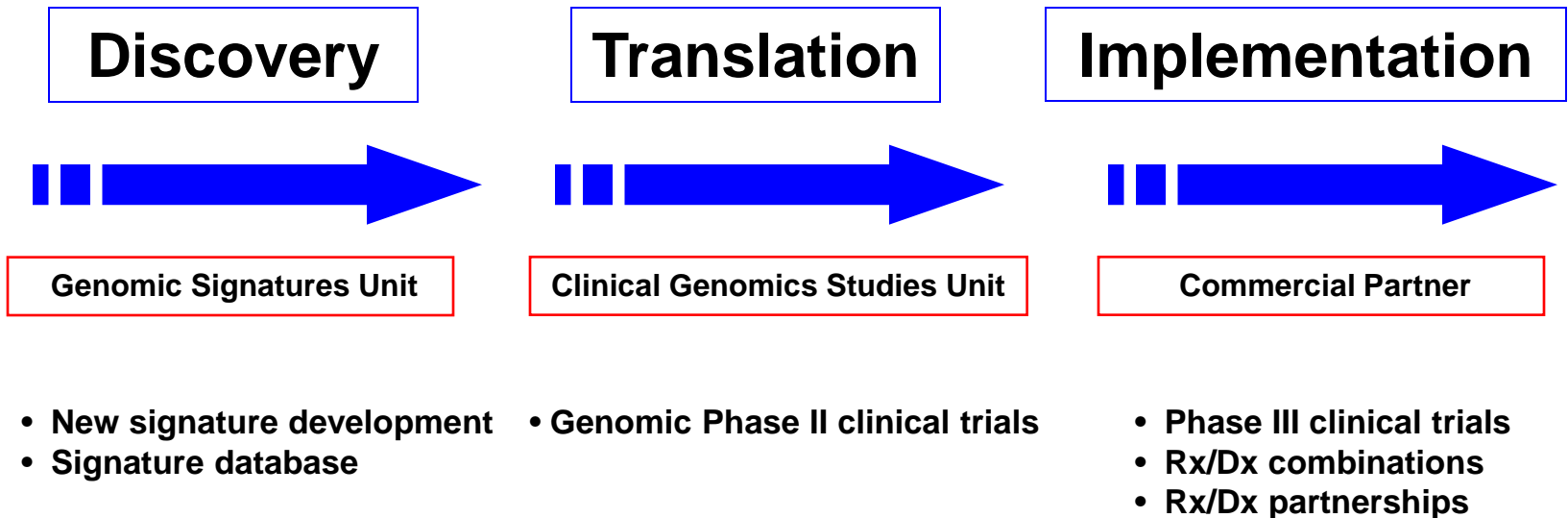


Genomic Guided Clinical Trials to Evaluate the Clinical Utility of Cancer Pharmacogenomics

**Geoffrey S Ginsburg, MD, PhD
Director, Center for Genomic Medicine
Duke Institute for Genome Sciences & Policy**

**NCI Cancer PGx Workshop
July 21, 2009**

A Paradigm for Discovery and Development of Cancer PGx Biomarkers



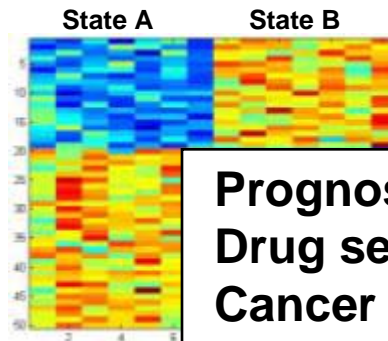
Concept of a Genomic Signature

Biological State A

Biological State B

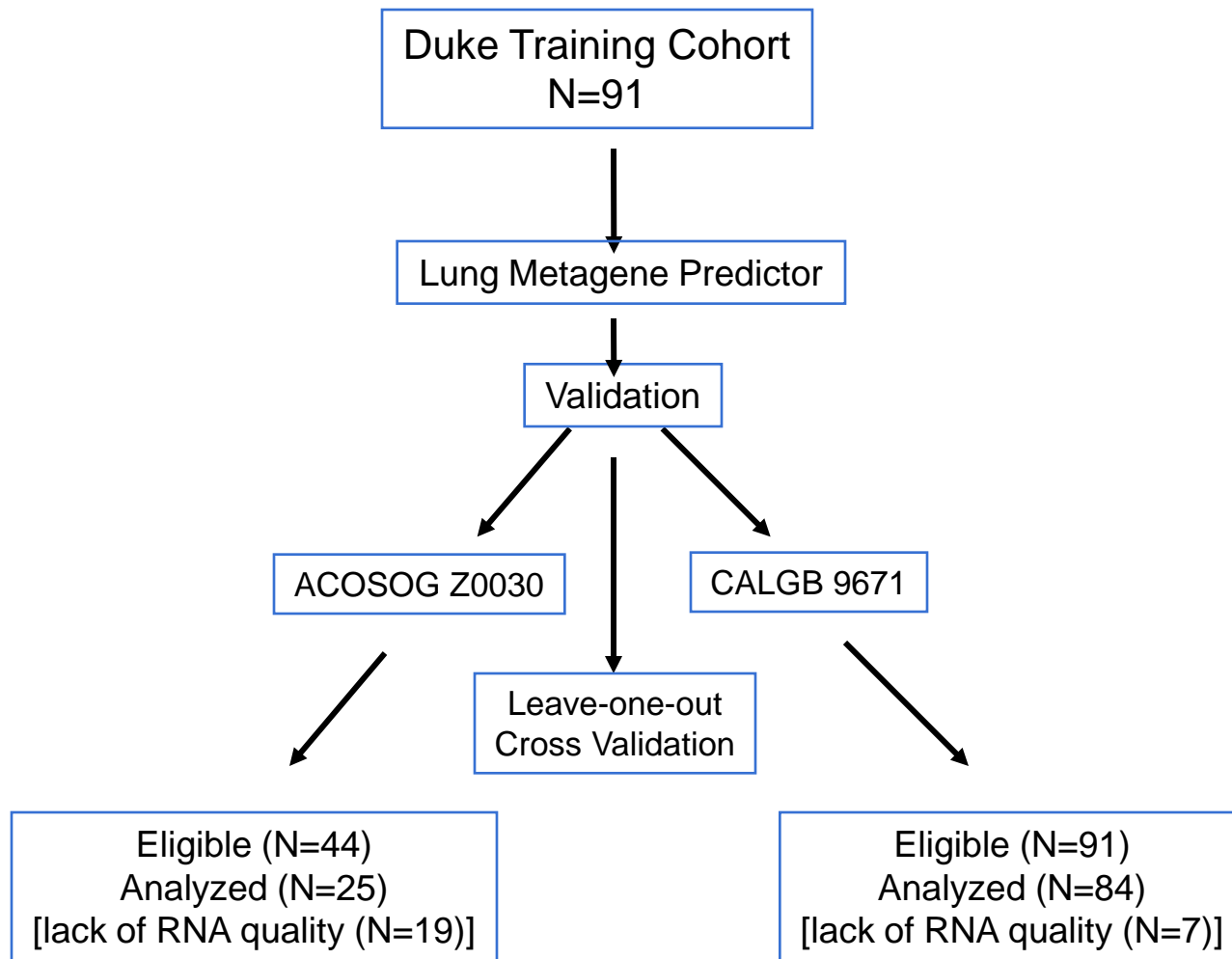


Genome-scale gene expression data



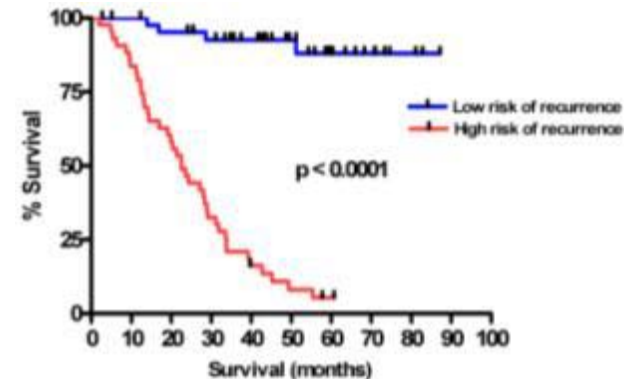
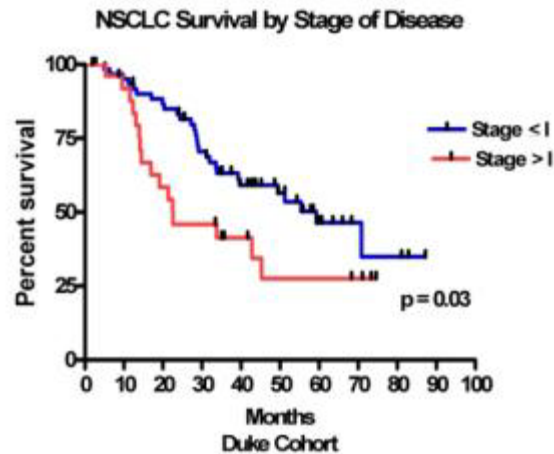
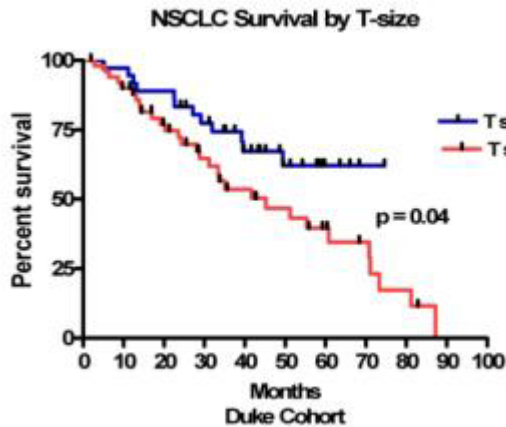
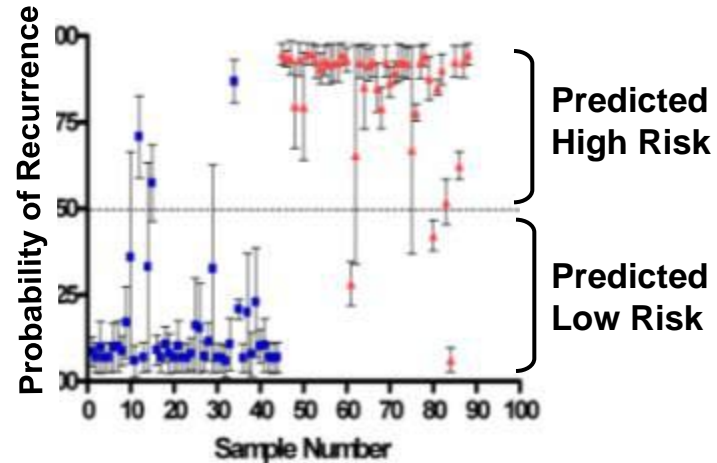
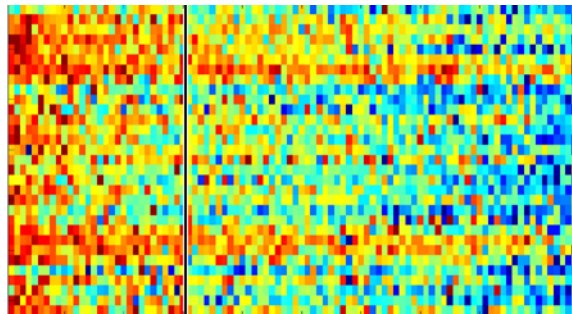
**Prognosis
Drug sensitivity
Cancer biology**

Lung Cancer *Prognosis* Genomic Signatures: The General Approach

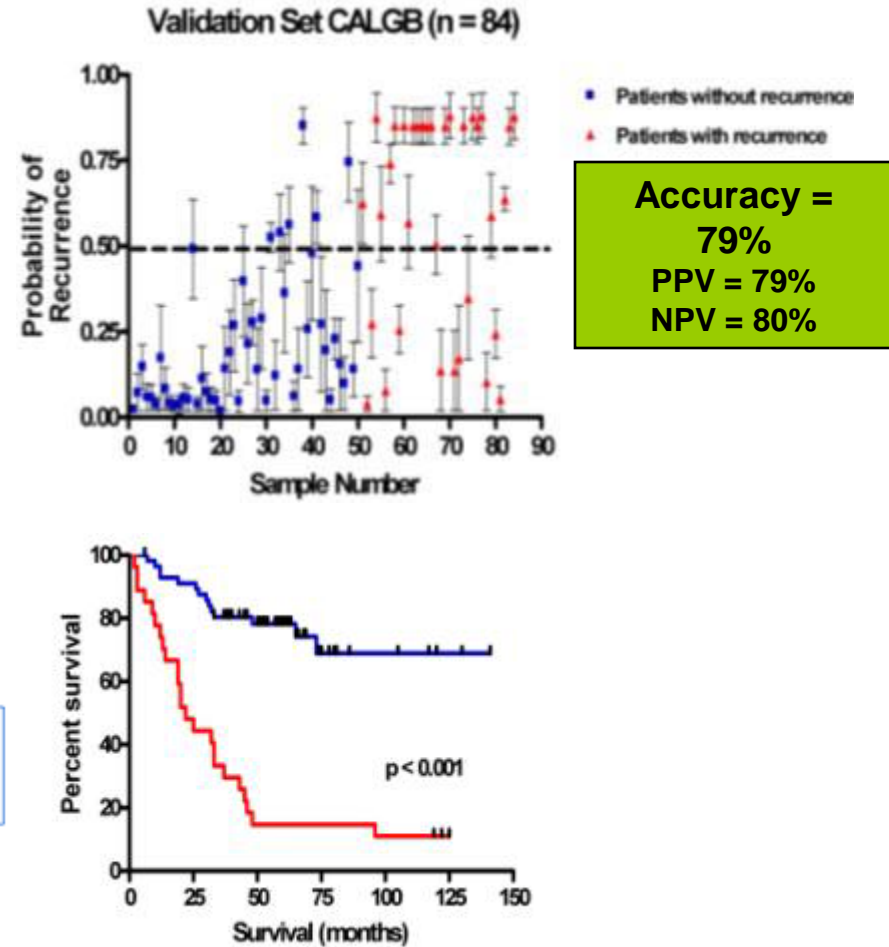
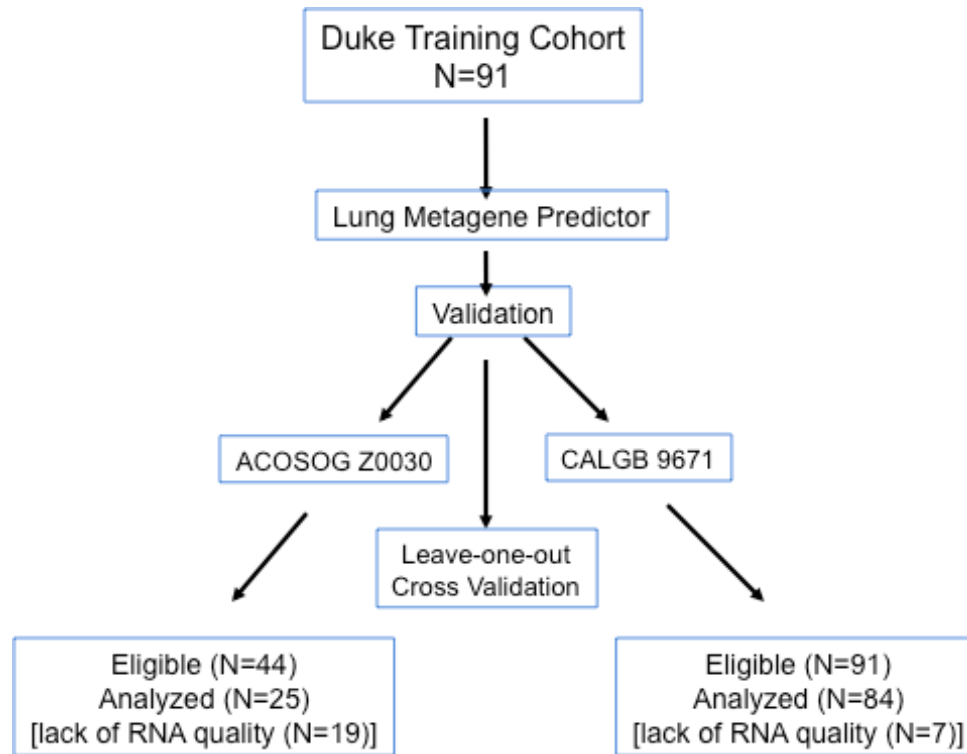


A Metagene Predictor of Recurrence

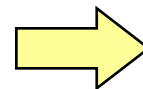
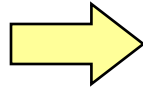
Low Risk High Risk



Independent Validation

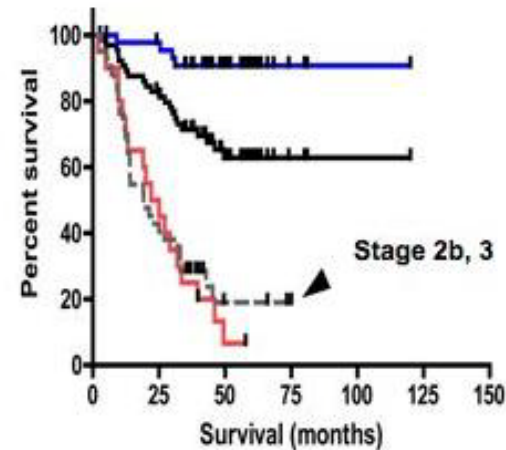
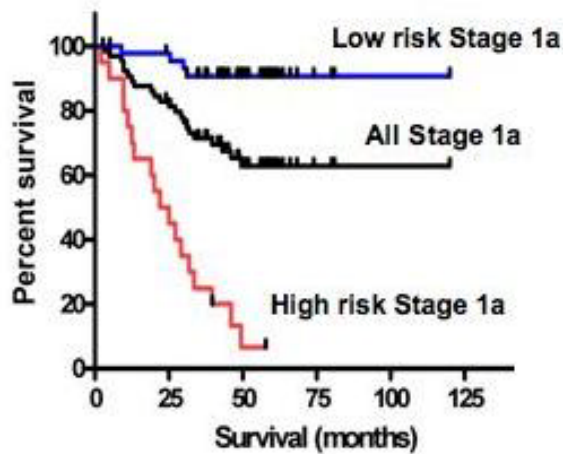


An Opportunity to Improve Prognosis in Lung Cancer



Stage Ia: Observation

Stage Ib-III: Adjuvant Therapy



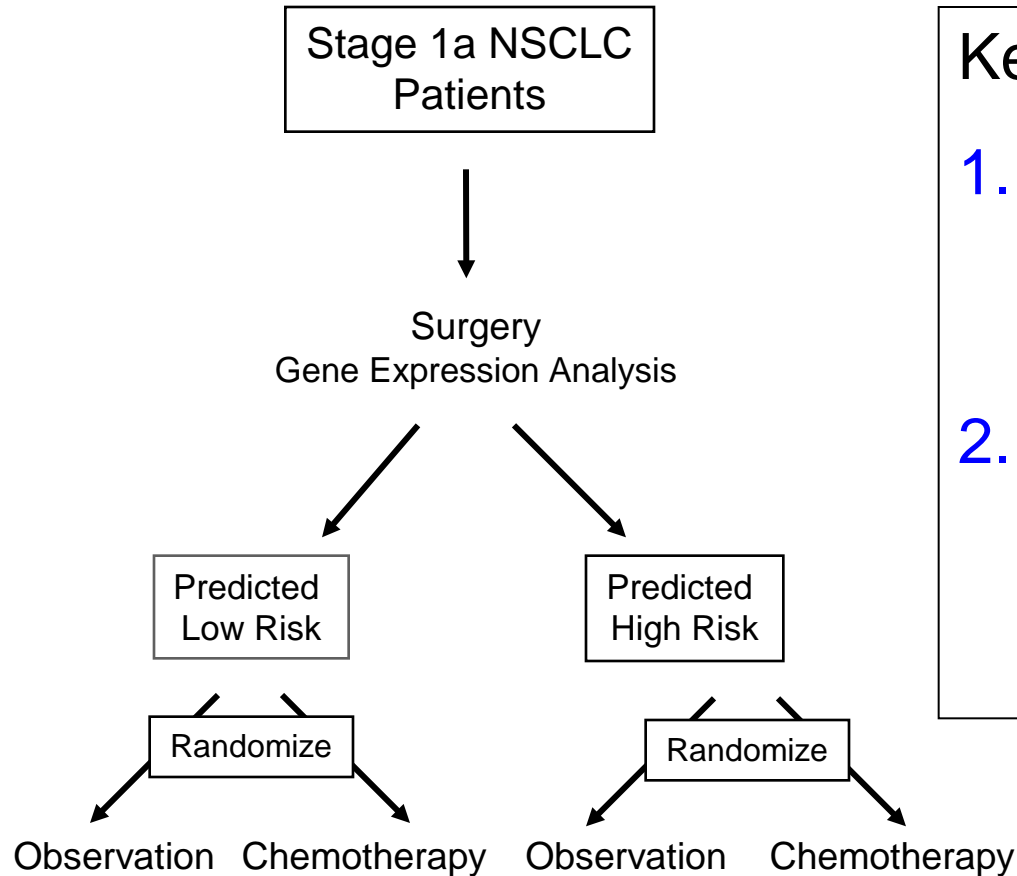
CALGB 30506 - A Phase III Trial to Evaluate Genomic Prognosis

Key Points:

1. Does the genomic assay accurately predict low vs high risk?
2. Do patients predicted to be at high risk for recurrence benefit from chemotherapy?

Approved by NIH/NCI/CTEP

Initiated in May 2009



How Best to Treat? Many Choices But No Guidance

*Regimens developed for groups
of cancer patients, not individuals*

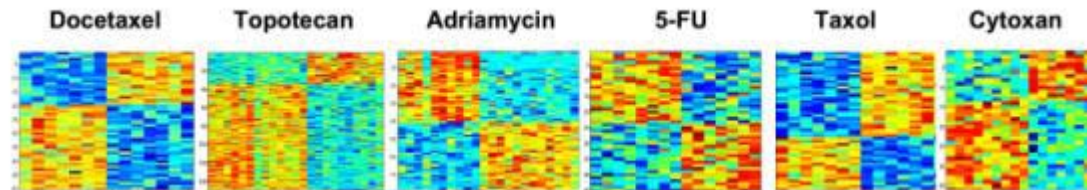
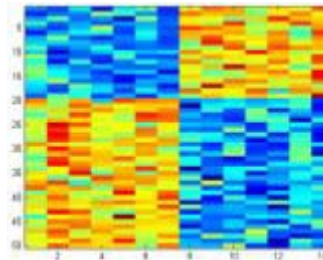
Signatures of Drug Sensitivity

Drug Resistant

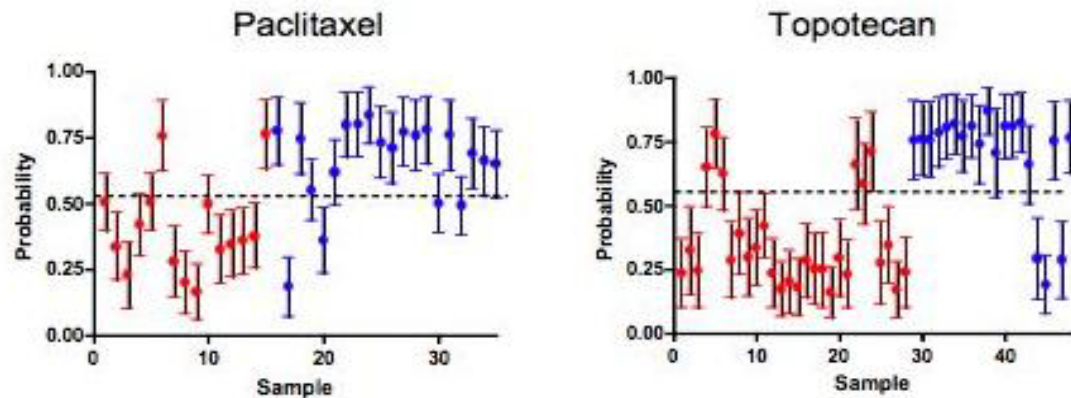
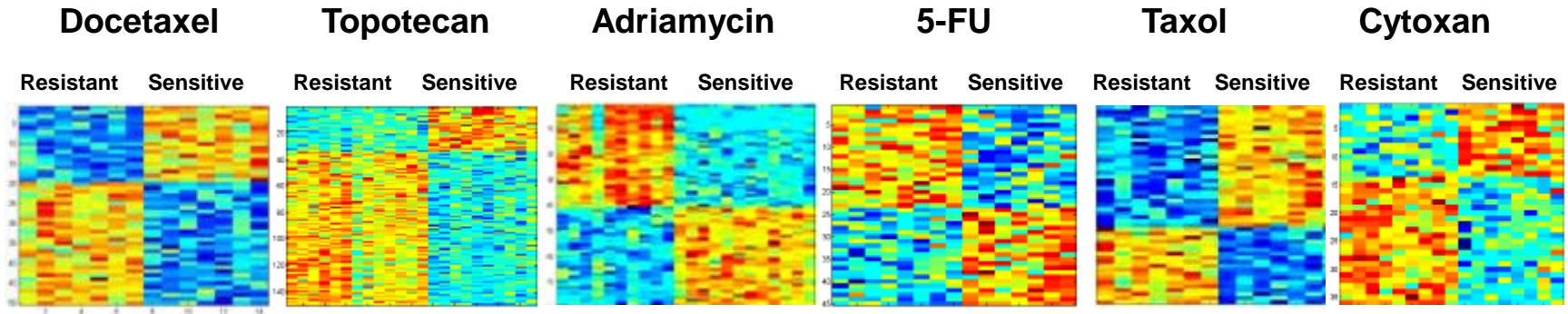
Drug Sensitive



Resistant Sensitive

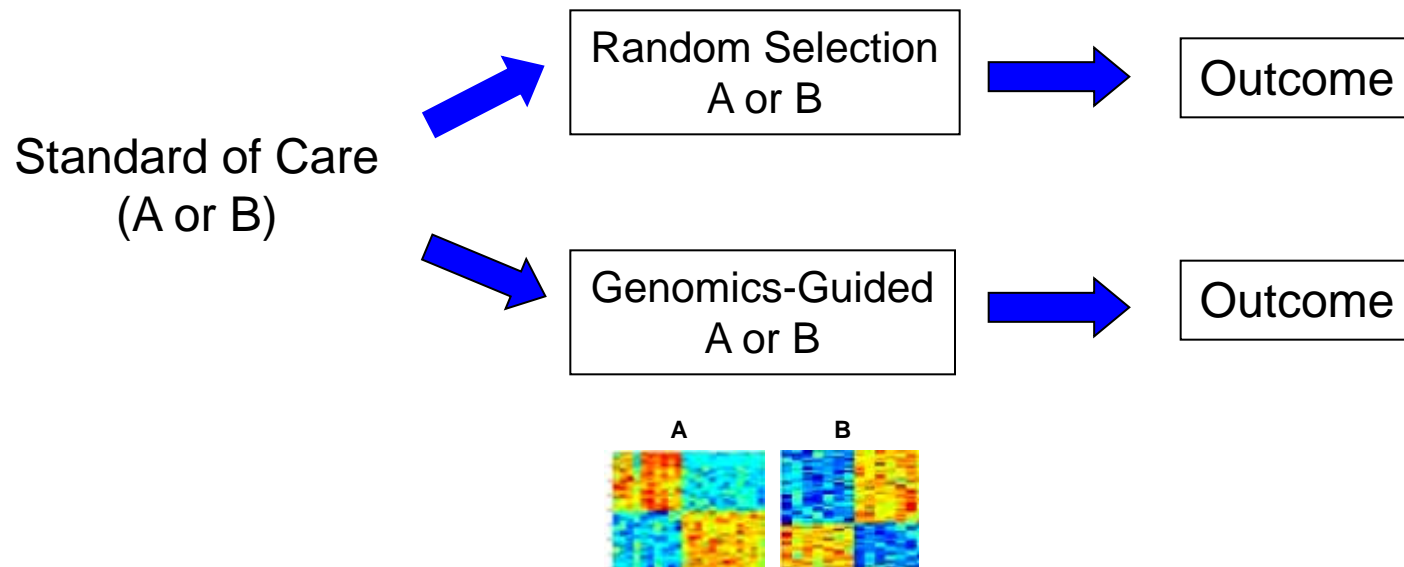


A Panel of Signatures to Guide the Use of Cytotoxic Chemotherapies



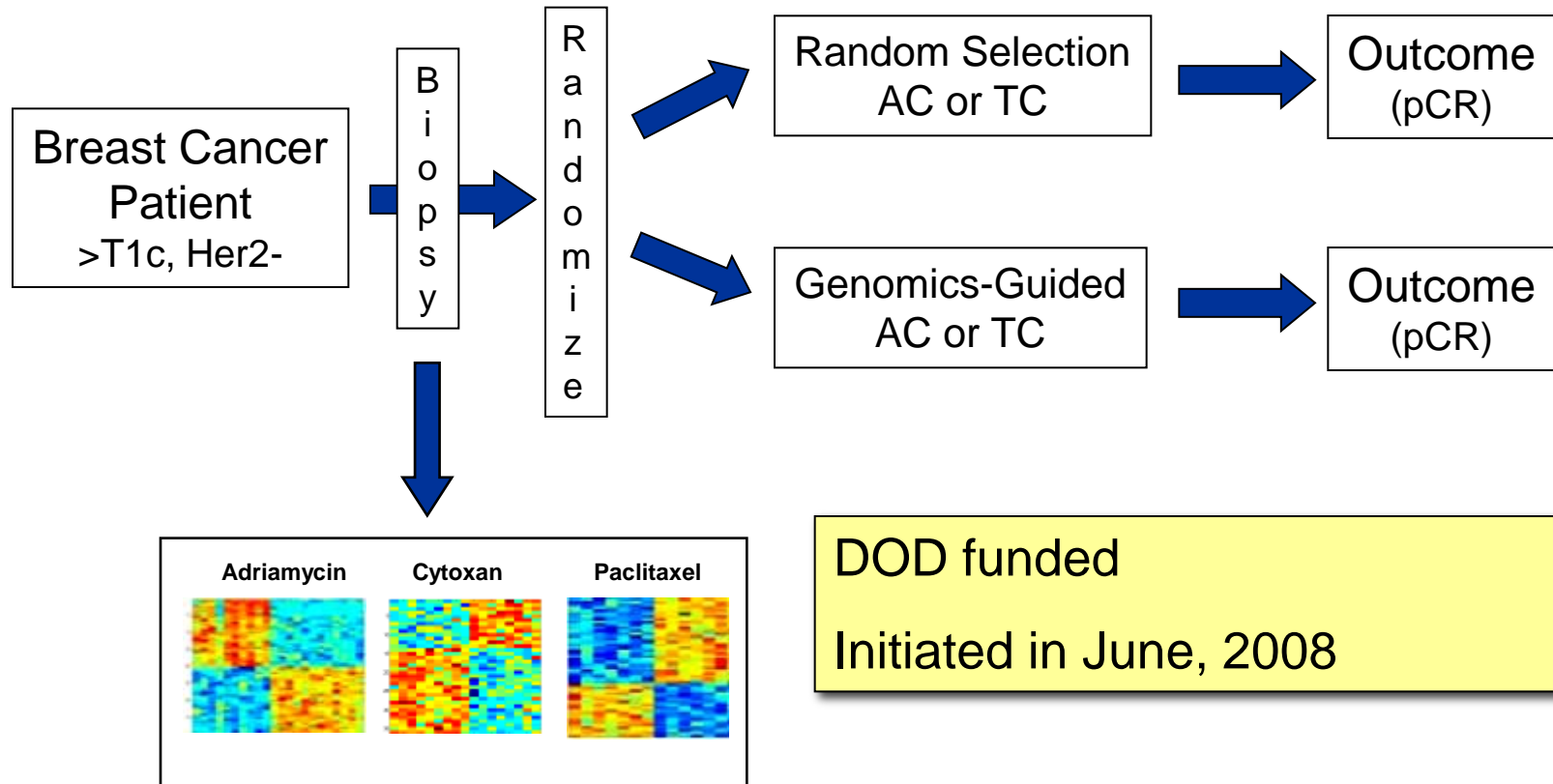
> 600 In vivo validations were performed for adriamycin, paclitaxel, gemcitabine, cyclophosphamide and topotecan
(Nature Medicine, 2006)

A Prototype for Clinical Utility Studies: Guiding *Standard of Care* Therapies

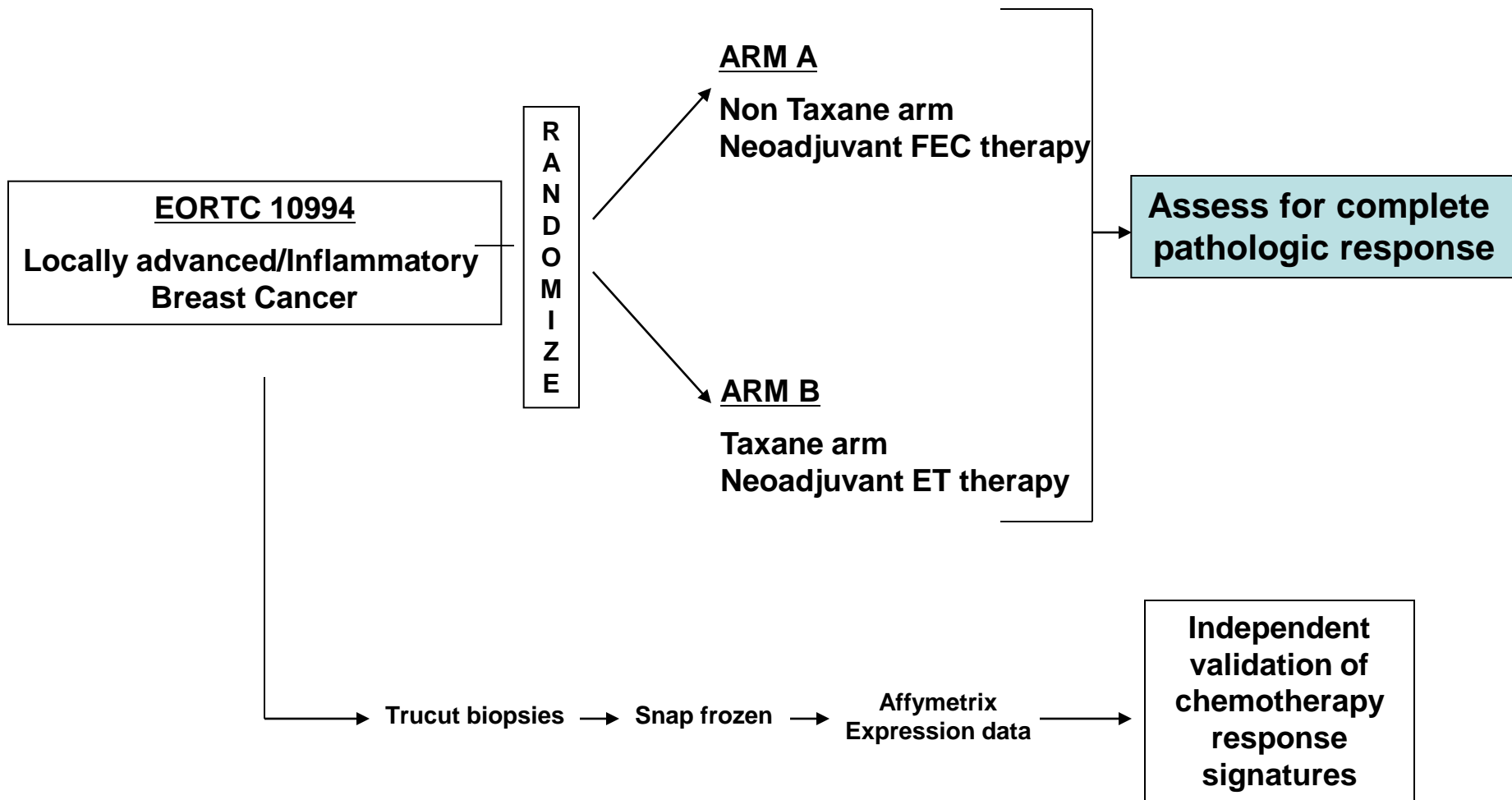


Health and Economic Outcomes

A Breast Cancer Neoadjuvant Trial

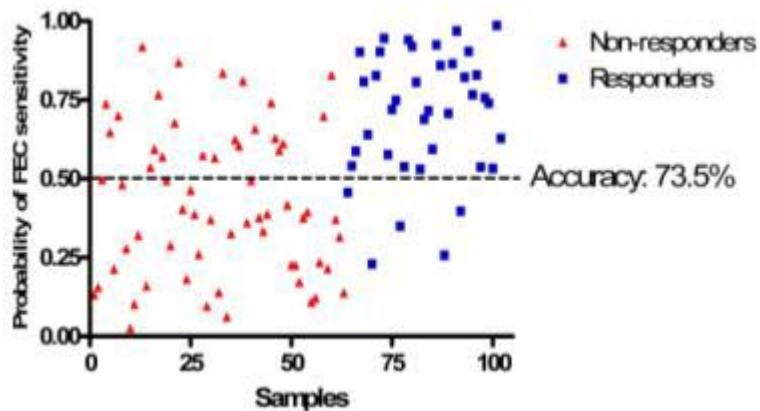


EORTC10994 Multicenter Prospective Neoadjuvant Phase III Breast Cancer Trial BLINDED VALIDATION (n = 162)



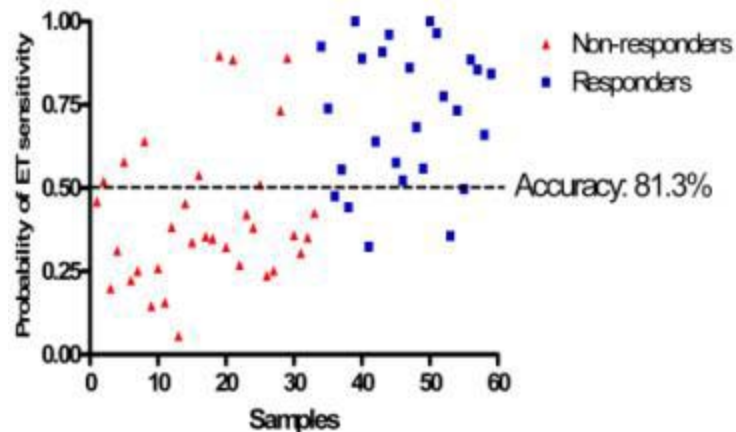
EORTC10994 Multicenter Prospective Neoadjuvant Phase III Breast Cancer Trial BLINDED VALIDATION (n = 162)

ARM A
Neoadjuvant FEC



FEC predictor

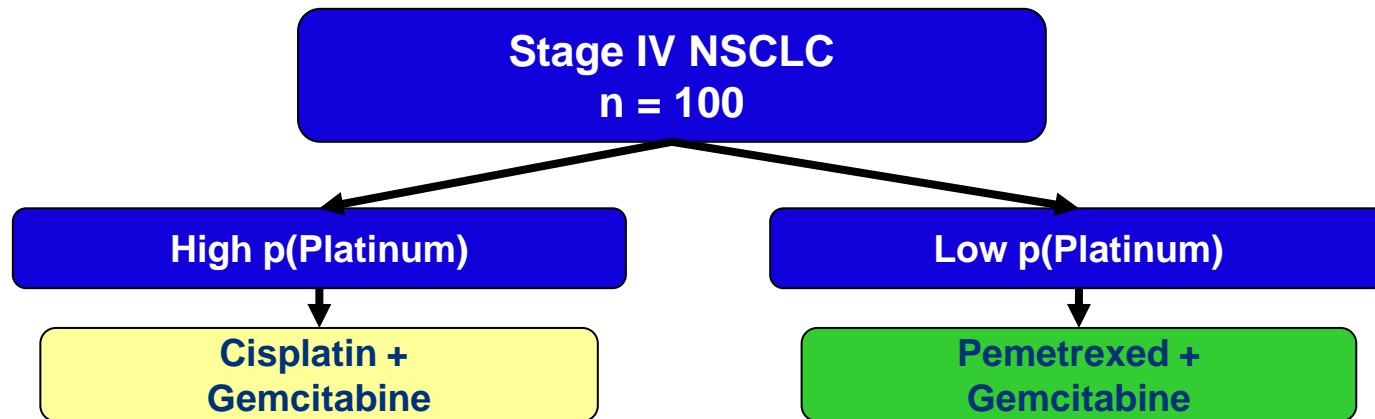
ARM B
Neoadjuvant ET



ET predictor

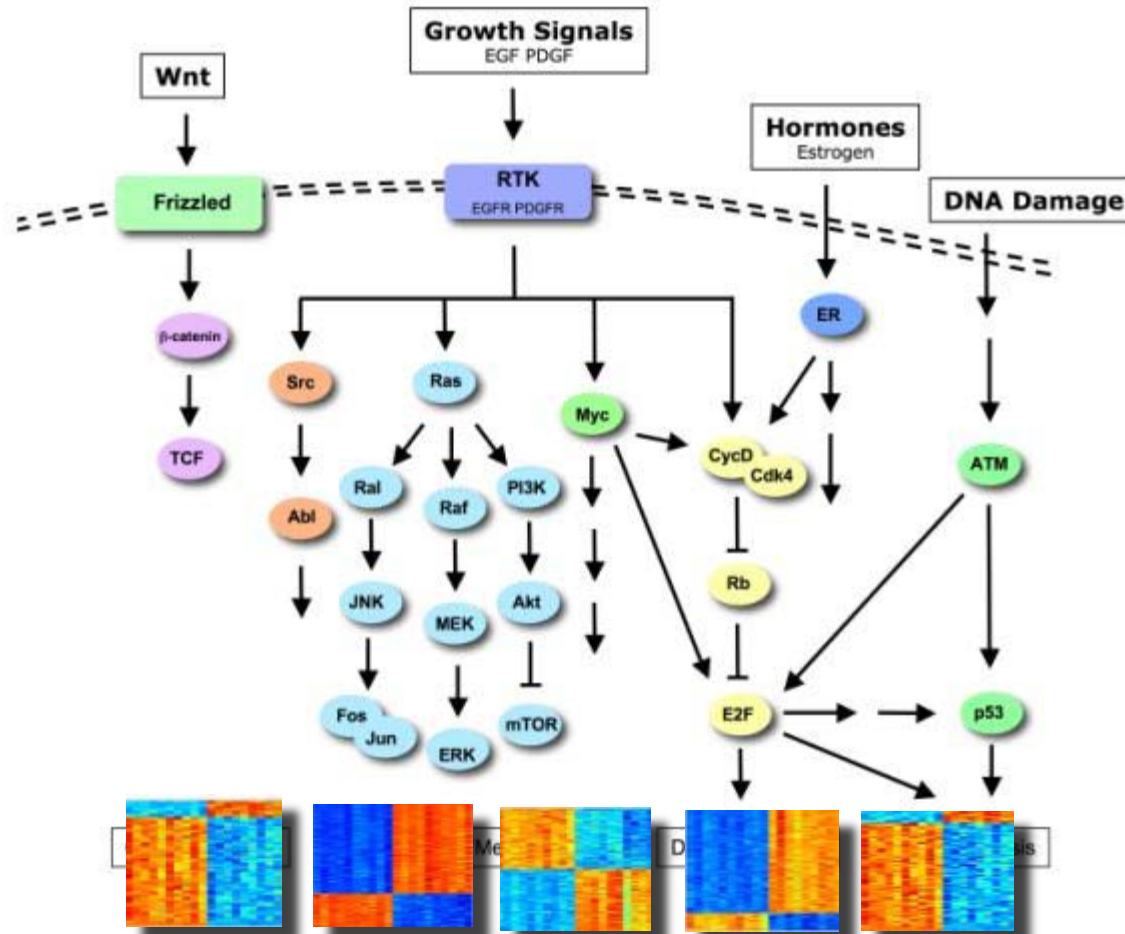
Novel Paradigms for Drug Development

Cytotoxic Predictor: *Moving Therapies to 1st Line*

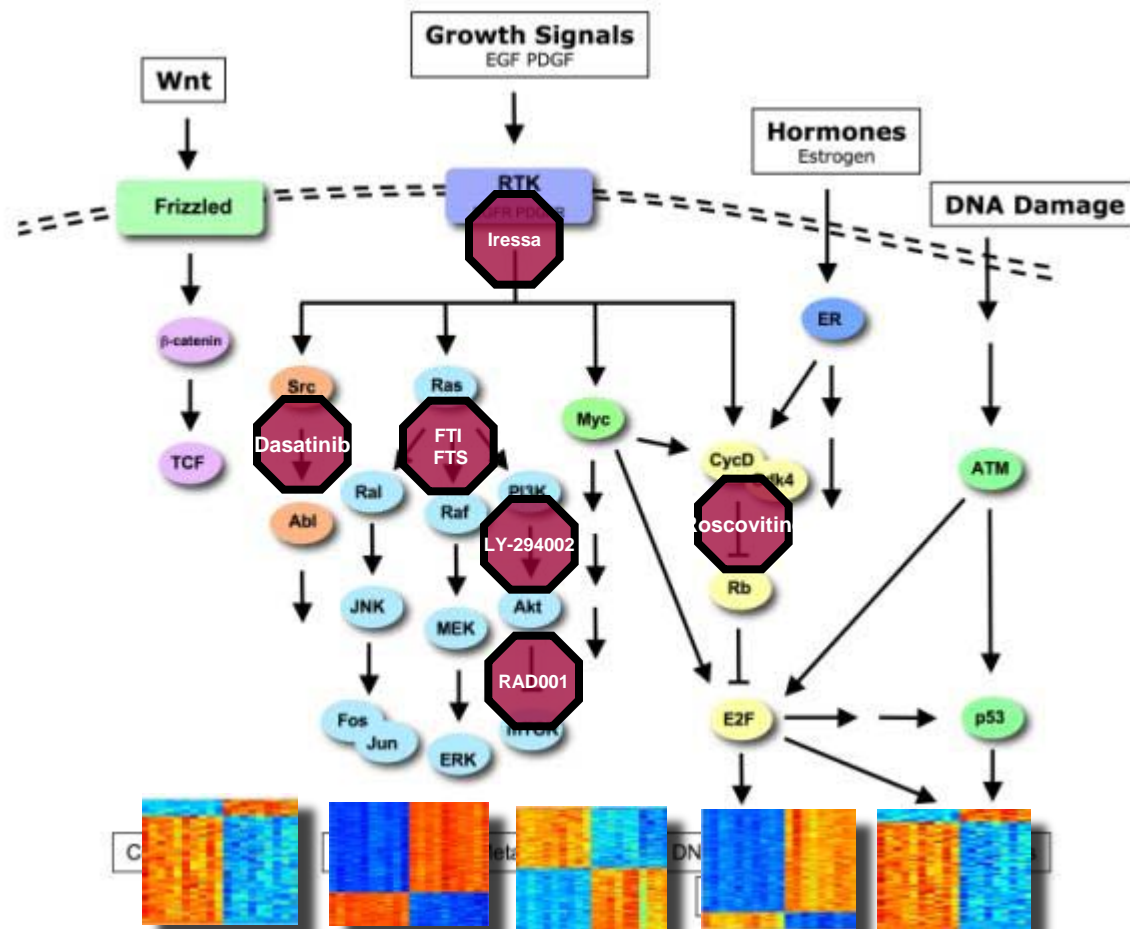


- Identifies patients resistant to standard of care, initiate 2nd line Tx
- Opportunity to move P+G to 1st line

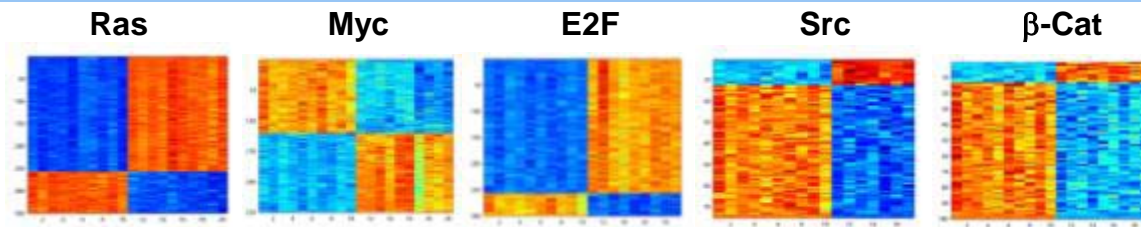
Surrogate Signatures for Pathway Activation Underlying the Oncogenic Phenotype



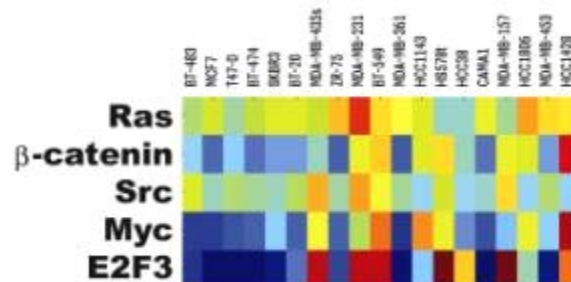
Linking Pathways Underlying the Oncogenic Phenotype with Therapeutics



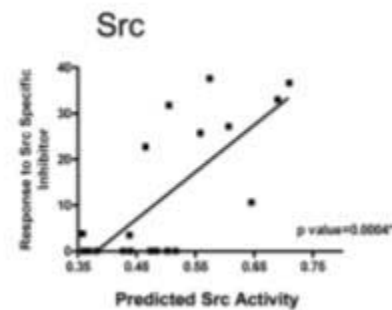
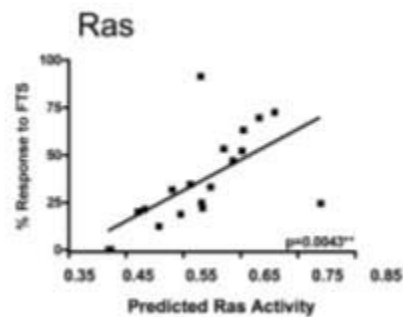
Pathway Signature = Drug Sensitivity Signature



Predict pathways in cell lines

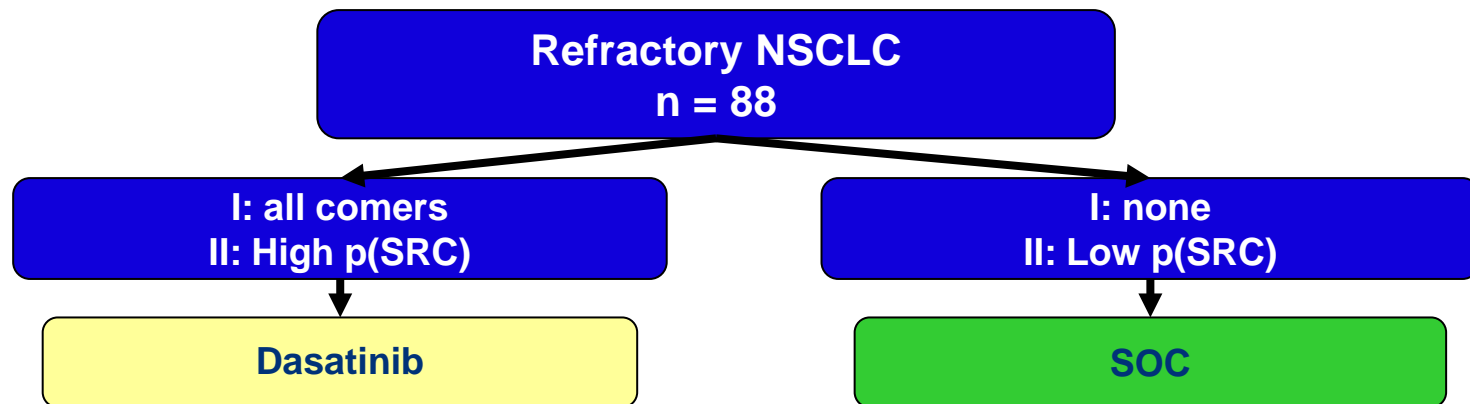


Compare with drug sensitivity



Novel Paradigms for Drug Development

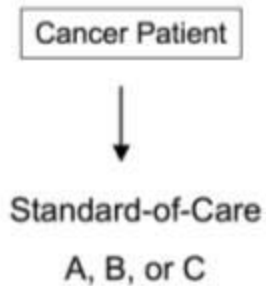
Pathway Predictor: *Enrichment/Targeted Rx*



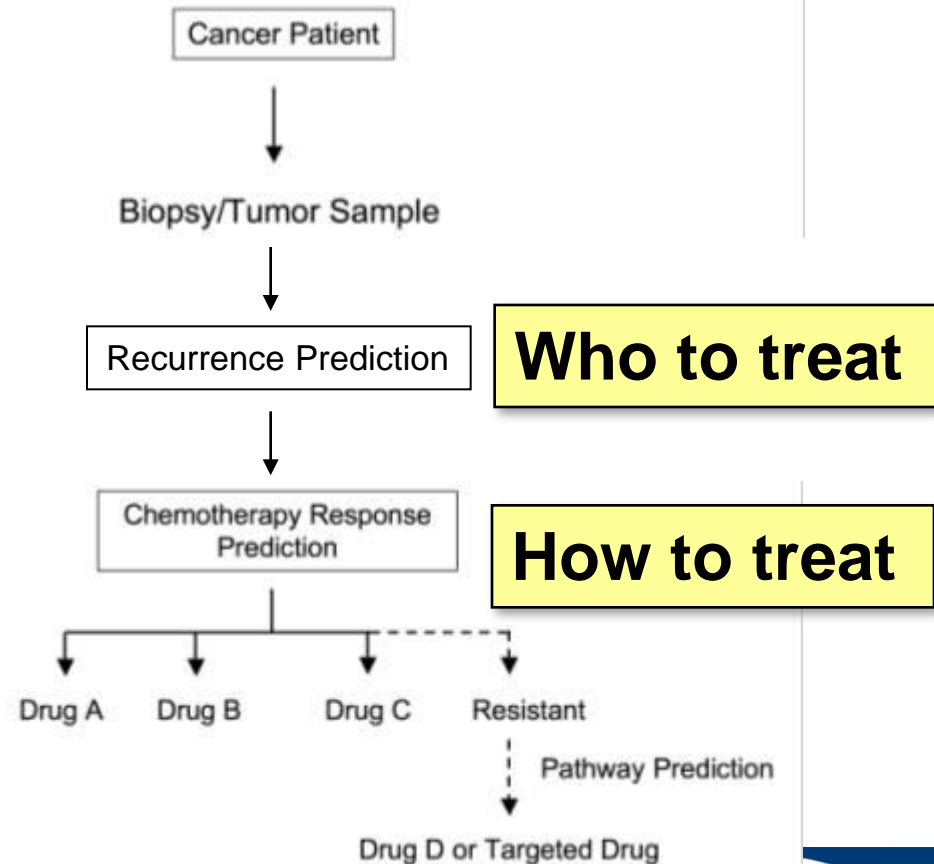
- Two-phase design: treat all comers with Dasatinib, measure SRC activity
- If non-resp are SRC- and resp are SRC+, then stratify in phase II

A Multi-Step Strategy for Personalized Cancer Therapy

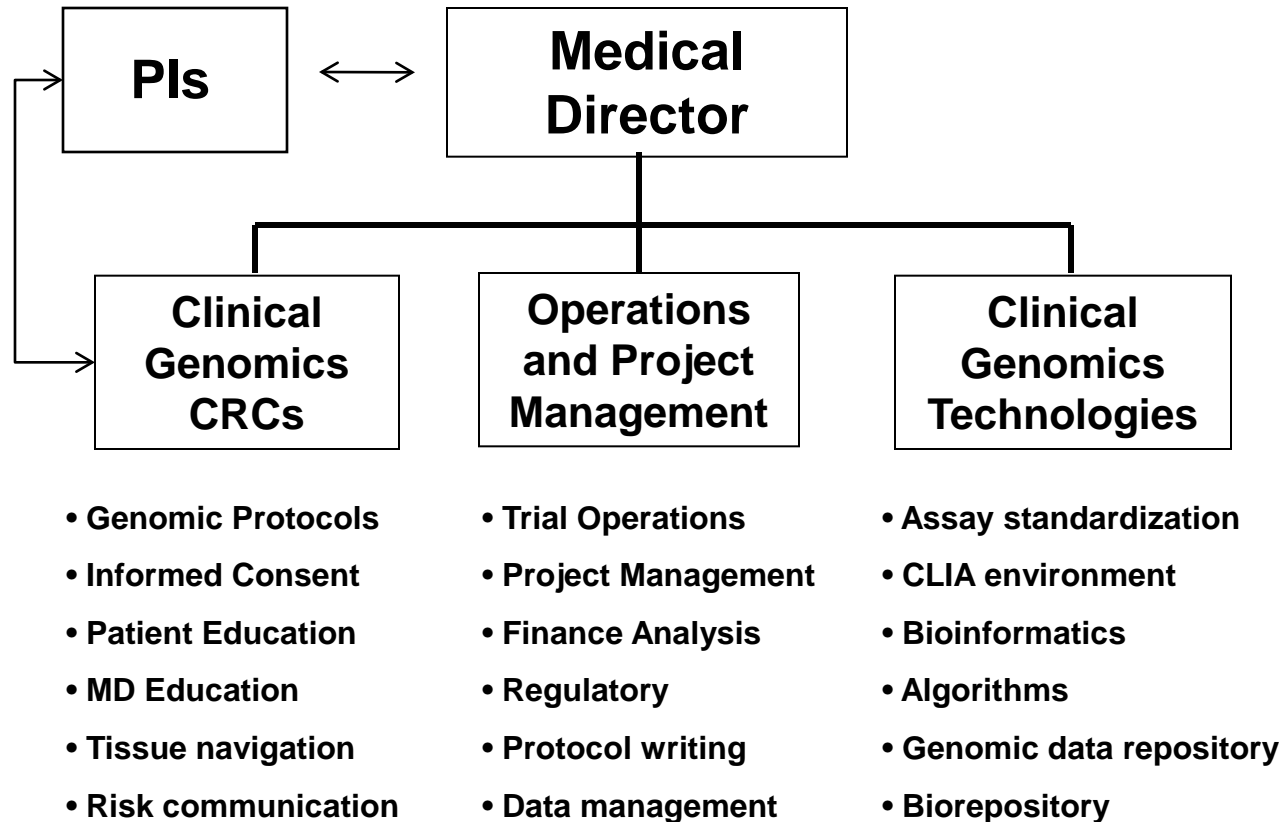
Current:



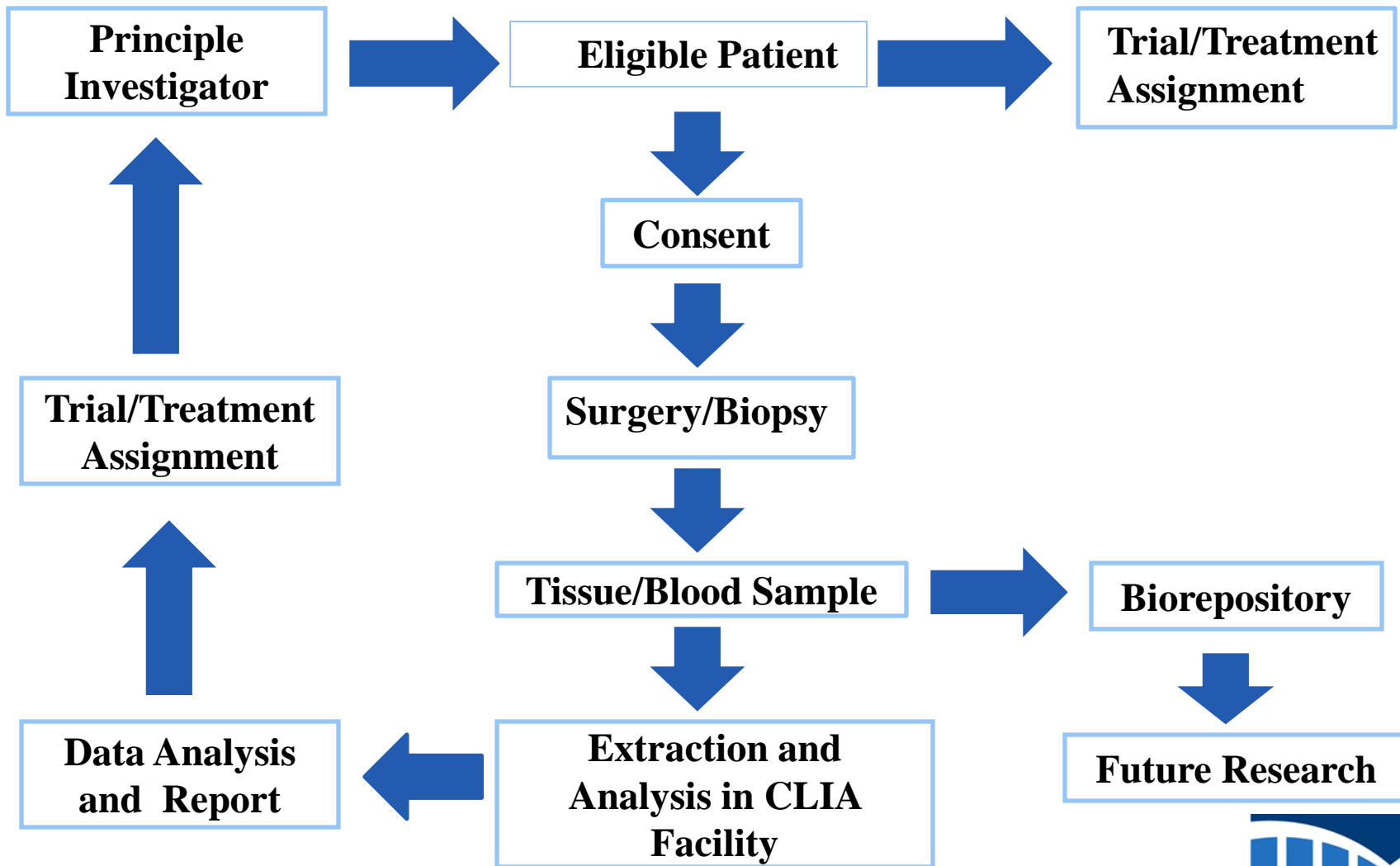
Genomics-guided:



The Duke Clinical Genomics Studies Unit: Driving Genomics Guided Trials



The Duke Clinical Genomics Studies Unit



Building the Infrastructure to Make this Work

- Biobanking
 - Coordinated efforts
 - Operational and informatics support
 - Standards
- Genomic Technologies
 - Core laboratories
 - Economies of scale
- Informatics
 - Reliable, interoperable EHRs
 - Integration of research, clinical, molecular data
- Biostatistics
 - Critical shortage must be addressed
 - Physician training in quantitative skills
- Decision Making
 - Understanding of human decision making
 - Biological, psychological and social factors
 - Education of health care professionals

Opportunities to Enable Scientific and Clinical Evaluation of Genomic Markers

- Patient registries (common and rare diseases)
 - Longitudinal follow up
 - Robust phenotypes
- Population studies linked to EHRs
- Prospective clinical trials
 - “Genomics Trials Cooperative Group”
- Industry
 - Public-private partnerships
 - Sample collection in phase II-IV trials
- A national virtual sample biorepository linked to research and clinical data