The I-SPY 2 trial in the US

the role of biomarkers for treatment assignment

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Netherlands Cancer Institute, Amsterdam

NKI-AVL

The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

University of California
San Francisco

UCSF

Comprehensive
Cancer Center

agendia

decodina cancer.

ISPY-2 Participating Organizations

Sponsor:
NCI, FDA, Pharma unrestricted

Investigational Agent Providers
Agents Approved and Under Consideration

Abbott
A Promise for Life

AMGEN

Genentech
A Member of the Roche Group

MERCK
Be well

Takeda
MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pfizer
Wyeth

Biomarker Device Providers
Stratifying & Qualifying

sentinelle
MEDICAL

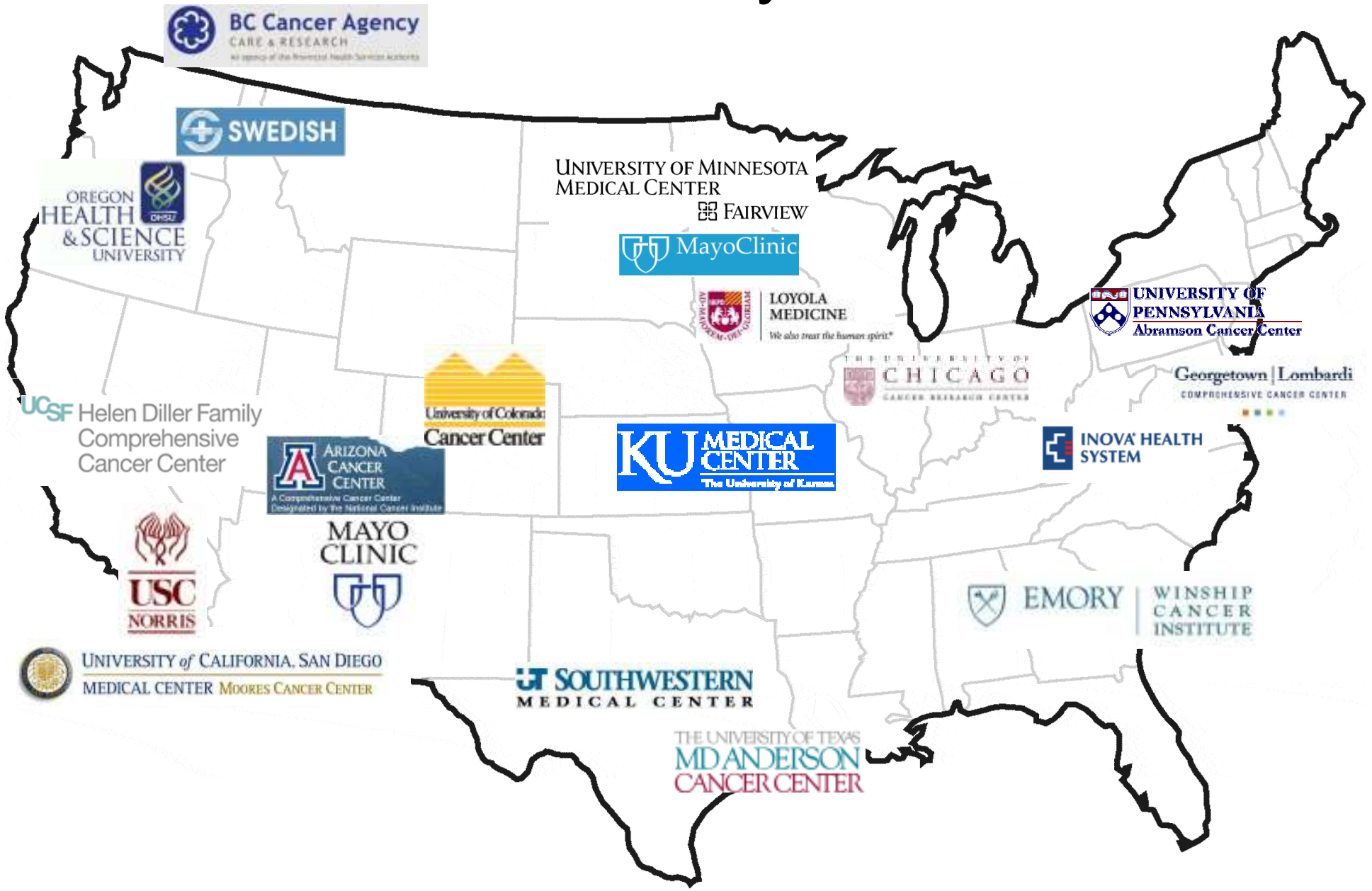
agendia
decoding cancer

BERKELEY LAB
LAWRENCE BERKELEY NATIONAL LABORATORY

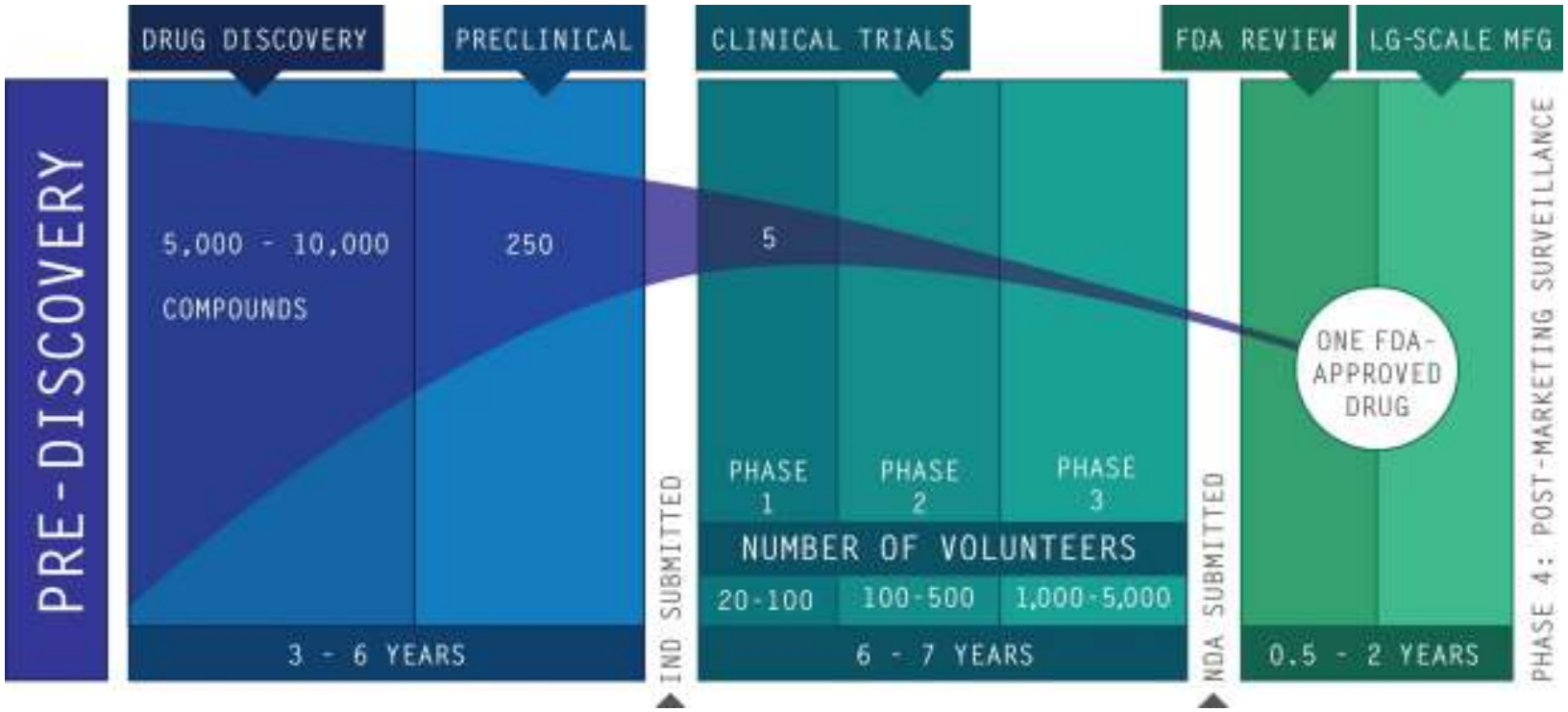
GEORGE MASON
UNIVERSITY

THERANOSTICS HEALTH
The Partner of Choice for Personalized Medicine

I-SPY 2 study sites



Drug Development – Current Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

More Efficient Clinical Trial Process

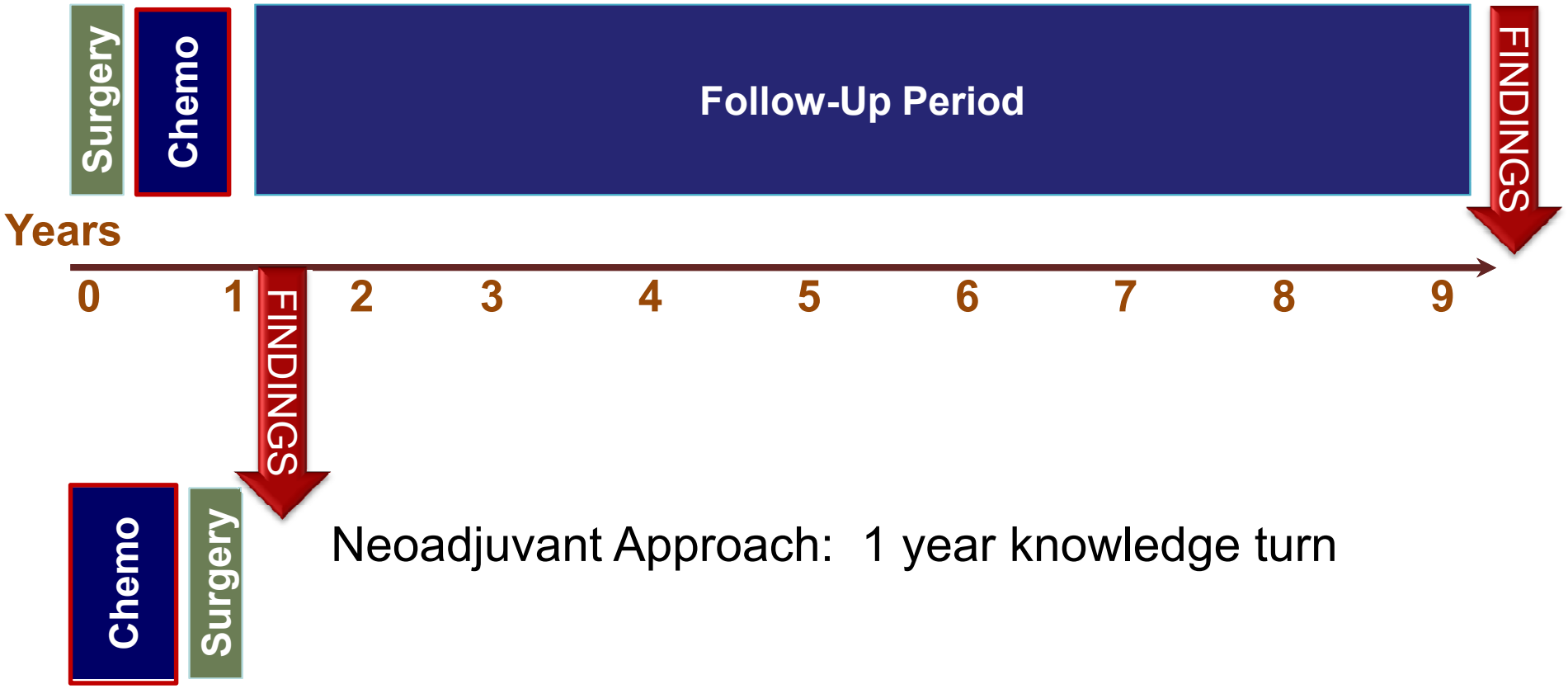
Inefficient clinical trials account for a majority for the time and cost associated with the failures of the current system

- Reduce time to conclusive results/Accelerate learning
- Reduce patient s/volunteers required
- Reduce cost of conducting trials
- Increase collaboration/Data sharing

The "Neoadjuvant" Approach Dramatically Accelerates Knowledge Turns

Metastatic Approach: 2 to 4 year knowledge turn

Adjuvant Approach: 6 to 9 year knowledge turn



Neoadjuvant Approach: 1 year knowledge turn

I-SPY Trial Program

Investigation of
Serial studies to
Predict
Your
Therapeutic
Response with
Imaging and Molecular
Ana-
Lysis

I SPY WITH MY LITTLE EYE … A BIO-MARKER BEGINING WITH X…

Who benefits from what systemic therapy

- Therapy response prediction

I-SPY 2 neoadjuvant trial program

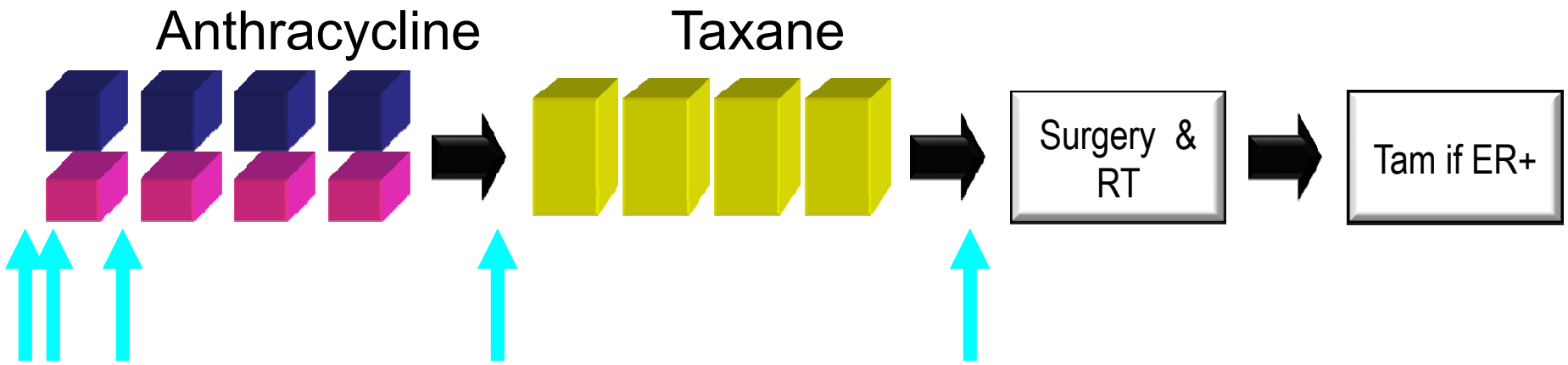
I-SPY PIs: Laura Esserman (UCSF)
Don Berry (MDAnderson)
Trial Operations: Angie DeMichele (UPenn)
Drug selection: Doug Yee (UMinnesota)
Patient Advocates: Jne Perlmutter (AnnArbor)
Imaging: Nola Hylton (UCSF)
Biomarkers: Laura van ‘t Veer (UCSF)

Molecular Biomarkers: Chuck Perou, Angie DeMichele, Marc Lenburg, Sarah Davis, Meredith Buxton, Chad Livasy, Chip Petricoin, Denise Wolf, Joe Gray et al

I-SPY 1 Clinical Trial Backbone

CALGB 150007 / ACRIN 6657

Layered Imaging and Molecular Biomarker Studies Onto Standard Clinical Care Neo-adjuvant therapy



- Serial MRI Scans
- Serial Core Biopsies

Questions

- Does early response help us to predict early relapse?
  - Complete Pathologic Response: pCR
  - Residual Cancer Burden: RCB
- How do the molecular signatures impact on the interpretation of pCR and RCB?

Trial Endpoints

- Early
  - MRI response after 1 cycle of chemotherapy
    - Longest Diameter, Volume
- Intermediate
  - pCR Pathologic Complete Response
  - RCB Residual Cancer Burden
  - % change in MR volume
- Late
  - 3 year Recurrence Free Survival
  - 3 year Overall Survival

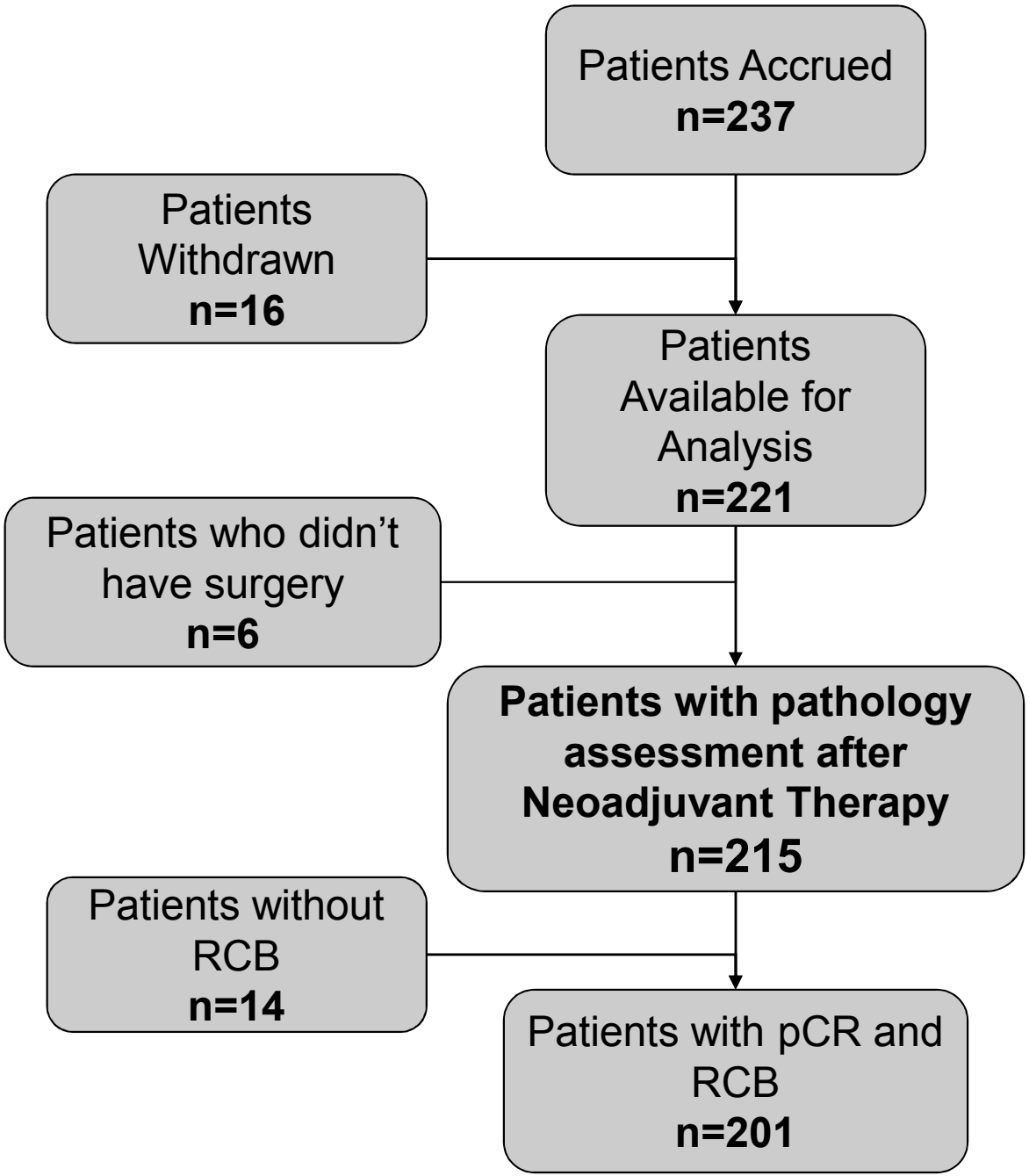
Response measure at time of surgery: Residual Cancer Burden

- Integrates several pathologic features
  - Lymph node status
  - Extent of Tumor Bed
  - Tumor size
  - Tumor cellularity
- Output is continuous or 4 discrete categories
  - RCB 0 pCR, no invasive tumor
  - RCB I scattered residual disease
  - RCB II moderate tumor burden
  - RCB III significant tumor burder

Symmans et al JCO 2007

Total Accrual: 237	
Institution Name	**Accrual**
University of Pennsylvania Medical Center	**36**
Georgetown University Hospital	**4**
University of North Carolina	**36**
Memorial Sloan Kettering Cancer Center	**22**
University of Washington	**5**
University of Alabama at Birmingham Medical Center	**51**
University of Chicago	**2**
University of Texas Southwestern	**14**
University of California San Francisco	**66**

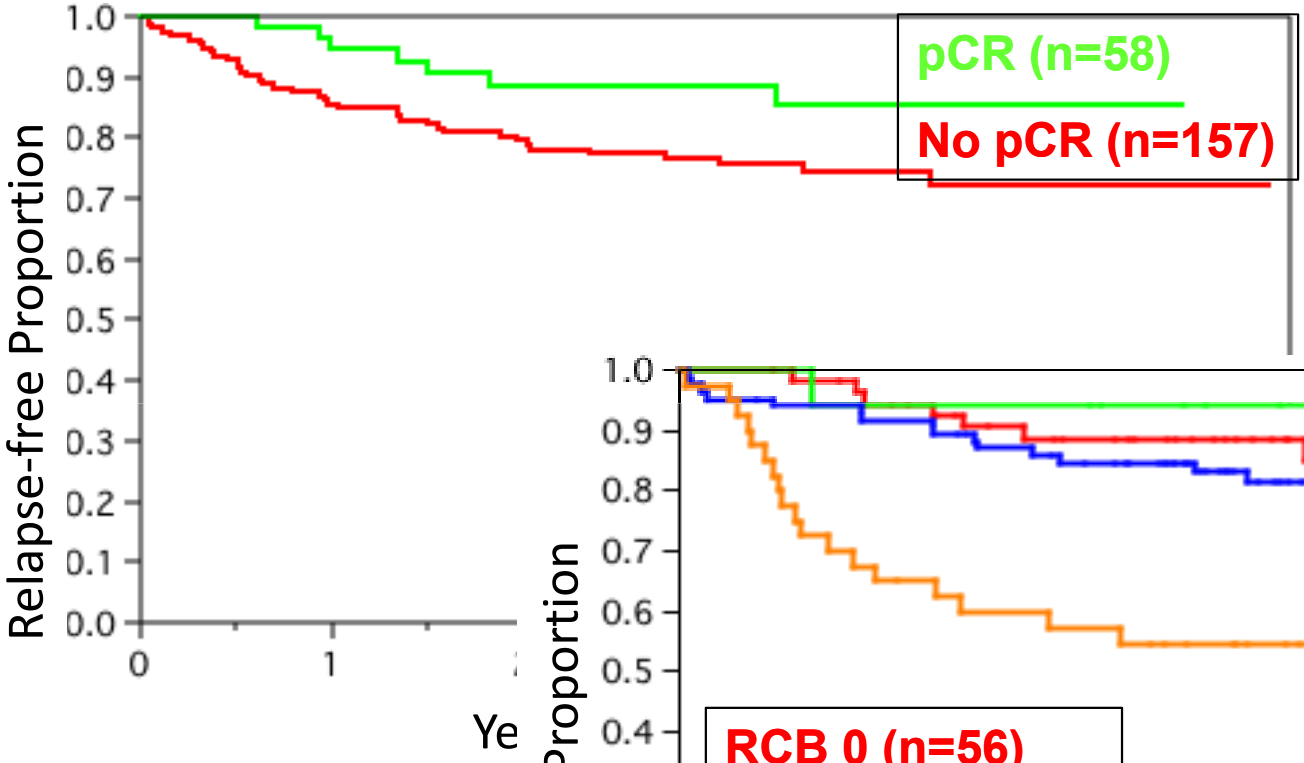
- **1042 frozen cores from 201 patients**
- **1301 paraffin cores from 223 patients**
- **948 serum samples from 158 patients.**

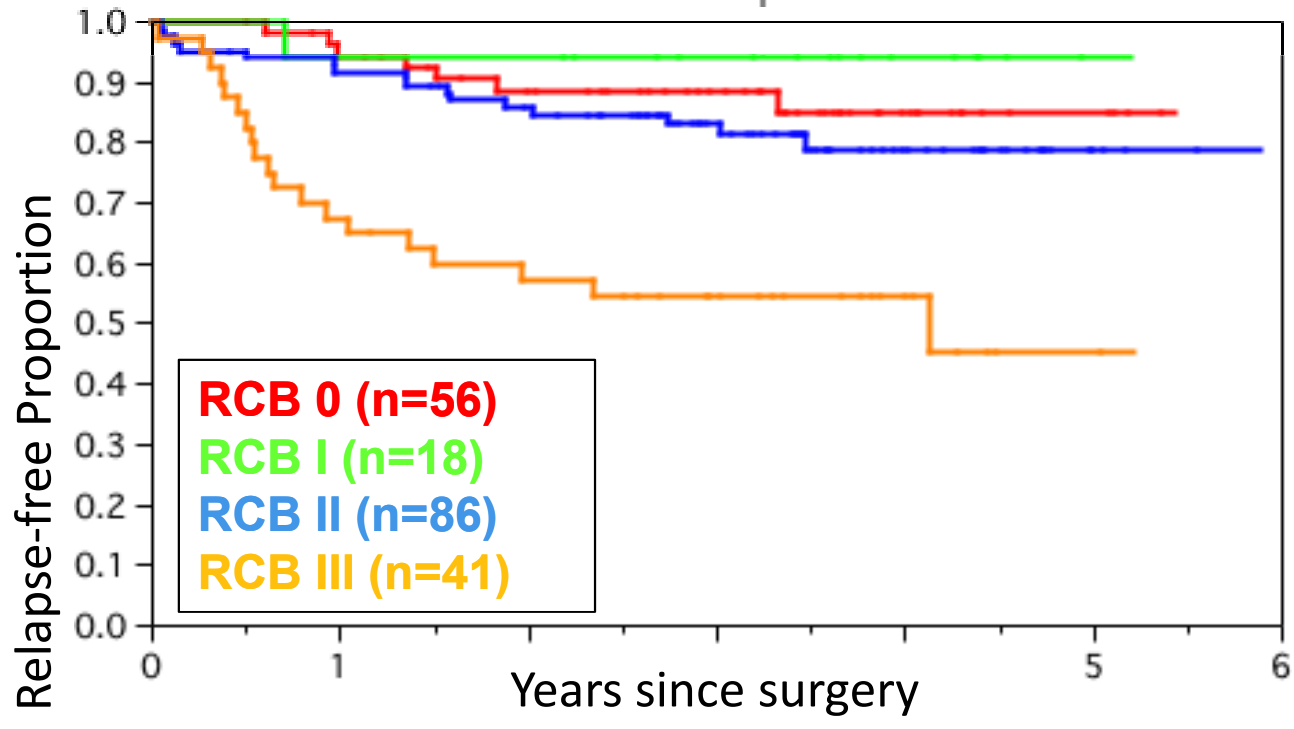

Patients Accrued
n=237
Patients Withdrawn
n=16
Patients Available for Analysis
n=221
Patients who didn't have surgery
n=6
Patients with pathology assessment after Neoadjuvant Therapy
n=215
Patients without RCB
n=14
Patients with pCR and RCB
n=201

Questions

- Does early response help us to predict early relapse?
  - Complete Pathologic Response: pCR
  - Residual Cancer Burden: RCB
- How do the molecular signatures impact on the interpretation of pCR and RCB?

Relationship of pCR and RCB with Early Relapse for all I-SPY 1 Patients





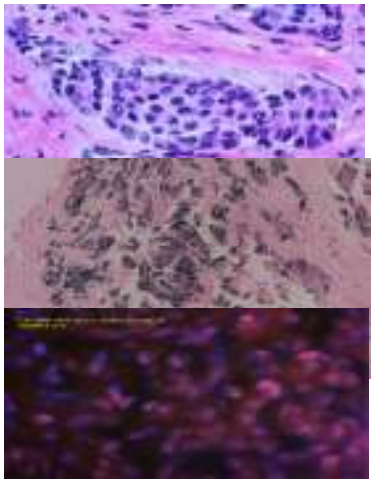
Questions

- Does early response help us to predict early relapse?
  - Complete Pathologic Response: pCR
  - Residual Cancer Burden: RCB
- How do the molecular signatures impact on the interpretation of pCR and RCB?

I-SPY 1 Biomarker Platforms

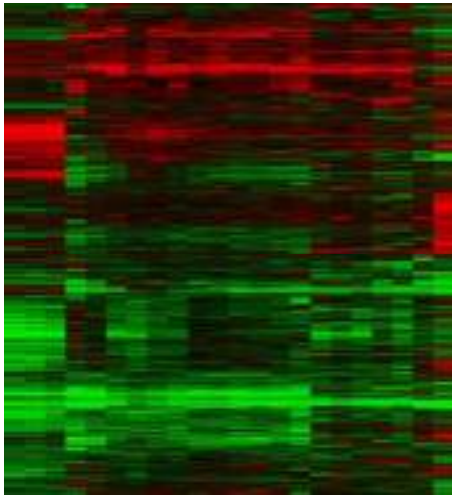
Tissue: Core

H&E, IHC, FISH



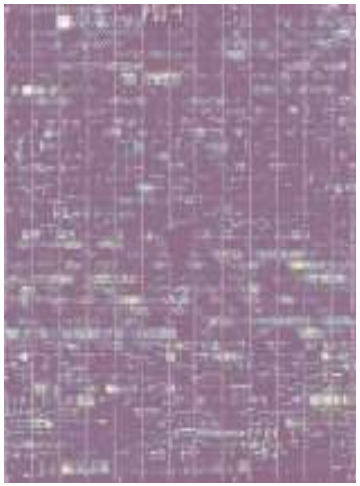
UNC, Penn

Expression Arrays



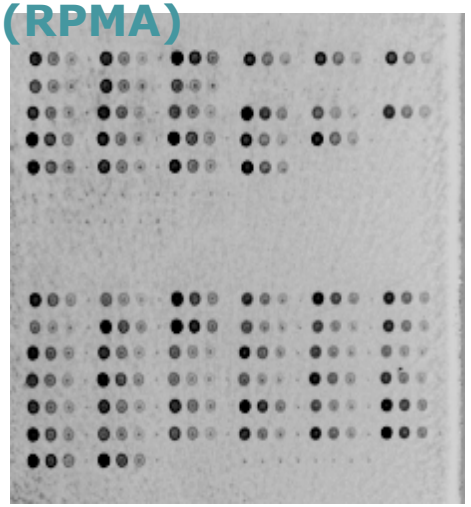
UNC, UCSF, NKI

p53 GeneChip



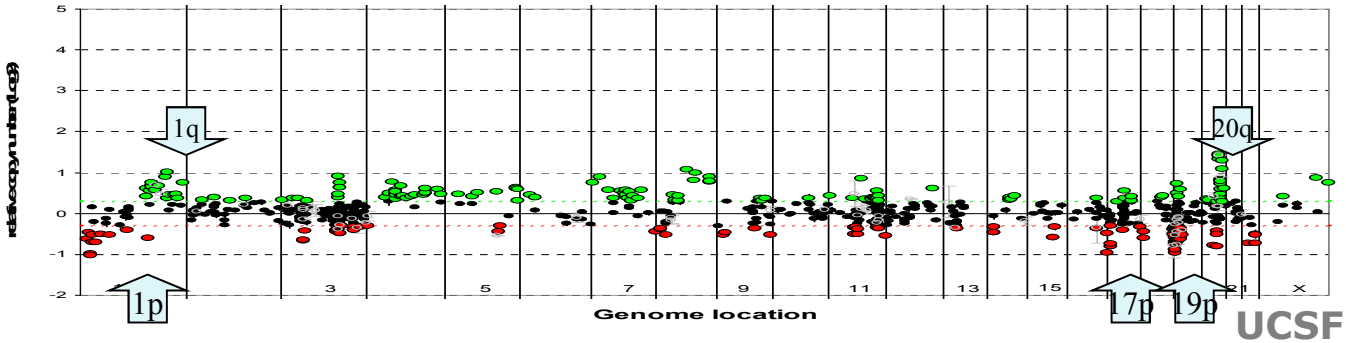
UNC

Protein Arrays (RPMA)



GMU

CGH

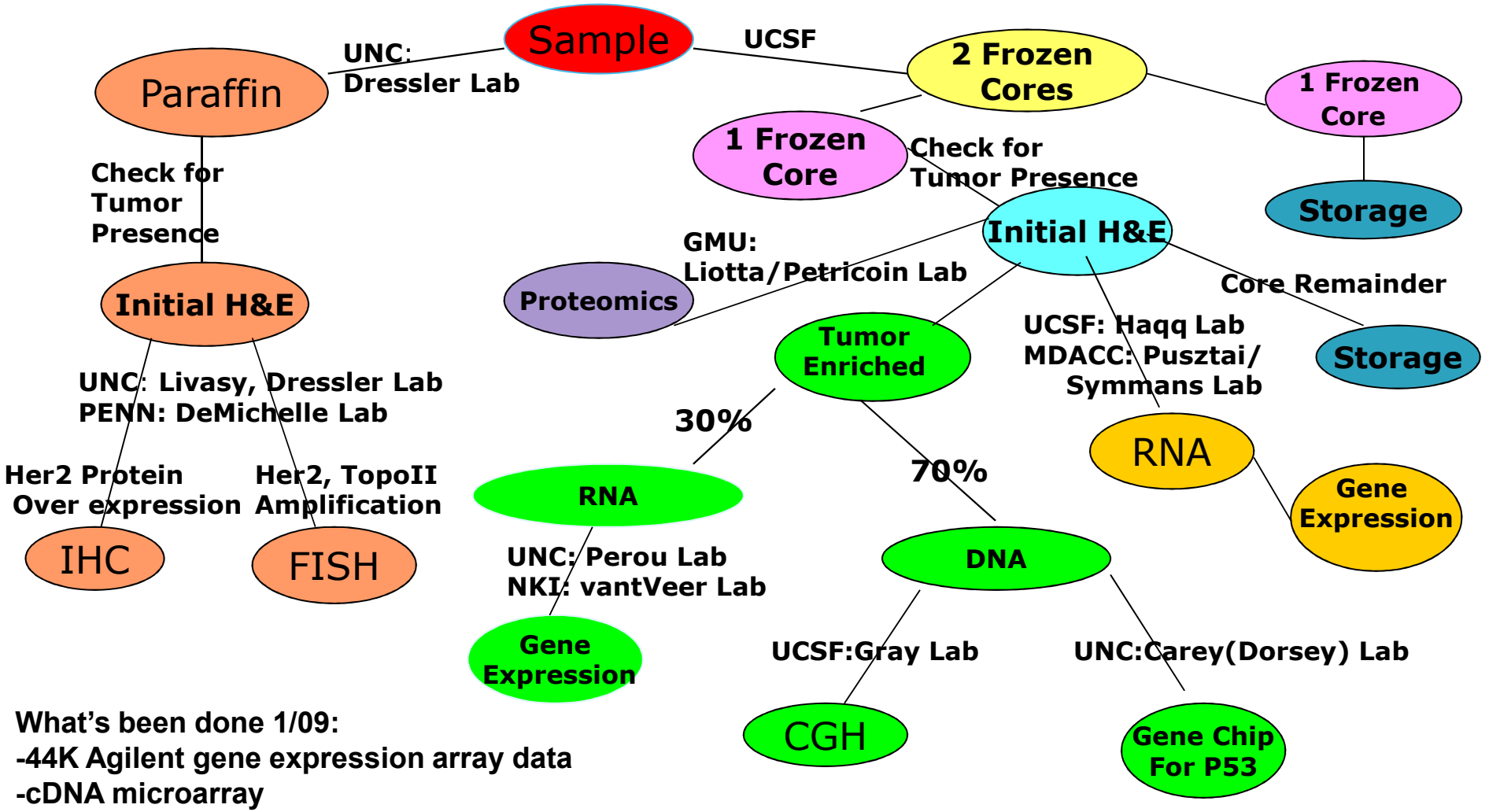


UCSF

Serum

Id1 proteins
autoantibodies
phospho proteins

Tissue Distribution & Analyses Schema



What's been done 1/09:

- -44K Agilent gene expression array data
- -cDNA microarray
- -MIP (CGH) array
- -p53 sequencing
- -RPMA
- -IHC/FISH

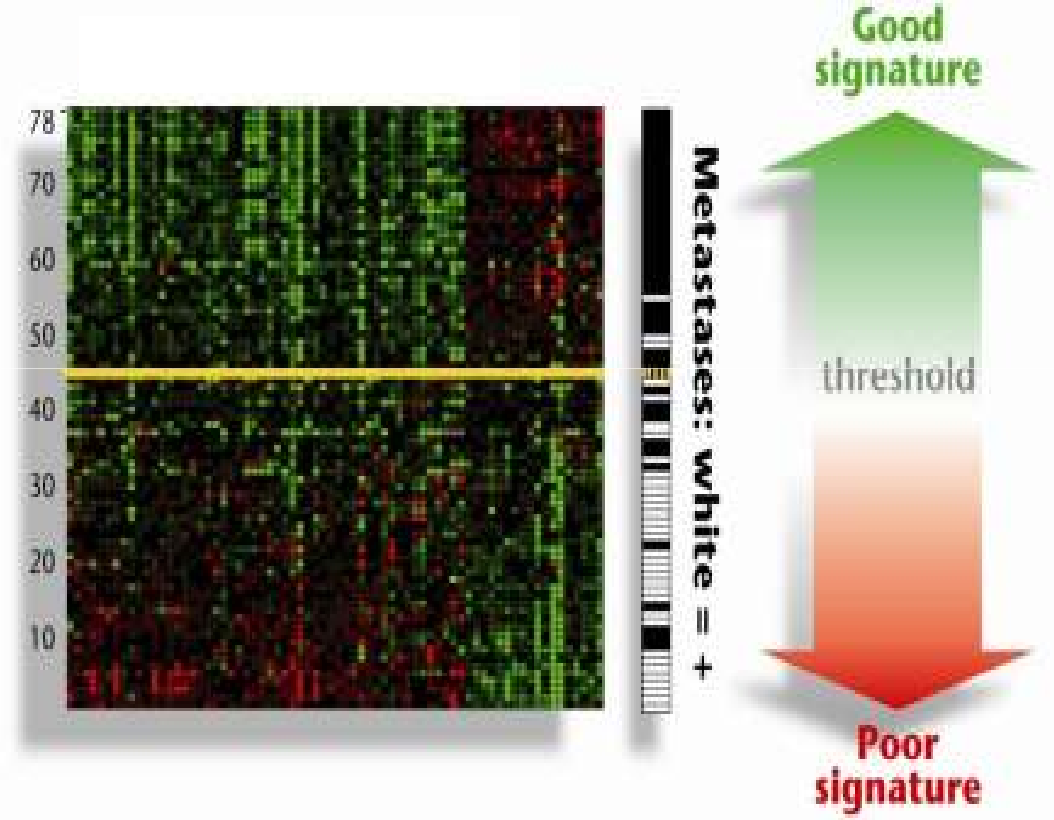
Data uploaded in
NCI caIntegrator **NCI: caBIG, Madhavan**
UCSC Cancer Genomics Browser **UCSC: Haussler, Kent, Zhu, Wang**

I-SPY: Majority Poor Prognosis Tumors

NKI 70 Gene Profile

"Good" Signature	**9%**
"Poor" Signature	**91%**

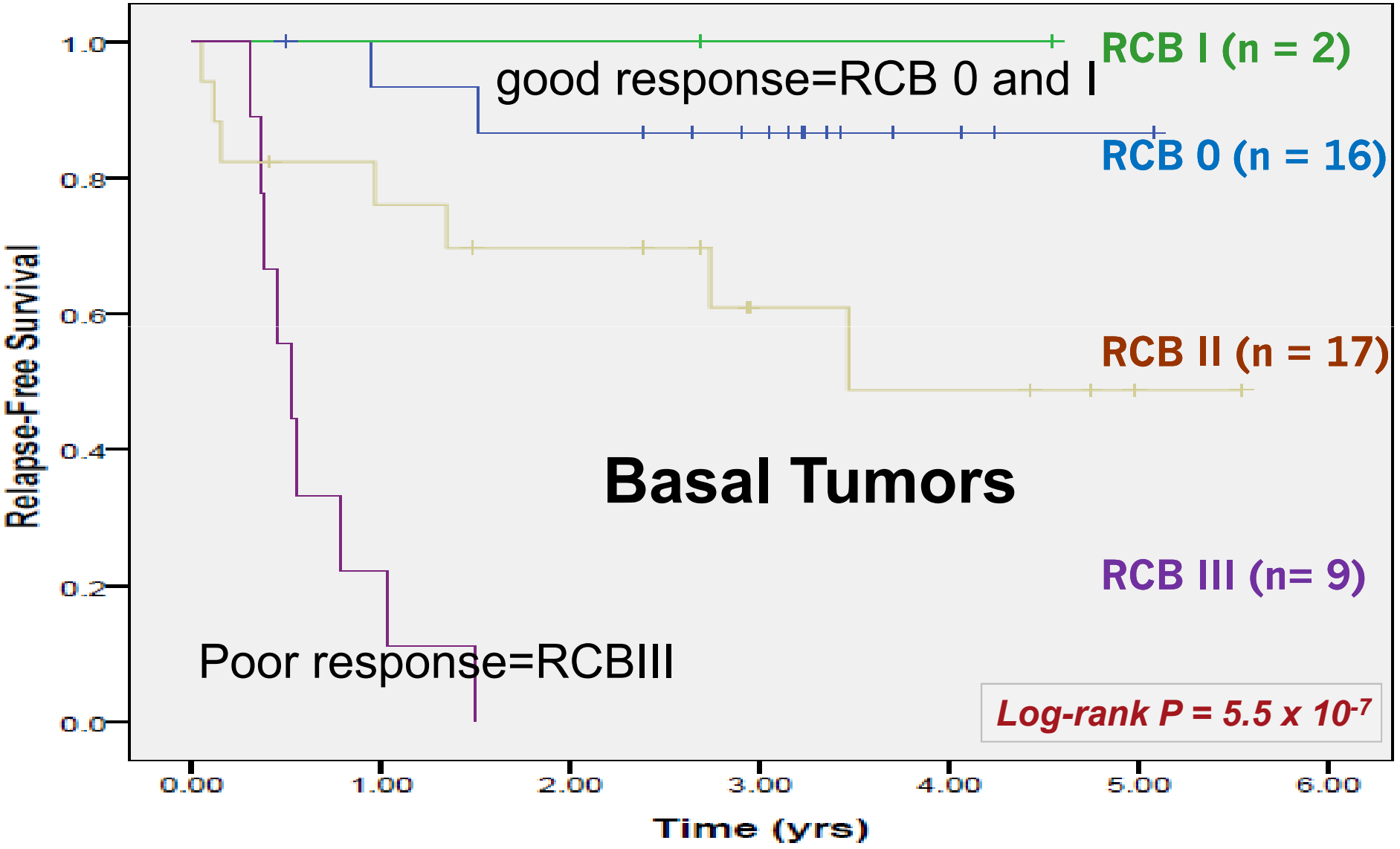
Mean Tumor Size= 6.0
Present as clinical mass
55% < Age 50



pCR Rates: RNA Classifiers

Gene Profile	Distribution (n = 149)	pCR (n = 144)	P-value
ROR-S (intr subtypes)			
Low	26%	5%	
Moderate	38%	22%	
High	37%	40%	8.8 x 10-4
NKI 70			
Good Signature	9%	0%	
Poor Signature	91%	27%	0.038
Wound Healing			
Quiescent	23%	6%	
Activated	77%	30%	0.0049
p53 Mutation Gene signature			
Wildtype	50%	11%	
Mutation	50%	38%	3.7 x 10-4

Relationship of RCB with Early Relapse for 'poor biology' I-SPY 1 Patients



Recurrence-free survival after neoadjuvant therapy: 1) Good Prognosis Biology Tumors

All do well REGARDLESS of pathological response (pCR and non-pCR) in neo-adjuvant phase

No response, still good outcome, risk of recurrence low

Good Biology Tumors do not benefit from Chemotherapy

Esserman et al, DeMichele et al, van't Veer et al, ASCO, ASCOBreast, SABCS 2009

Recurrence-free survival after neoadjuvant therapy: 2) Poor Prognosis Biology Tumors

pCR (and RCB) in neo-adjuvant phase are VERY significant predictors of early relapse in the context of a poor prognosis profile

No response, no good outcome, risk of recurrence high

Response, better outcome, risk of recurrence lower

Poor Biology Tumors (subset) do benefit from Chemo

Esserman et al, DeMichele et al, van't Veer et al, ASCO, ASCOBreast, SABCS 2009

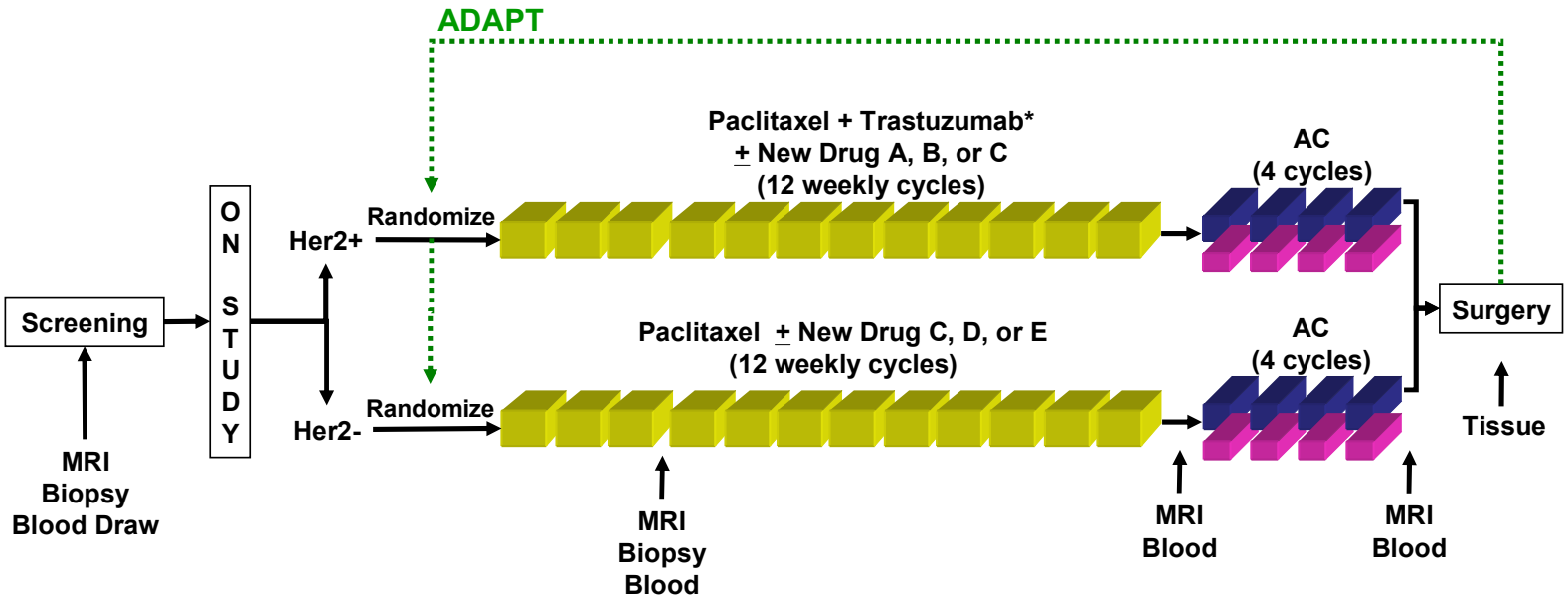
Rapidly Learn to Tailor Agents
I-SPY 2

Adaptive Design, Integration of Biomarkers

I-SPY 2 is Designed to

- Screen phase 2 agents in combination with standard chemotherapy in neo-adjuvant setting
  - Endpoint is pCR
  - “threshold” for ‘graduation’ is 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair
- Select high risk biology patients only, in highest need of (more) effective therapies
- Accelerate process of identifying drugs that are effective for specific breast cancer subtypes
  - Integration of biomarkers
- Reduce the cost, time, and numbers of patients needed to get effective drugs to market

I-SPY 2 Adaptive Trial Outline



**New Drug may be used in place of Trastuzumab in Experimental Treatment Arm*

Accrual: Anticipate 800 patients over 3–4 years

Enroll: ~20 patients per month

Participating Sites: 15–20 across US and Canada

I-SPY 2 Adaptive Trial Schema: Screening & Randomization

Eligibility Assessment Process

Patient presents with newly diagnosed ≥ 2.5cm invasive tumor

Core biopsy to assess eligibility

Eligibility determined by:
- Ability to tolerate MRI
- Ability to generate 44k Agilent microarray

Is patient:
- **MammaPrint Low**
- ER + and HER2 –

No

Patient On Study
Randomized to treatment arm based on:
- ER, PR status
- HER2 Status
- MammaPrint score

Yes

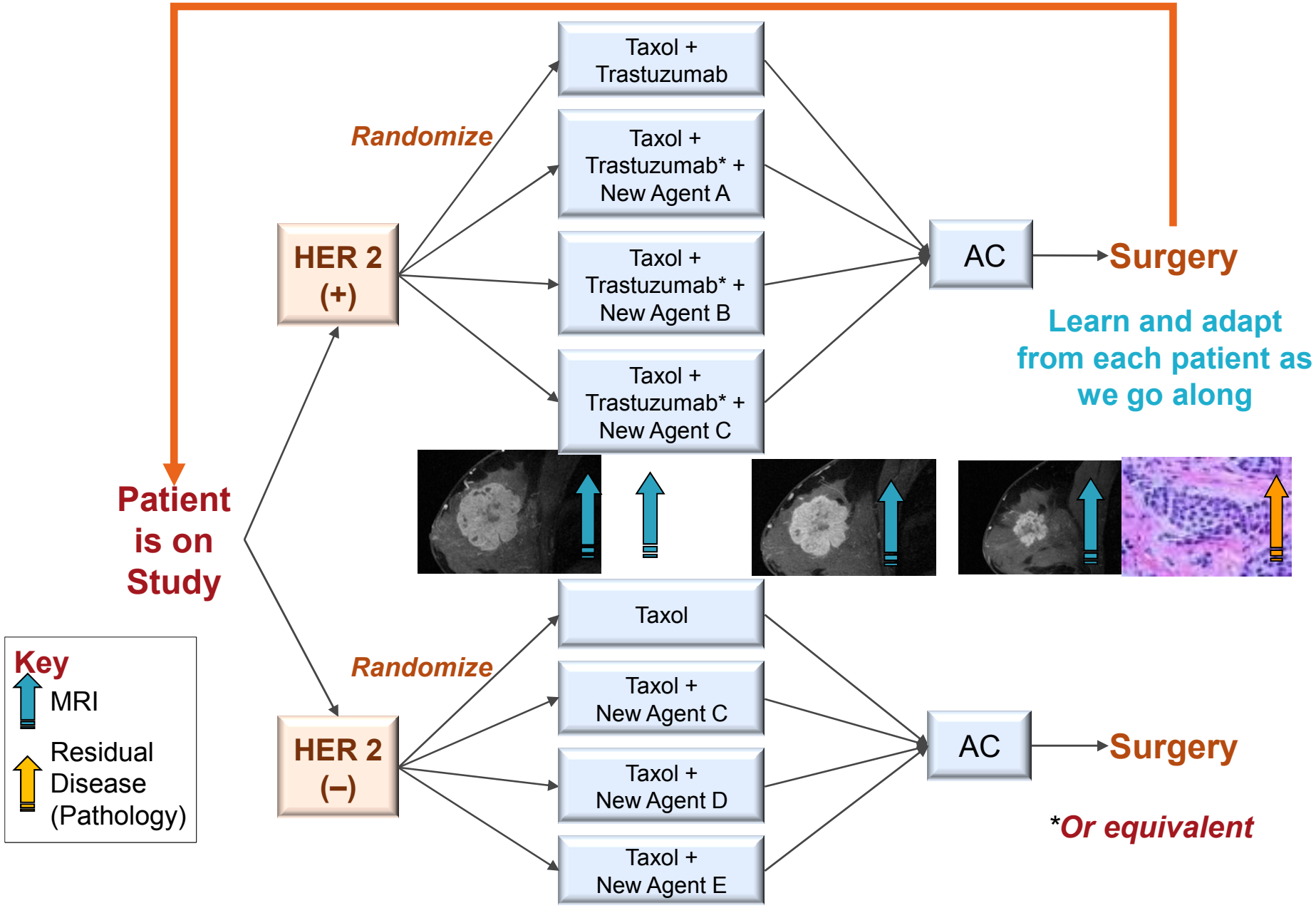
Patient not on study
Not considered good candidate for chemotherapy

TARGET PATIENT POPULATIONS FOR PROPOSED TIER 1 AGENTS

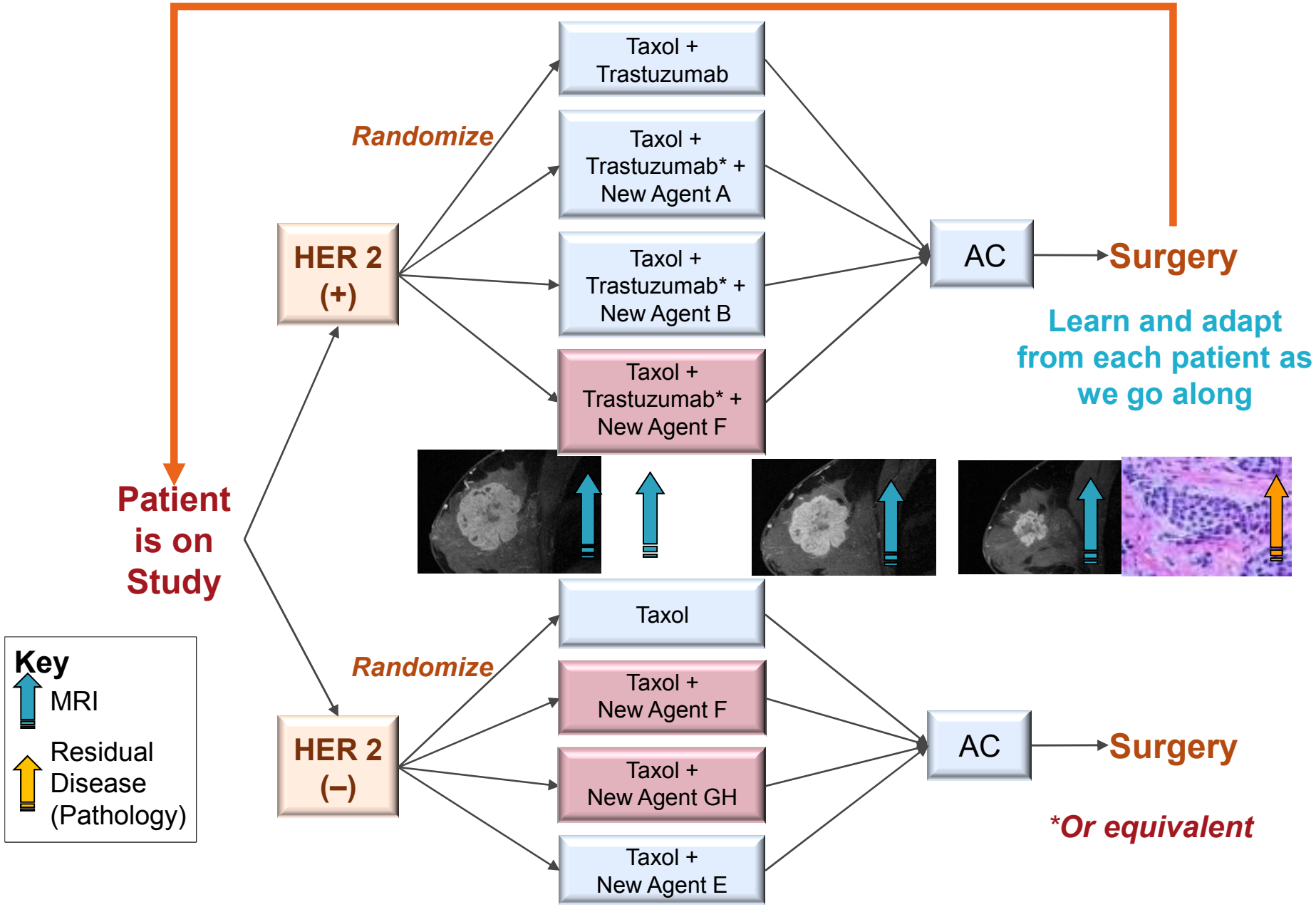
Agent	HER2+ / Any HR Cancers	HER2- / HR+ Cancers	HER2 - / HR - Cancers
PARP Inhibitor	No	Yes	Yes
IGFR Inhibitor	No	Yes	Yes
HER2 TKI Inhibitor	Yes*	No	No
APO/TRAIL	No	Yes	Yes
Vascular Disrupting Agent	No	Yes	Yes

** Investigational agent will be given in place of trastuzumab for HER2+ study participant.*

I-SPY 2 Adaptive Trial:
Introduce several new agents for a given profile

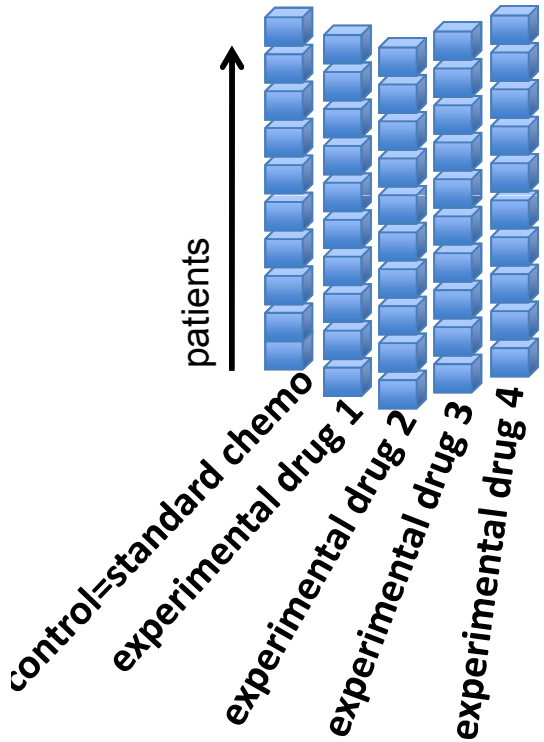


I-SPY 2 Adaptive Trial:
Learn, Drop, Graduate, and Replace Agents Over Time



First part - ‘Learning’
random randomization and observation

At start of trial:
patients randomly
assigned to arm

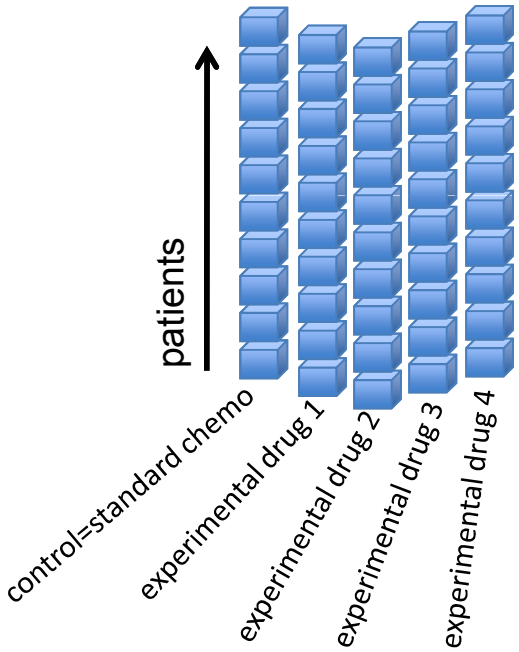


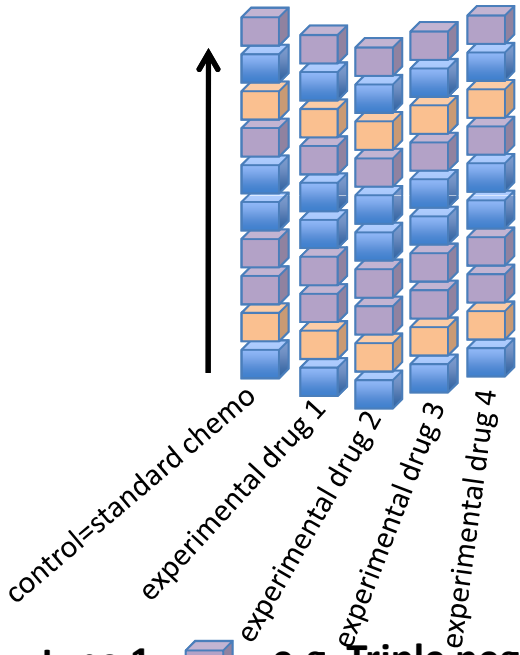
all experimental arms
plus standard chemo

First part - ‘Learning’ random randomization and observation

At start of trial:
patients randomly assigned to arm

At entry of trial:
patients tumor biology assessed, ER,PR,Her2, MammaPrint-index (stratified per arm)





type 1 **e.g. Triple negative**
type 2 **e.g. ER pos MammaPrint-very high**
type 3 **e.g. ER pos**
type 8 **etc etc**

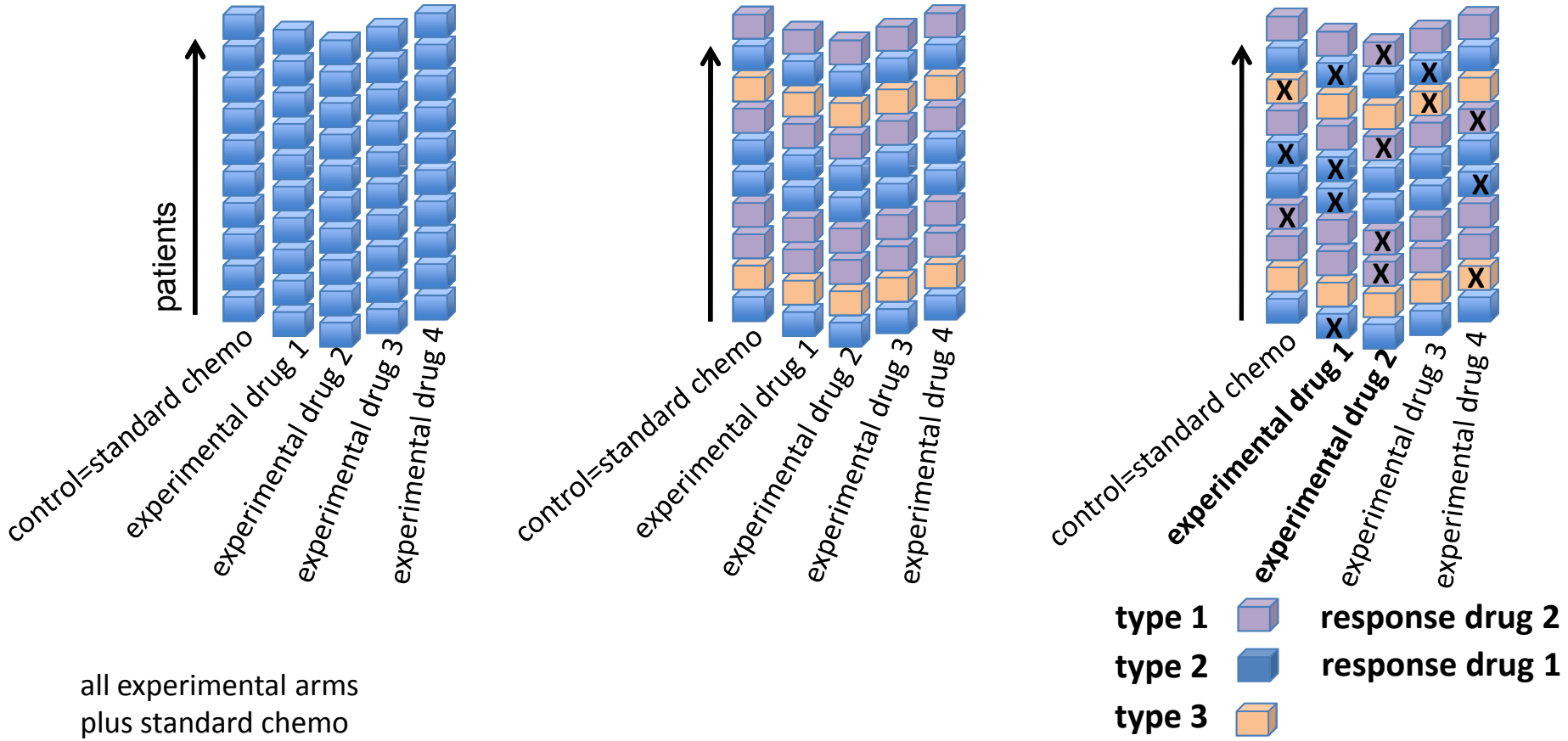
all experimental arms
plus standard chemo

First part - 'Learning' random randomization and observation

At start of trial:
patients randomly assigned to arm

At entry of trial:
patients tumor biology assessed, ER,PR,Her2, MammaPrint-index (stratified per arm)

At surgery:
tumor response assessed (pCR=X) and evaluated for biology specific association



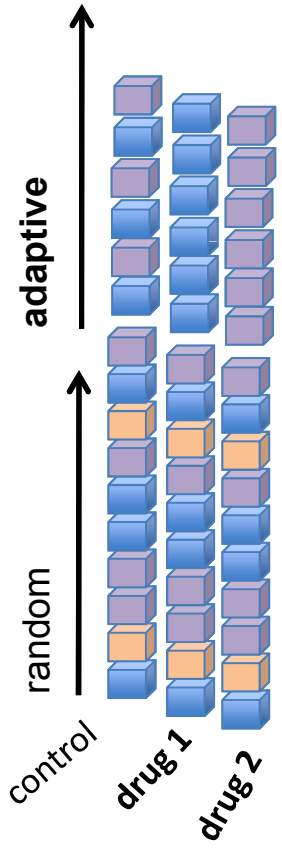
all experimental arms plus standard chemo

Continued in to - ‘Adaptive’ part assigned randomization and evaluation

At entry of trial: assigned randomization based on patients tumor biology, ER,PR,Her2, MammaPrint-index

Biology type 2 -> drug 1 or control

Biology type 1 -> drug 2 or control



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At entry of trial: assigned randomization based on patients tumor biology, ER,PR,Her2, MammaPrint-index

Biology type 2 -> drug 1 or control

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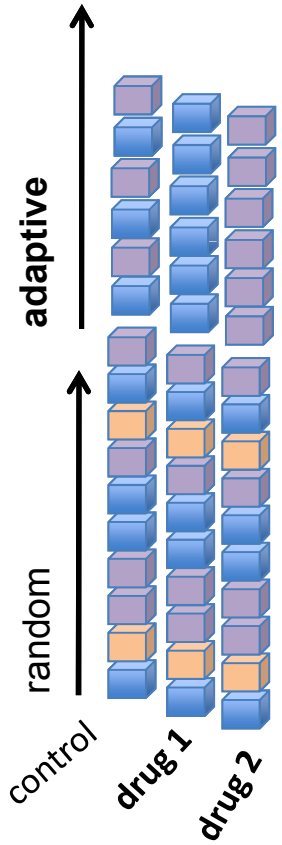
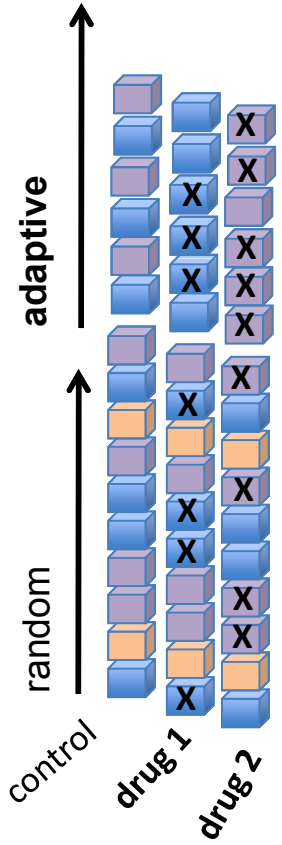


all experimental arms plus standard chemo

At surgery:
tumor response assessed (pCR=X) and evaluated for biology specific association



- endpoint is pCR
- “threshold” is 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair
- anticipated 100-120 patients needed per arm to find successful drug-biomarker combination or a failure

Biomarkers in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established/Approved Biomarkers
  - IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers (discovery of new markers of response prediction)

FDA Cleared or Approved

CLIA

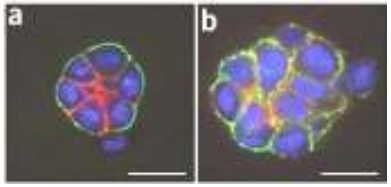
Qualifying Biomarker

Lawrence Berkeley National Lab 60 Cell Line Analysis

Trial Preparation

I-SPY 2 investigational agents are applied to the 60 LBNL Breast Cancer Cell Lines identified using the Panomics QuantiGene Plex 2.0 Assay.

Cell lines are evaluated based on response to agents to predict effectiveness of the agents by cell line



a = normal cells b = malignant cells

Participant Treatment

Biopsy is taken from the trial participant's tumor and predictive gene expression profile generated using the Panomics QuantiGene Plex 2.0 Assay in a CLIA certified lab.

Trial Participants are treated with an investigational agent based on trial randomization

Results of treatment on participants are evaluated

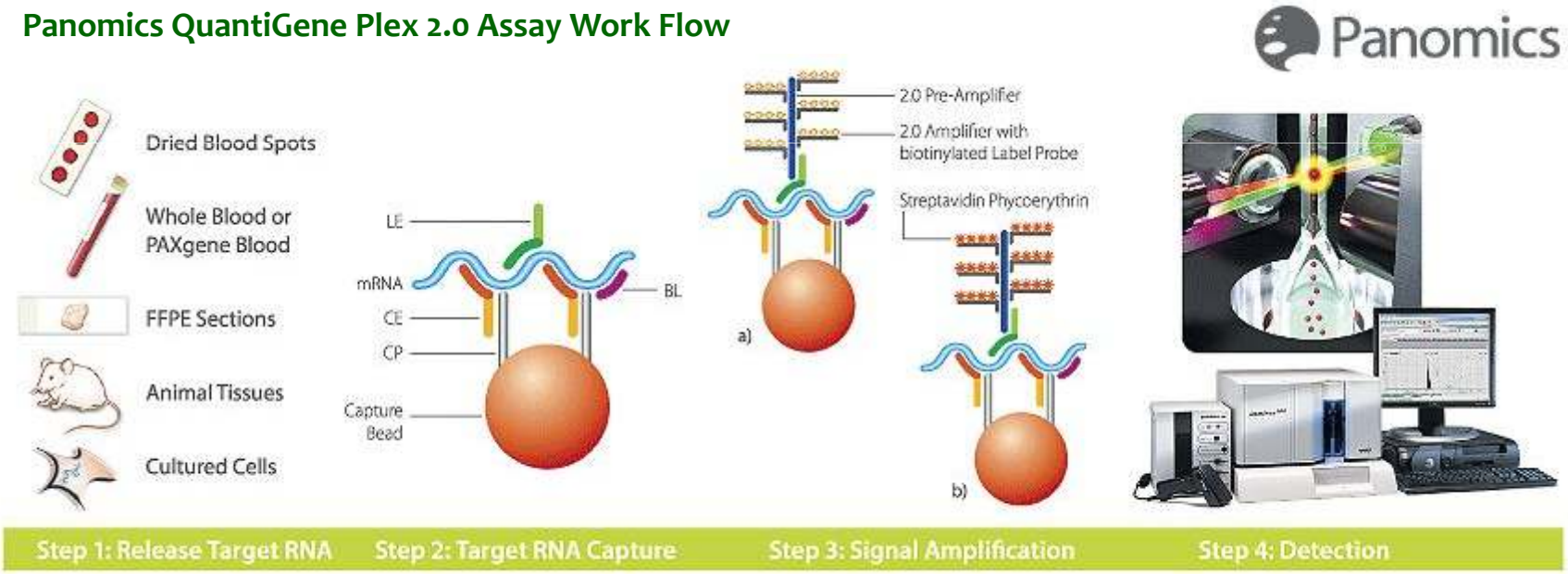
Post-Treatment Analysis

Actual participant responses are compared to predicted responses based on cell line. signature

Qualifying Biomarker: Predictive Markers
Lawrence Berkeley National Lab 60 Cell Line Analysis using the Panomics QuantiGene Plex 2.0 Assay

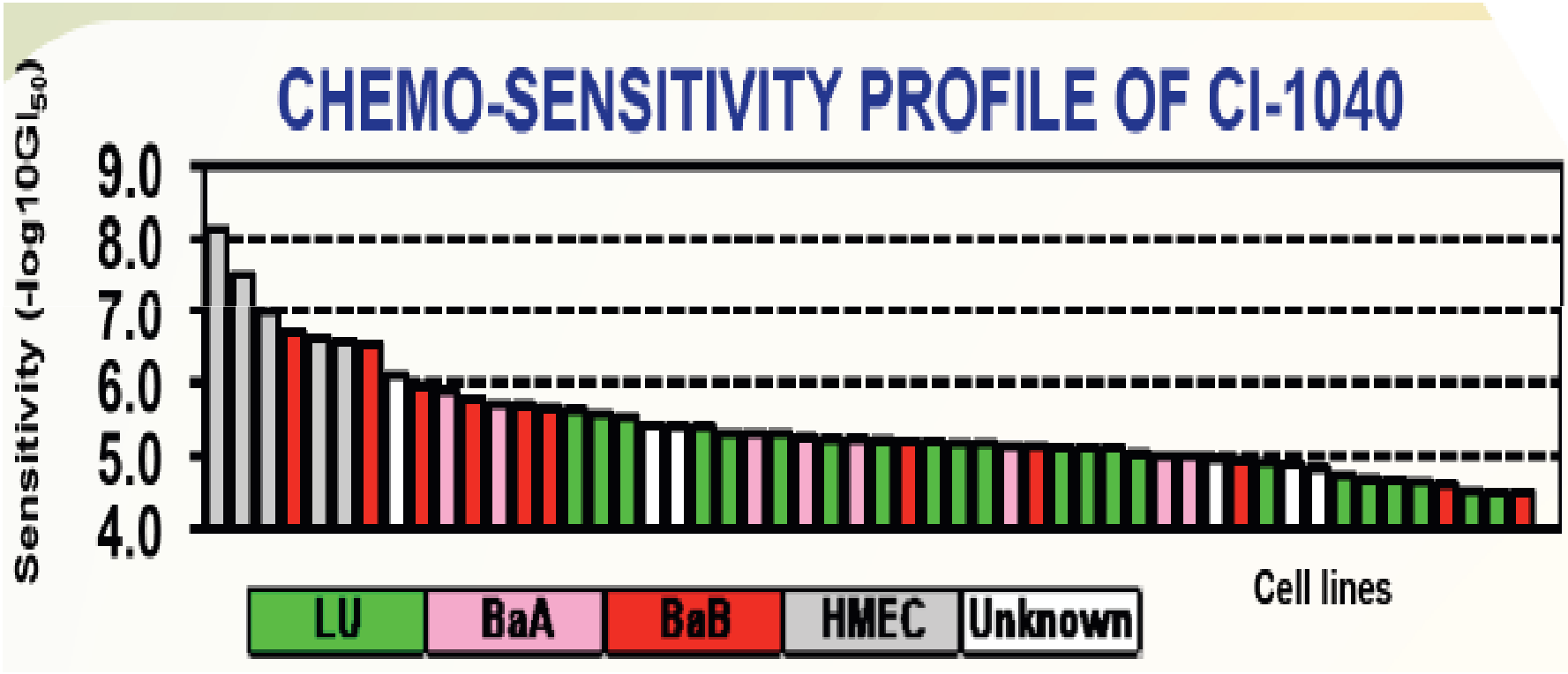
The participant's tumor is matched to one of the 60 cell lines using the gene expression profile determined using the Panomics QuantiGene Plex 2.0 Assay.

Panomics QuantiGene Plex 2.0 Assay Work Flow



Joe Gray et al

Targeting MEK in 46 cell lines
Gray Lab – a pilot



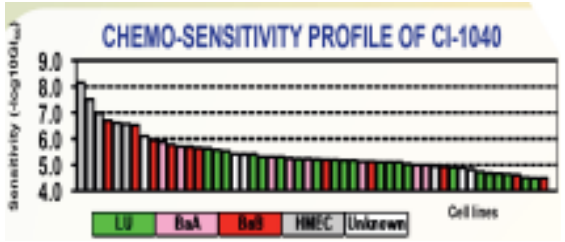
Sensitive ----------Resistant

Red: basal-type; Green: luminal-type cell lines

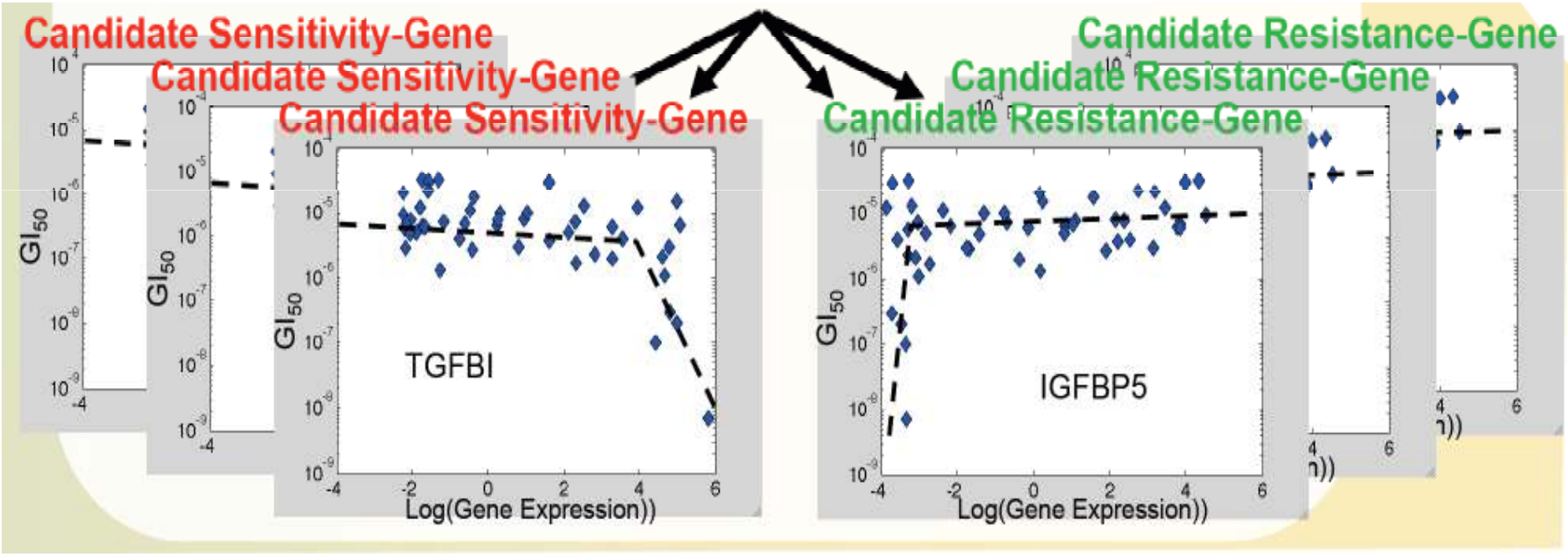
SABCS poster #2042 Wolf et al

Korn 2009

in vitro derived MEK response markers



SABCS poster #2042
Wolf et al



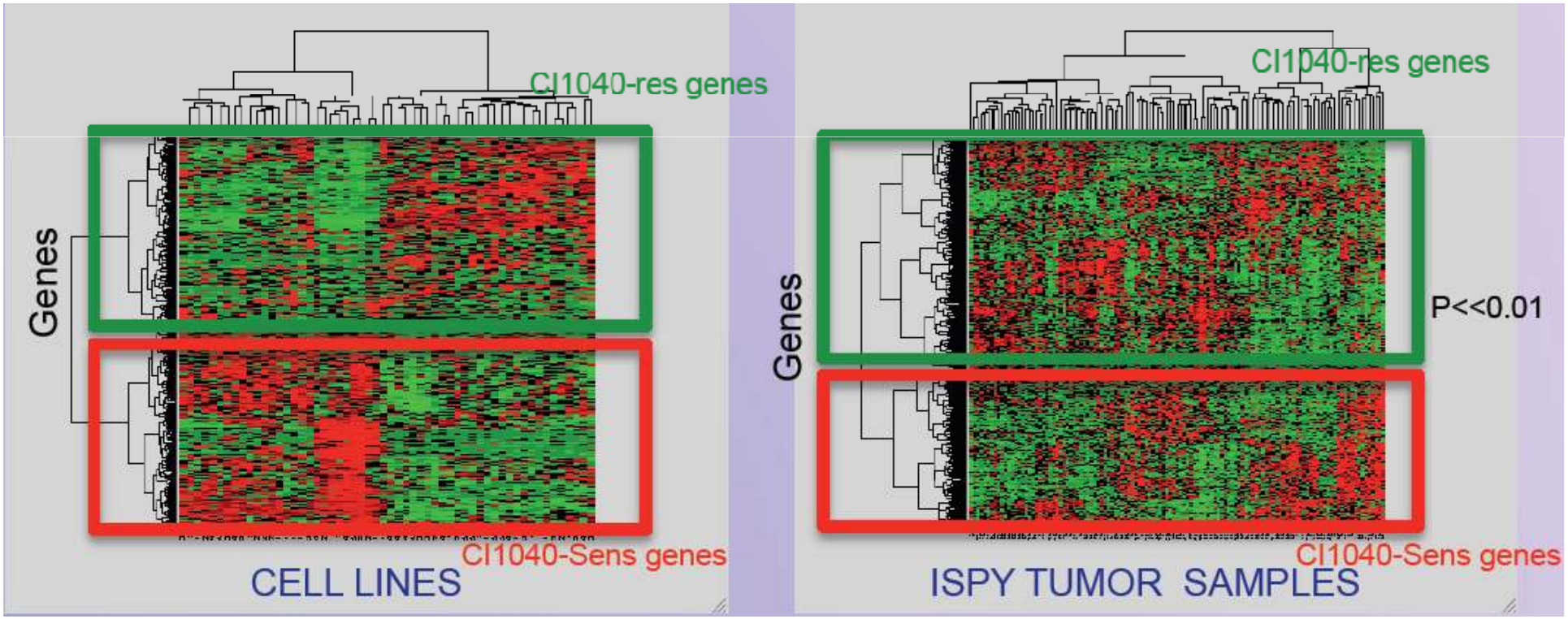
Analysis of *in vitro* data using adaptive splines identified 406 genes predictive of response to **CI1040**, **135 and 271** were expressed **more highly in CI1040-resistant or –sensitive cell lines respectively**

in vitro derived MEK response markers

Co-expressed predictor genes in cell lines also co-expressed in human tumor biopsies

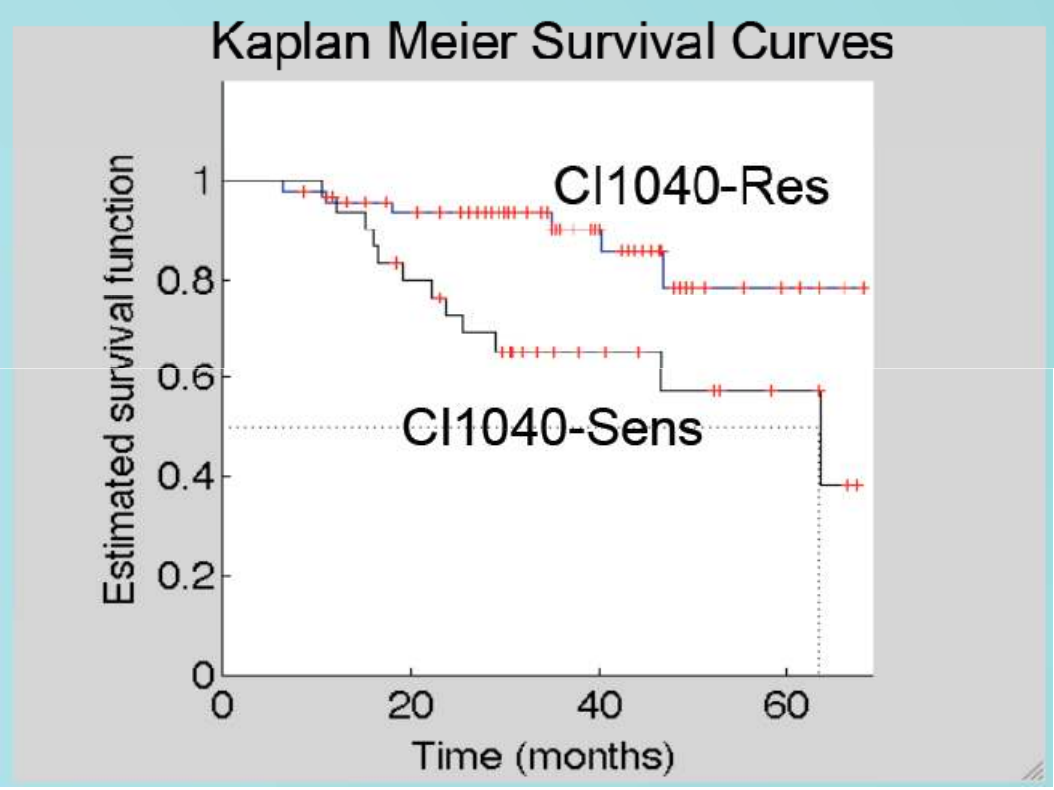
Cell Lines

Human Tumor Biopsies



Hierarchical clustering with 135 and 271 that were expressed more highly in CI1040-resistant or –sensitive cell lines respectively

I-SPY1 patient biopsies evaluated for MEK response markers



SABCS poster #2042
Wolf et al

Hypothesis:
MEK inhibitor sensitive patients could potentially benefit

I-SPY clinical trial patients received standard taxol/anthracyclin neo-adjuvant therapy; biopsies pre-treatment analysed for gene expression
Median survival 3.6 years

Breast Cancer subtypes and marker identification to guide therapy

testing *in vitro* derived response markers
in human breast cancer biopsies

- Existence of cell line response expression patterns in human tumors (Clinical trial I-SPY1)
- Provide a system were cell line response markers are ‘qualified’ in patients treated with the same drug (Clinical trial I-SPY2)
- Provide a system were validated markers can be used to drive treatment selection for specific drugs (Clinical trial I-SPY2)

neo-adjuvant design integrating molecular and imaging data to optimize effective treatment assignment