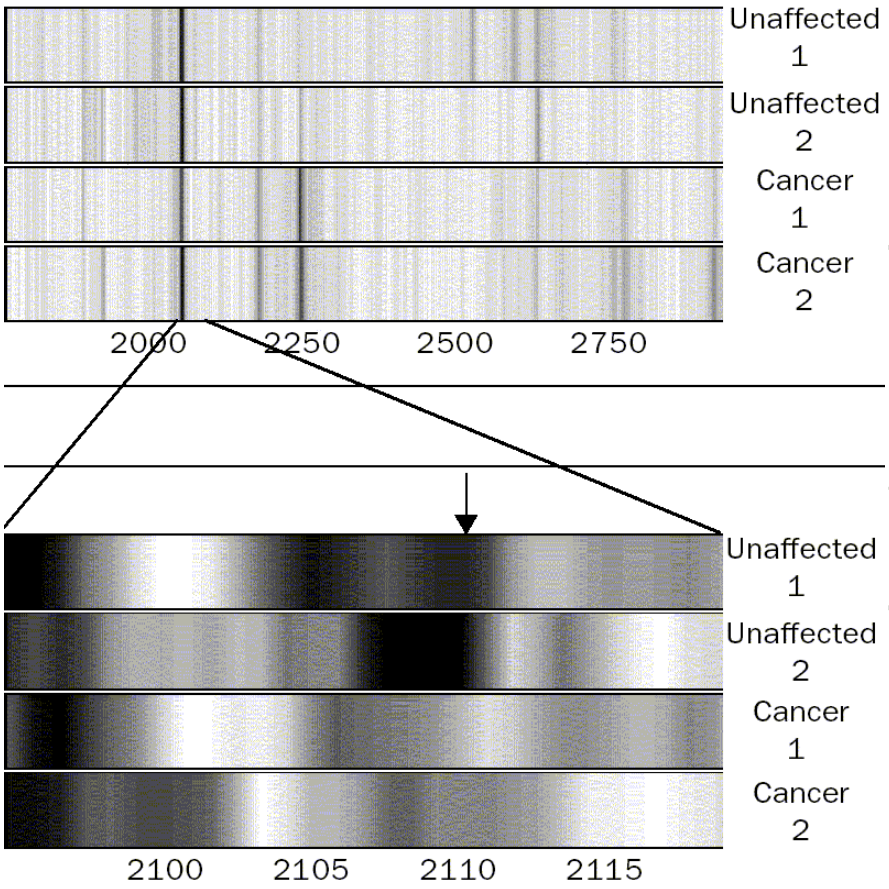
(Golub *et al.*, 1999)

Gene Expression Correlates of Leukemia
Genes sorted according to correlation with ALL/AML distinction



(Golub *et al.*, 1999)

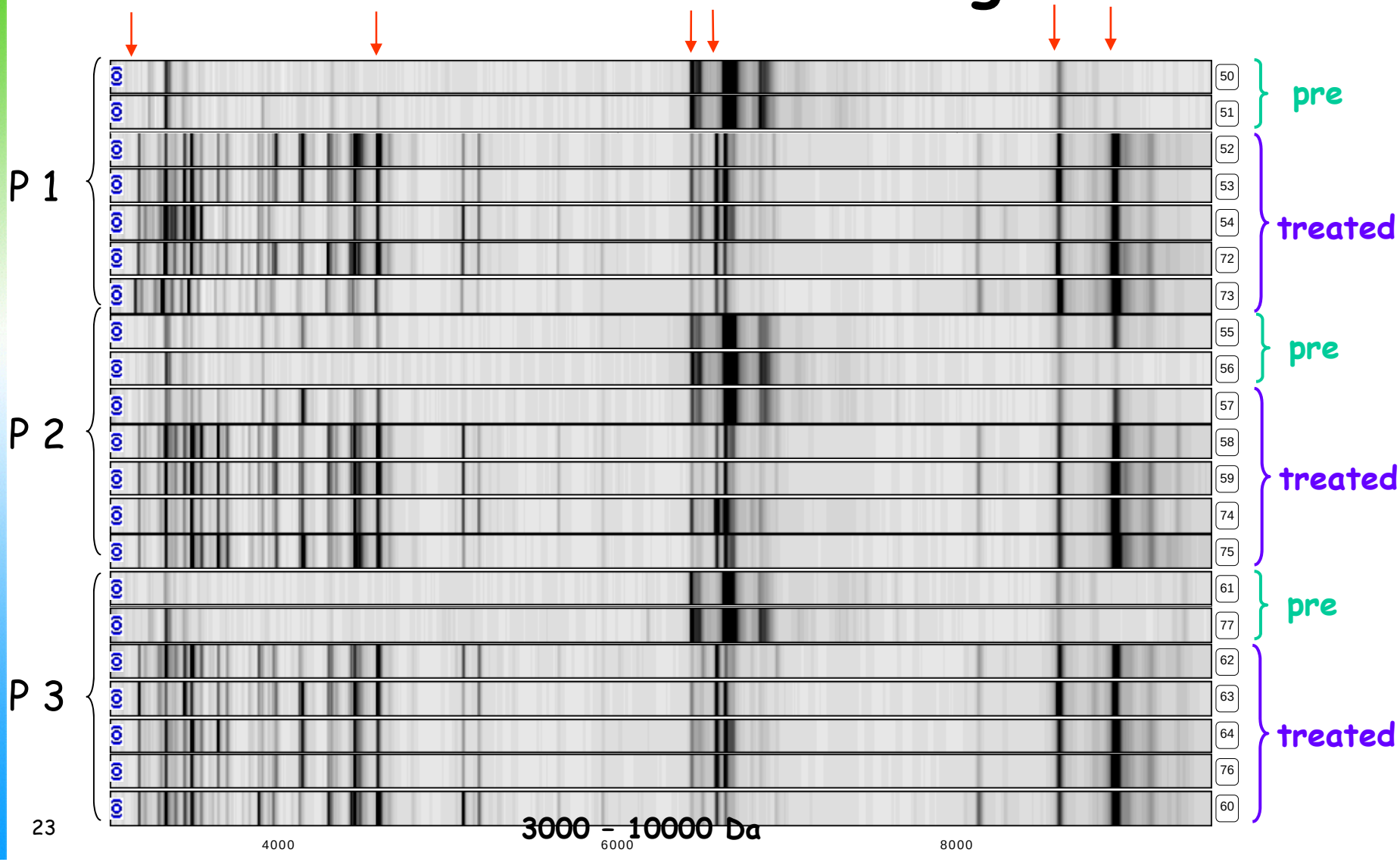
Proteomics can be used for predictive biomarker screening



	Classification by proteomic pattern		
	Cancer	Unaffected	New cluster
Unaffected women			
No evidence of ovarian cysts	2/24	22/24	0/24
Benign ovarian cysts <2·5 cm	1/19	18/19	0/19
Benign ovarian cysts >2·5 cm	0/6	6/6	0/6
Benign gynaecological disease	0/10	1/10	9/10
Non-gynaecological inflammatory disorder	0/7	0/7	7/7
Women with ovarian cancer			
Stage I	18/18	0/18	0/18
Stage II, III, IV	32/32	0/32	0/32

Petricoin, 2002

Proteomics profiles from a pilot study already revealed several potential biomarkers to monitor drug effects



Biomarker driven development/ Predictive medicine
Why will it start in oncology?

Clinics

- Cancer is a family of complex and heterogeneous diseases
- Oncologists are specialists
- Awareness of new technologies (eg. Genotyping)
- Oncology deliver clear quality of life benefits & survival periods
- Efficacy and safety of established therapies is low (20-40%)
- Narrow therapeutic index of conventional drugs

Market

- Subsets of cancer patients are small, new Rx aimed for them would not threat the blockbusters
- High competitive pressure (several drugs in several pipelines)
- Reimbursement easier for Rx with clear cost-benefit ratios (pricing)
- High public awareness that cancer is an increasing disease
- Possibility for pharma companies becoming a niche leader

Herceptin is an example for a targeted therapy

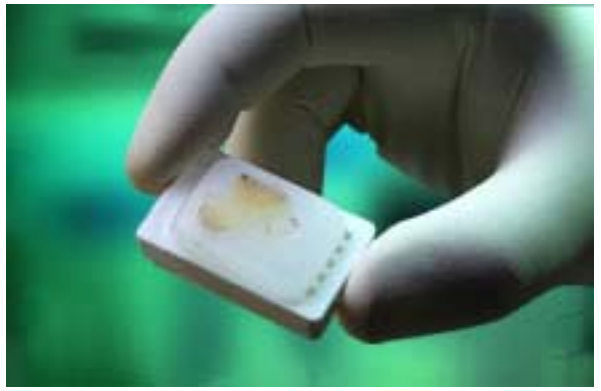
- Herceptin (Trastezumab) is a monoclonal Antibody against the her2/neu receptor
- HER-2 is over expressed or amplified in 25-30% of all women with breast cancer
- Herceptin is efficacious in ~20% of HER-2 positive patients
- The overall response rate in total target population is about 5%
  - Three diagnostic tests FDA approved (costs < $100)
  - Screening valuable until > 1.5% responders (est. treatment costs are $7000 per patient)

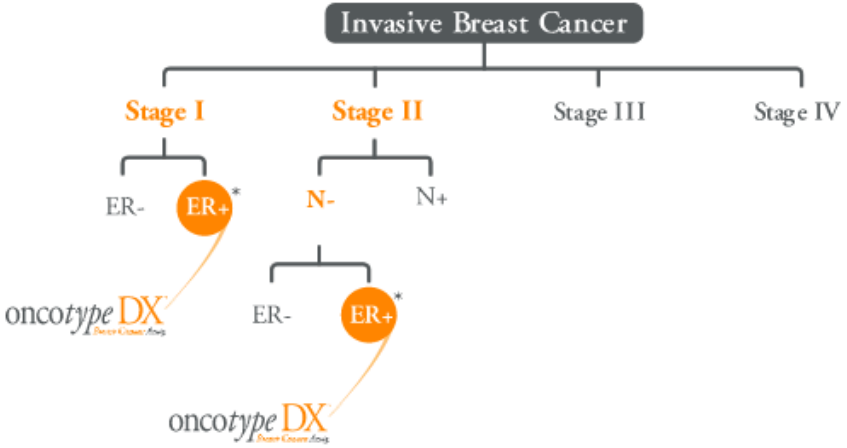
Oncotype offers a Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

21 genes are investigated in paraffin-embedded tumor tissue via RT-PCR

Goals

- Predicting distant disease recurrence
- Identify patients best benefiting from treatments
- Avoiding adverse events in those who will not benefit





Iressa is an example for targeted medicine

WALL STREET JOURNAL. , May 5, 2005. *CANCER DRUG DEEMED FAILURE, HELPS ASIANS*

"Iressa as proved effective at treating lung cancer in Asian patients, even as it flopped in helping Caucasians, Blacks and just about everyone else…..through a curious quirk in medicine. Asians respond well to therapy because they have a certain genetic mutation in their cancer cells that Iressa is good at targeting….."

"…..As a result, Astra-Zeneca which initially planned big sales of Iressa in the US, is now adjusting its marketing plan to focus on Japan, China and other Asian markets."

Conclusions

- High density biomarker data will change our view on disease, medicine and impact on research and drug development
- Complexity is to be expected
  - Low responder rates and nowadays low toxicity
- "Complex" multiplexing technologies will be the tools (Genomics, Transcriptomics, Proteomics, Metabonomics…)
- Validation is crucial (tools and profiles)
- Classical Anamnesis together multiplexed assays will become the new gold standard?
- Good statistical planning is crucial for the outcome of "Predictive Medicine" studies.

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Back-ups

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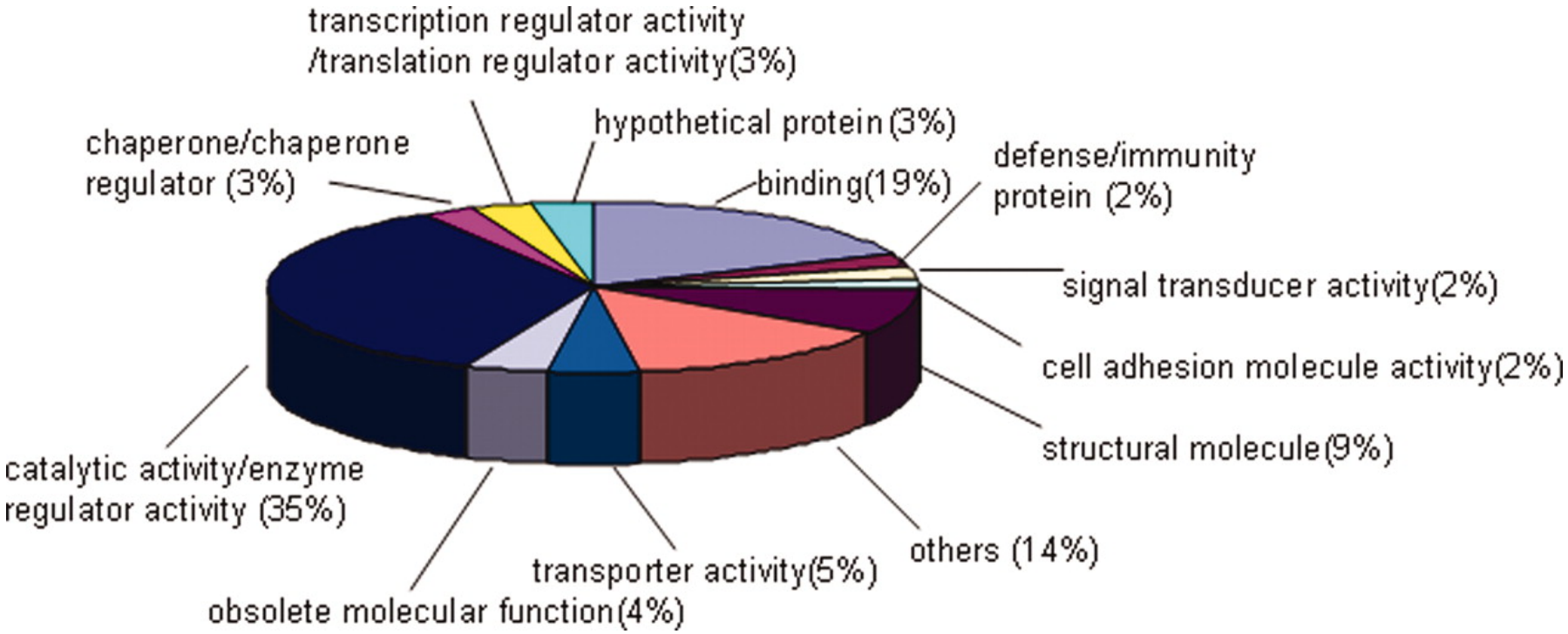
BPS analysis results of Tree2

Prediction Success

Group	# samples	% correct	post N=143	pre N=54
post	**152**	**84**	**128**	**24**
pre	**45**	**76**	**11**	**34**

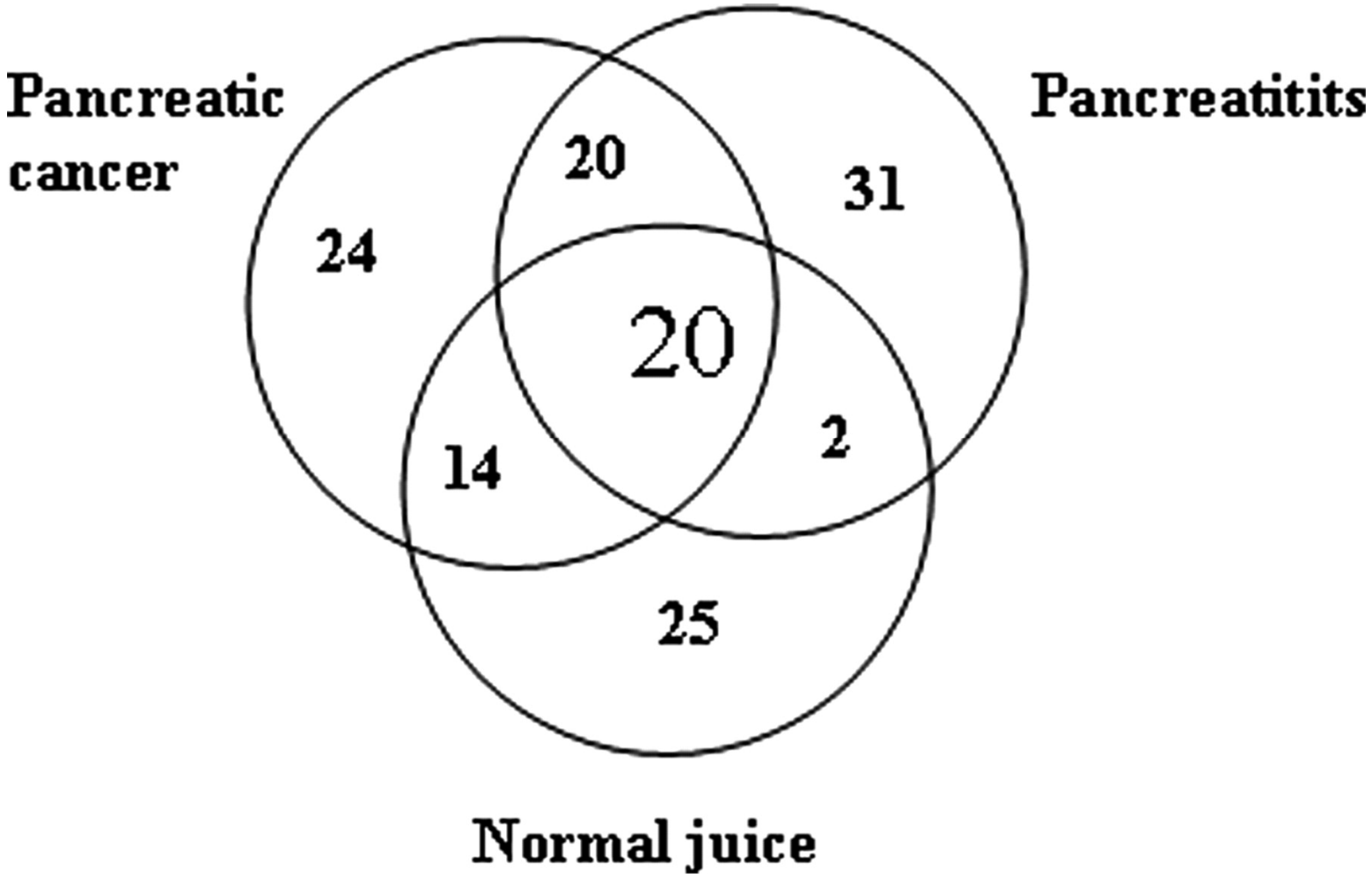
Multivariate data analysis using three variables from two different sample fractions profiled on two different array surfaces resulting in 84% (128/152) correct classified post treatment samples and 76% (34/45) correct classified pre treatment samples.

Protein categories identified in pancreatic cancer



Chen, R. (2005) Mol. Cell. Proteomics 4: 523-533

Comparison of proteins identified in ICAT analysis of pancreatic juice from cancer sample, pancreatitis sample, and normal sample



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Two types of stratification under PGx will entail different consequences

Patient stratification

- Different dosing based on patient genotype
- Could increase market size
- Change to get into occupied market
- The 'Blockbuster' model of drug development would still hold
- Expanding the patient subgroup by growing experience
  - Herceptin

Disease stratification

- Different drugs given based on patient genotype
- Would decrease market size for an individual drug
- Emphasis on a group of 'minibusters' rather than one blockbuster
- Expanding indications to other diseases with same underlying genetic cause of disease
  - Glivec

Modified from Shah, Nat Biotech 2003