

# Precision Medicine Initiative for Oncology

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# Precision Medicine Initiative

## Proposed FY16 Support

Agency	\$ Million
NIH	200
• <i>Cancer</i>	70
• <i>Cohort</i>	130
FDA	10
Office of the National Coordinator for Health Information Technology	5
<b>TOTAL</b>	<b>\$215</b>

## Precision Medicine Initiative: Oncology

### What Problems Are We Trying to Solve?

- For most of its 70-year history, systemic cancer treatment has relied on drugs marginally more toxic to malignant cells than to normal tissues
- Molecular markers to predict benefit or understand therapeutic resistance in the clinic have usually been lacking

### Proposed Solution to These Problems

- Use genomics to identify and target molecular vulnerabilities of individual cancers

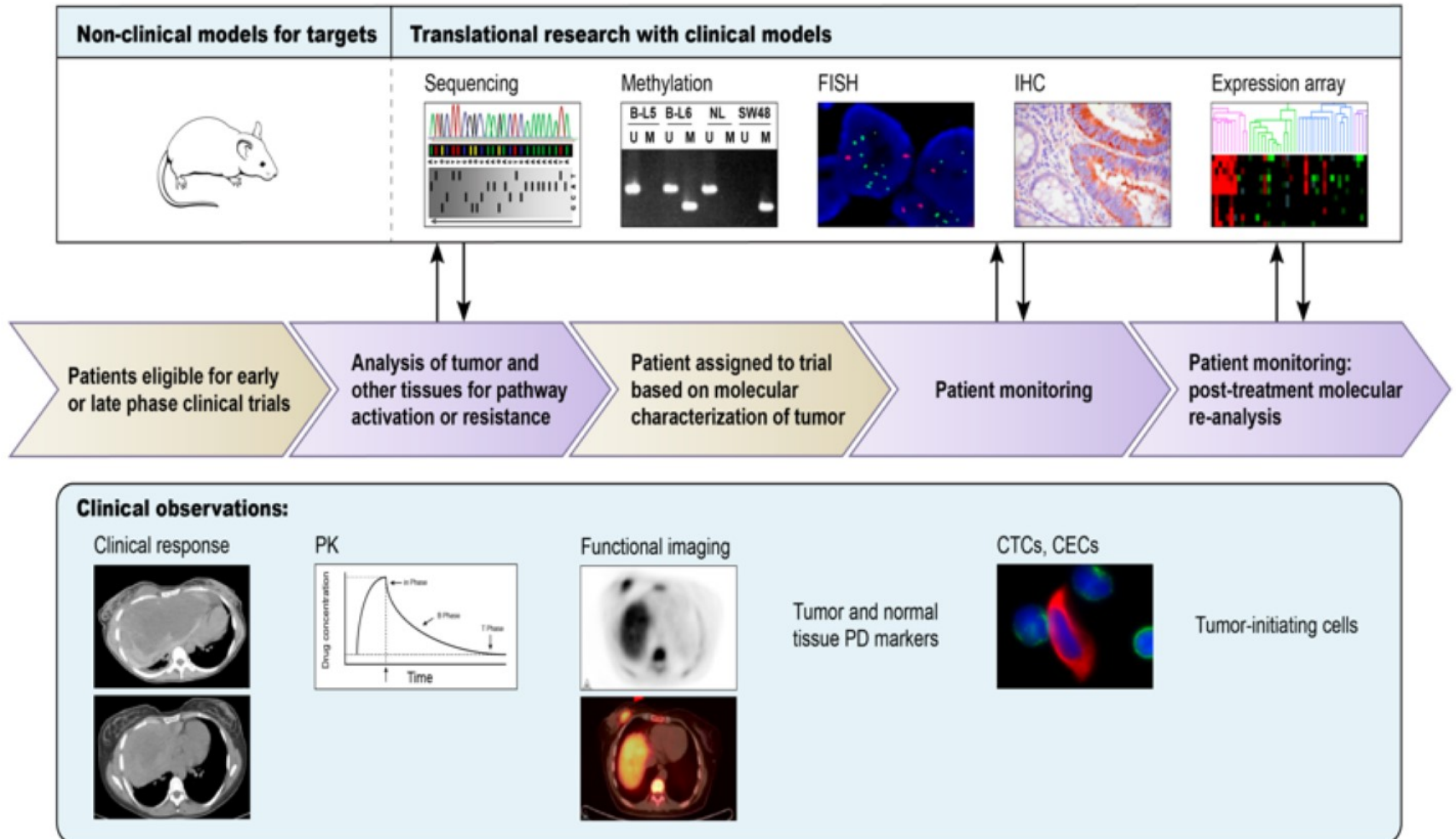
# A Modified Definition of Precision Medicine

Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.

*Modified by D. Lowy, M.D. from: IOM's Toward Precision Medicine, 2011*



# Precision Medicine/Oncology in Practice



## Precision Medicine Initiative: Oncology

### Increase Genomics-Based Clinical and Preclinical Studies of Cancer Treatment

- Expand genomics-based clinical trials
- Understand & overcome resistance to targeted drugs; drug combinations; and mechanistic understanding of immunotherapy
- Repository of patient-derived pre-clinical models for evaluating targeted therapeutics: Lou Staudt
- National cancer database to integrate genomic information with clinical response and outcome: Warren Kibbe

## Precision Oncology Trials Launched

2014:

**MPACT**

**Lung MAP**

**ALCHEMIST**

**Exceptional Responders**

2015:

**NCI-MATCH**

**ALK Inhibitor**

**MET Inhibitor**

## **NCI-MATCH: Features (1)**

**[Molecular Analysis for Therapy Choice]**

- Foundational treatment/discovery trial; assigns therapy based on molecular abnormalities, not site of tumor origin for patients without available standard therapy
- Regulatory umbrella for phase II drugs/studies from > 20 companies; single agents or combinations
- Available nationwide (2400 sites)



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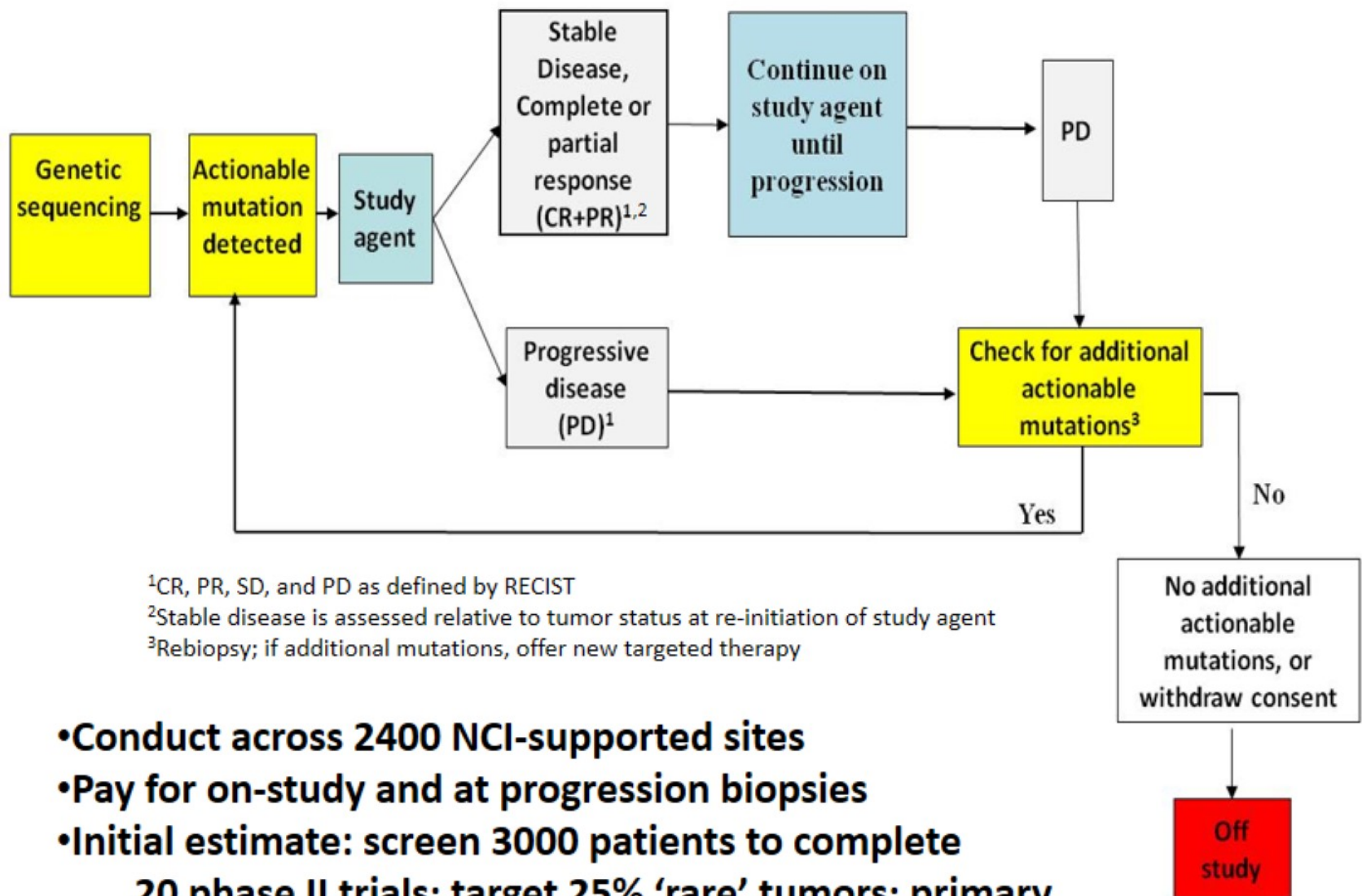
## **NCI-MATCH: Features (2)**

**[Molecular Analysis for Therapy Choice]**

- Validated and standardized gene sequencing at 4 sites; >96% concordance for “locked down” analysis of mutations in 143 genes using Ion Torrent PGM™ custom panel; fresh biopsies at study entry
- Co-developed by NCI and ECOG-ACRIN, part of NCTN; PI’s drawn from all network groups; trial planning by >150 clinical and pre-clinical scientists
- First patients to be entered July 2015



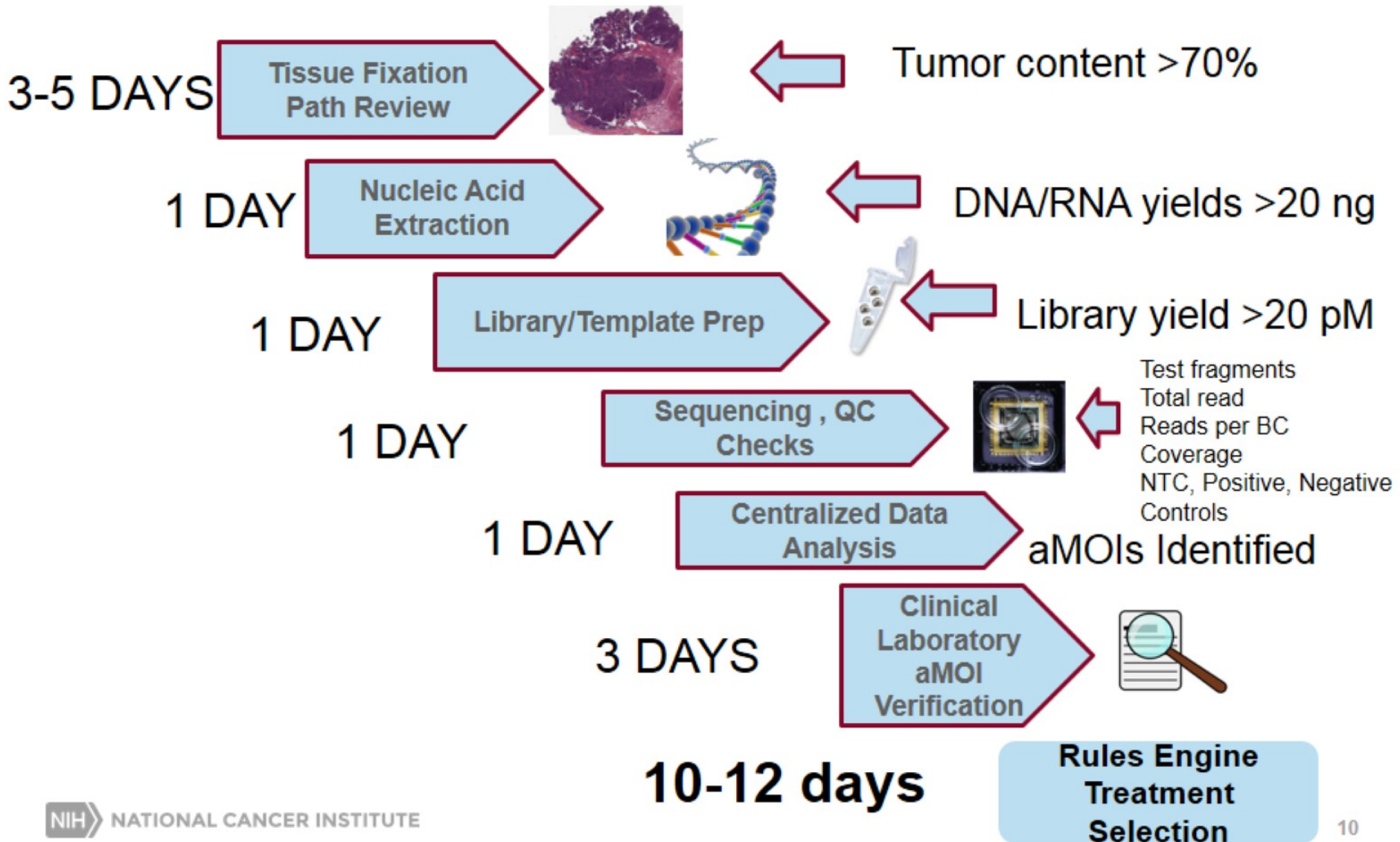
# NCI MATCH



- **Conduct across 2400 NCI-supported sites**
- **Pay for on-study and at progression biopsies**
- **Initial estimate: screen 3000 patients to complete 20 phase II trials; target 25% 'rare' tumors; primary endpoint RR 5% vs. 25%**

# MATCH Assay: Workflow for 10-12 Day Turnaround

Biopsy Received at Quality Control Center



## NCI-MATCH: Initial Ten Studies

Agent(s)	Molecular Target(s)	Estimated Prevalence
Crizotinib	ALK Rearrangement (non-lung adenocarcinoma)	4%
Crizotinib	ROS1 Translocations (non-lung adenocarcinoma)	5%
Dabrafenib and Trametinib	BRAF V600E or V600K Mutations (non-melanoma)	7%
Trametinib	BRAF Fusions, or Non-V600E, Non-V600K BRAF Mutations (non-melanoma)	2.8%
Afatinib	EGFR Activating Mutations (non-lung adenoca)	1 – 4%
Afatinib	HER2 Activating Mutations (non-lung adenoca)	2 – 5%
AZD9291	EGFR T790M Mutations and Rare EGFR Activating Mutations (non-lung adenocarcinoma)	1 – 2%
TDM1	HER2 Amplification (non breast cancer)	5%
VS6063	NF2 Loss	2%
Sunitnib	cKIT Mutations (non GIST)	4%

*Agents and targets below grey line are pending final regulatory review; economies of scale—larger number of agents/genes, fewer overall patients to screen*

**≈ 35%**



# PMI Oncology: Improving Cancer Treatment through Genomics

2006 -2014

TCGA

Targeted

Trials: MPACT,

ALCHEMIST,

Exceptional

Responders,

LungMAP

Oncogenic drivers of the same tumor type may be heterogeneous, but same driver may be found in several different tumor types

2015

NCI-MATCH

*Announced June 1, Opens in July throughout the US (2400 sites)*

- Unprecedented & incorporates all tenets of precision medicine
- Treatment is based on genes and their mutations rather than on organ site

2015 & Beyond

## THE PRECISION MEDICINE INITIATIVE FOR ONCOLOGY

### *ACCELERATING PROGRESS FOR PATIENTS*

- Dramatically expand NCI-MATCH umbrella: to include new trials, new agents, new genes, and new drug combinations
- Increase mechanistic understanding of immunotherapy: to broaden its appropriate use
- Create a repository of patient-derived pre-clinical models and evaluate liquid biopsies: to improve understanding of cancer and drug resistance and to identify drug combinations that overcome resistance
- Establish a national cancer database integrating genomic information with clinical response and outcome: to accelerate understanding of cancer and improve its treatment

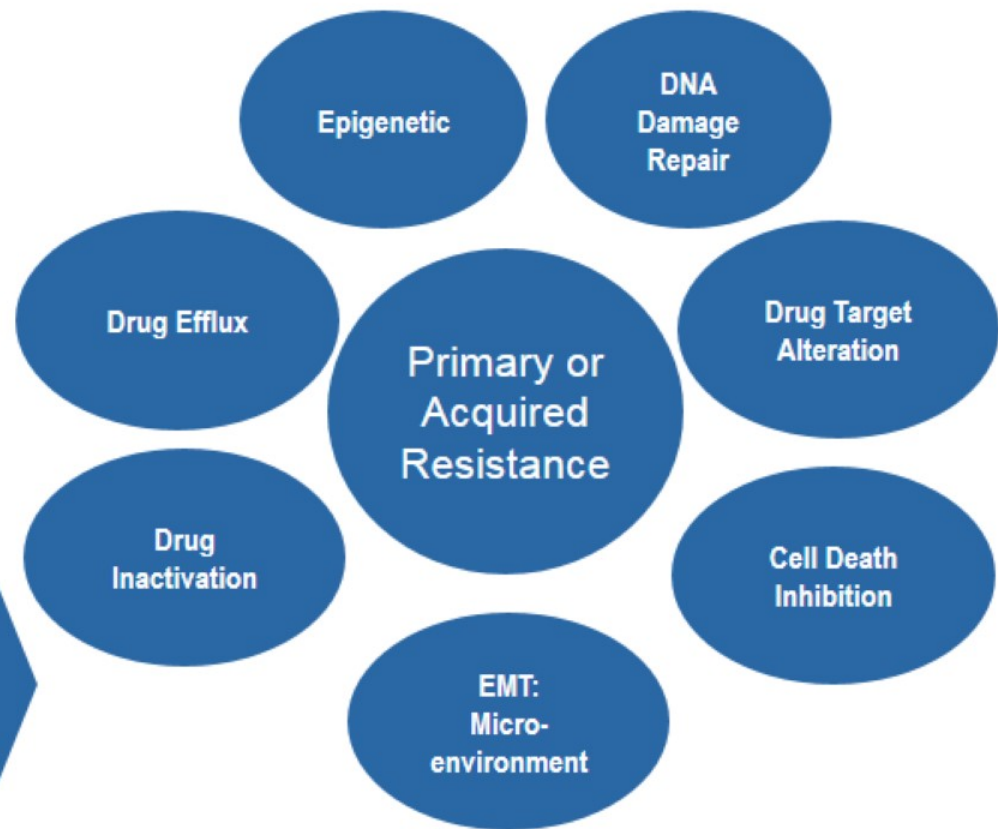


# *PMI for Oncology*

## Opportunities Enabled by PMI for Oncology: Expanding Genomically-Based Cancer Trials

- Accelerate Launch of NCI-Pediatric MATCH
- Broaden the NCI-MATCH Umbrella:
  - ✓ Expand/add new Phase II trials to explore novel clinical signals—mutation/disease context
  - ✓ Add new agents for new trials, and add new genes to panel based on evolving evidence
  - ✓ Add combination targeted agent studies
  - ✓ Perform Whole Exome Sequencing, RNAseq, and proteomic studies on quality-controlled biopsy specimens—extent of research based on resource availability
  - ✓ Add broader range of hematologic malignancies
- Perform randomized Phase II studies or hand-off to NCTN where appropriate signals observed
- Apply genomics resources to define new predictive markers in novel immunotherapy trials
- Expand approach to ‘exceptional responders’: focus on mechanisms of response/resistance in pilot studies

# Mechanisms of Resistance To Targeted Cancer Therapeutics



- Broad range of mechanisms
- Until recently, tools to interrogate possibilities in vivo quite limited
- Resistance to single agents inevitable: 1<sup>o</sup> or acquired; requires combinations but data to provide molecular rationale for the combination (both therapy & toxicity) not often available



# Principles of Combination Therapy to Overcome Resistance: Then (1975) and Now (2015)

## Cytotoxic

- Drugs are each active against the tumor in question (ORR)
- Drugs have different mechanisms of action to minimize resistance
- Drugs have different clinical toxicities to allow full dose therapy
- Intermittent intensive > continuous treatment for cytoreduction & to reduce immunosuppression

Cancer 35: 98, 1975

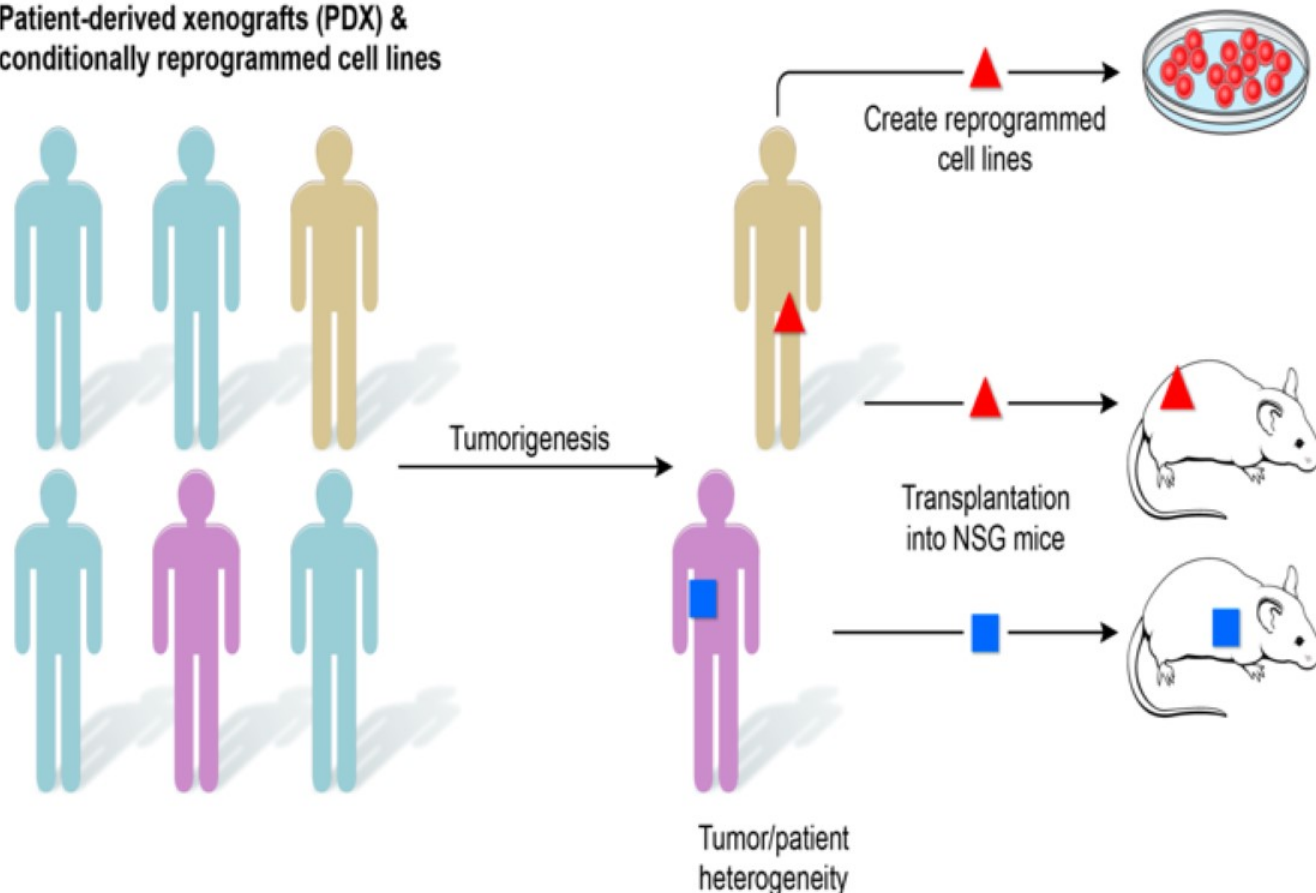
## Targeted

- Agent has therapeutic effect on molecular pathway in vivo
- Agents have complementary effects on the same target or other targets in the same pathway or pathways that cross-talk to control tumor growth
- Toxicities not overlapping with cytotoxics & moderate to allow prolonged administration; consider physiological consequences of target engagement—strong relationship to toxicity profile
- Schedule to maximize target inhibition: Either continuous Rx or high dose to suppress target a reasonable goal

Needs Full Experimental Verification

# New Patient-Derived Models for Precision Oncology to Study and Overcome Drug Resistance

Patient-derived xenografts (PDX) & conditionally reprogrammed cell lines



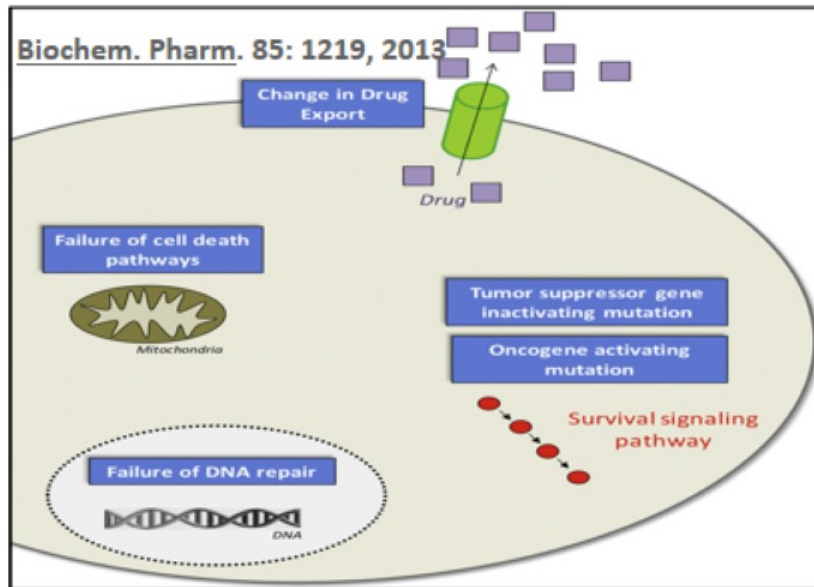
Molecularly characterize, treat/screen mice bearing transplants & cells with relevant drugs.

“Pre-clinical clinical trials”



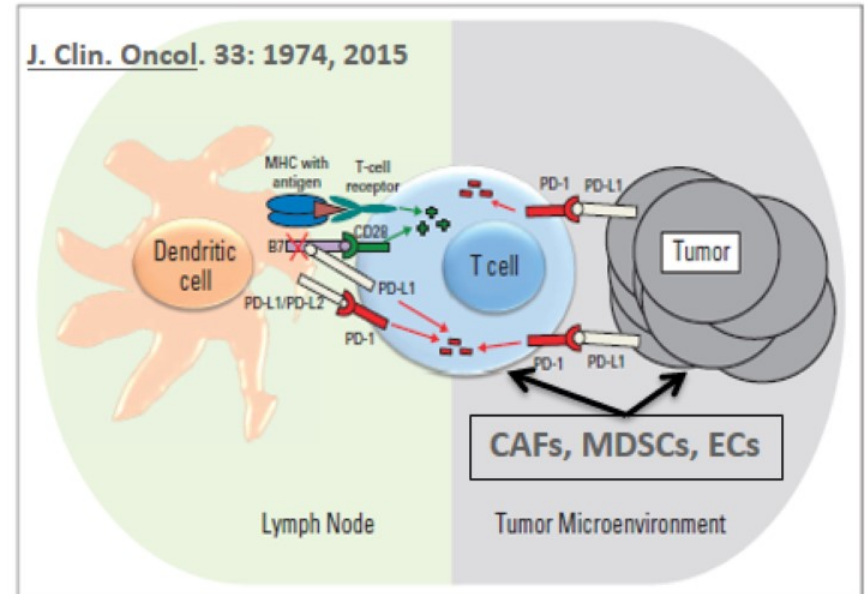
# Precision Medicine Approaches to Overcoming Resistance: Opportunities

## TUMOR CELL AUTONOMOUS



- Develop panel (>1000) of clinically annotated low passage organoids and conditionally reprogrammed lines for mutational evaluation, large scale systematic combinatorial drug screens, and resistance mechanism analysis
- On-study/at progression biopsies of NCI early phase trial patient cohort with resistant disease for molecular characterization (>500 pts/year); blood for CTC's, cfDNA, cfRNA, exosomes (liquid biopsies)

## TUMOR MICROENVIRONMENT



- Develop complementary Patient-Derived Models: clinically-annotated PDXs from drug-resistant tumors
- Use for pre-clinical modeling of molecularly targeted combinations and for co-clinical trials of NCI-IND agents
- Genomic underpinnings of immunotherapeutic checkpoint control

# Precision Medicine Initiative: Opportunities for Therapeutic Oncology

## Developing Input from Extramural Community

- Organoids & Reprogrammed Cell Lines: Lou Staudt, M.D., **July 2015**
- Exceptional Responders Workshop—Next Steps: Barbara Conley, M.D., **Fall 2015**
- Immunotherapy—Combination Approaches and NGS: Helen Chen, M.D., **Fall 2015**
- PDX Models, Combination Therapy, and Drug Resistance: J. Doroshow, M.D. and Dinah Singer, Ph.D., **Fall 2015**
- Genomic Data Commons workshop: W. Kibbe, Ph.D., **Fall, 2015**



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