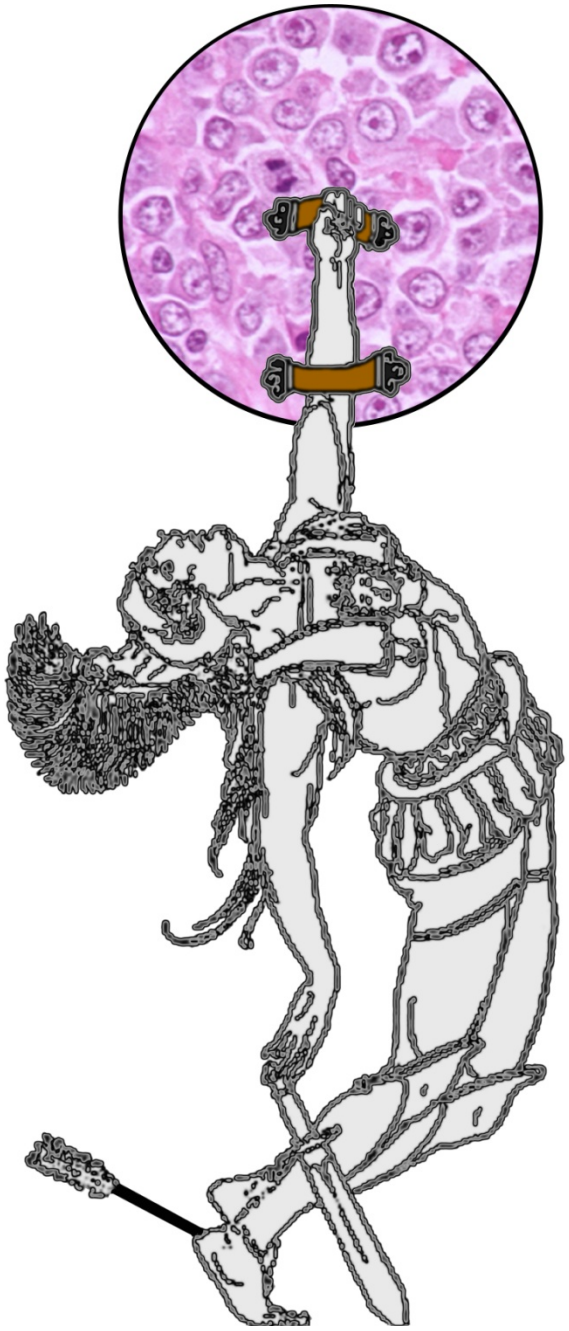
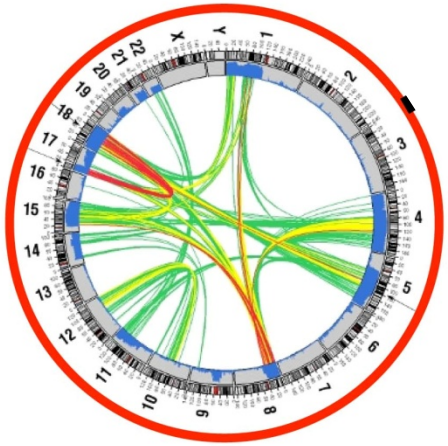


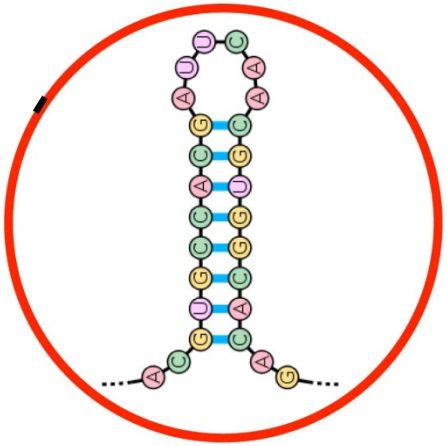
Vanquishing Cancer Through Genomics

…and by genomics I mean any systematic (genome-wide) approach to define the molecular basis of malignancy and identify curative strategies

Structural Genomics



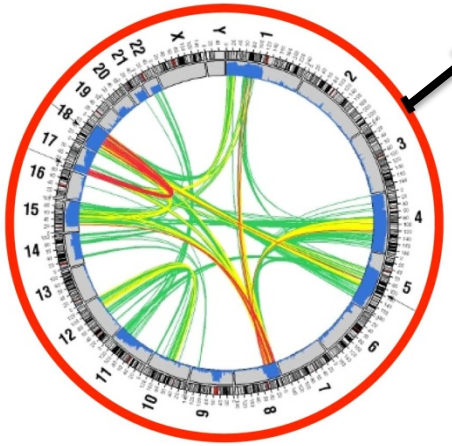
Computational Genomics



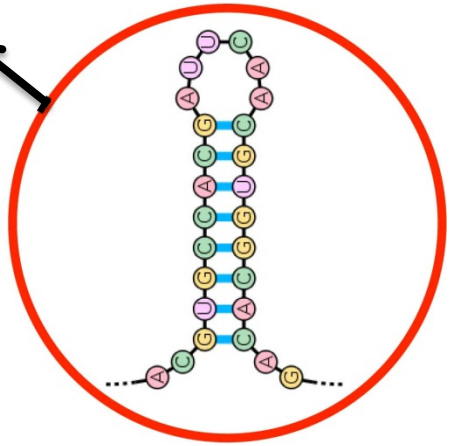
Functional Genomics

Structural Genomics

Essential cancer pathways

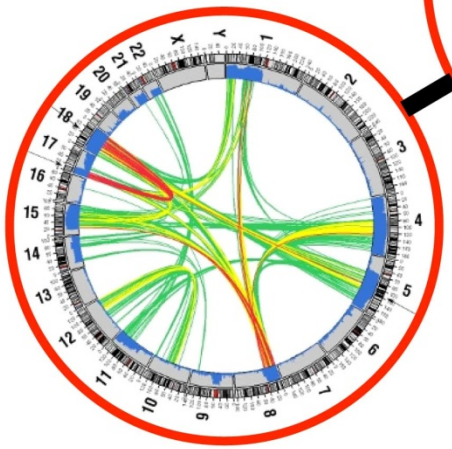


Computational Genomics

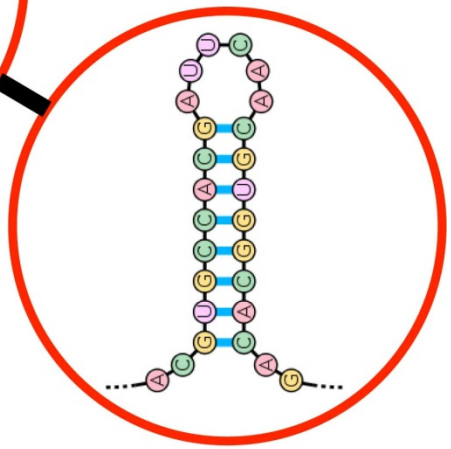


Functional Genomics

Structural Genomics



Computational Genomics



Functional Genomics

Metaphors of Cancer

- Cancer is a genetic disease

Pathways

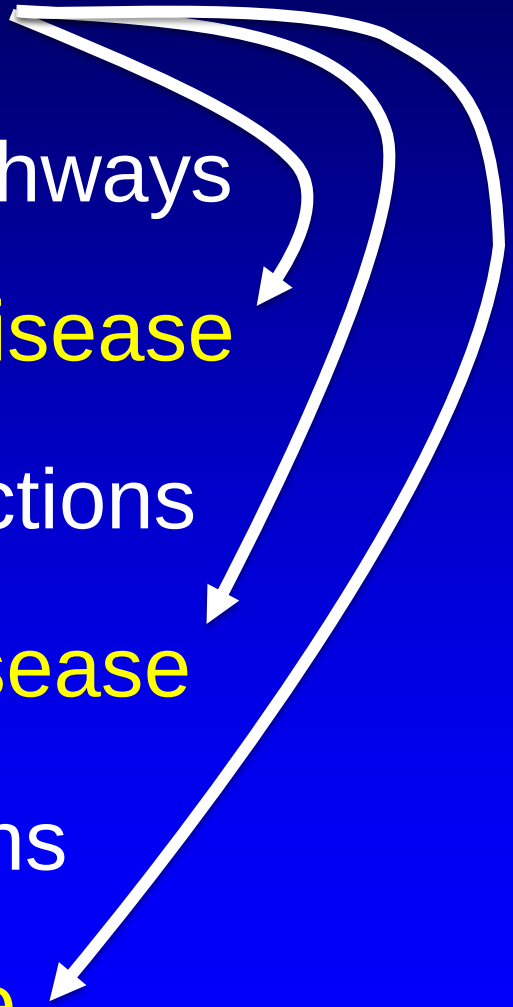
- Cancer is a cell biological disease

Cellular interactions

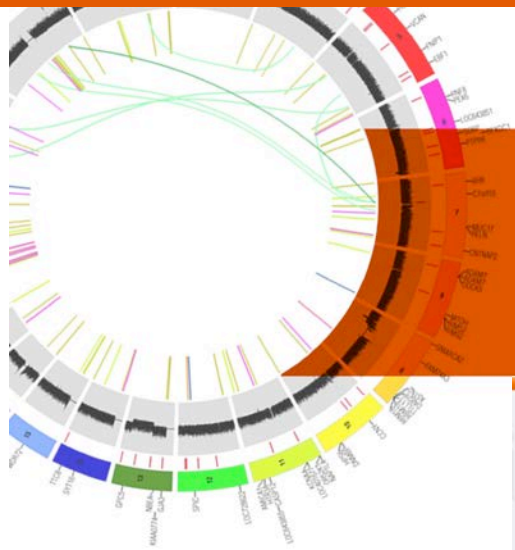
- Cancer is an organismal disease

Environmental interactions

- Cancer is a societal disease



NCI Center for Cancer Genomics: Current Initiatives



The Cancer Genome Atlas

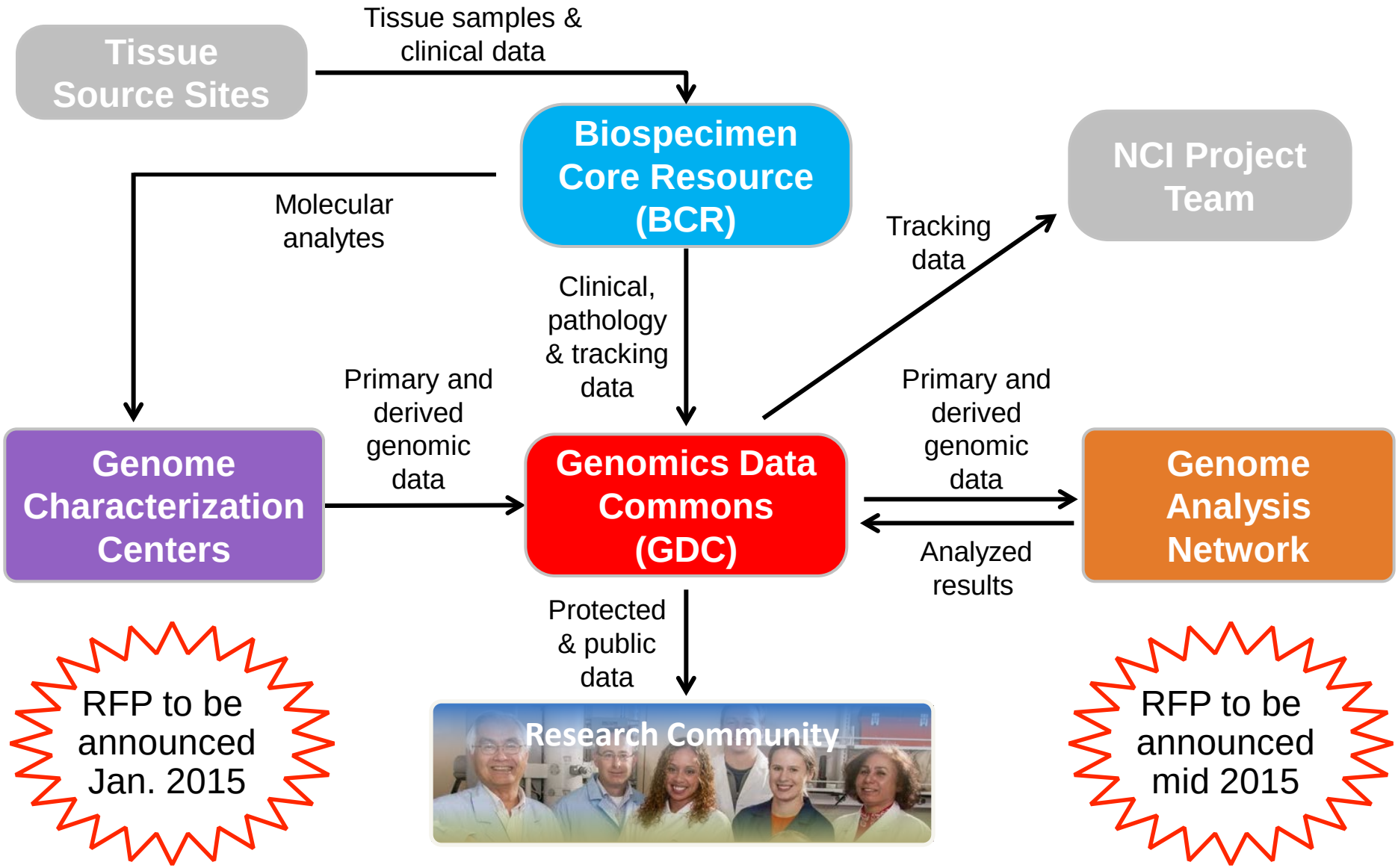
TCGA

TARGET

Therapeutically Applicable Research to Generate Effective Treatments

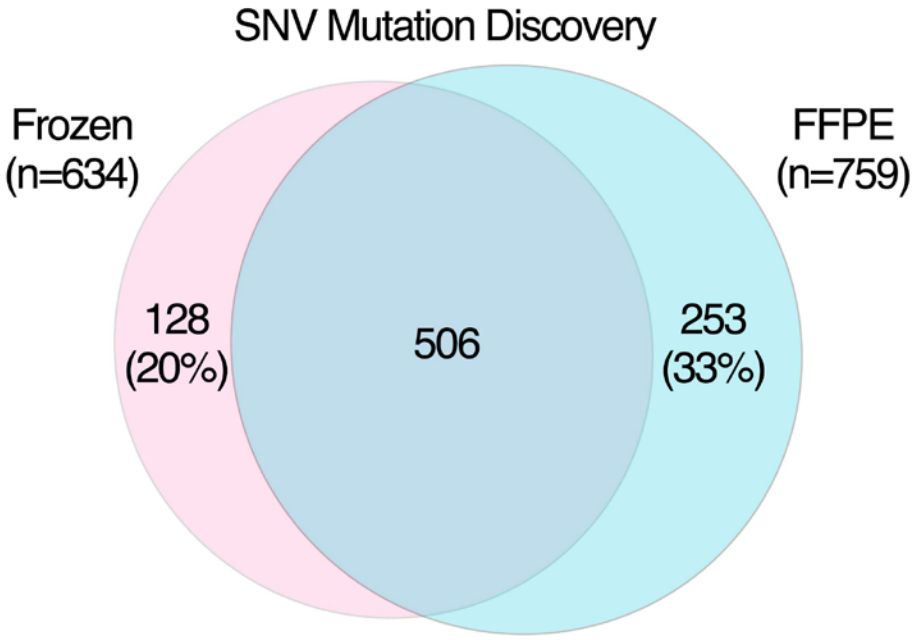
CTD²: A Bridge from Genomics to Cancer Therapeutics

NCI Center for Cancer Genomics: Genomic pipeline



Structural Genomics of Cancer: Two Game Changers

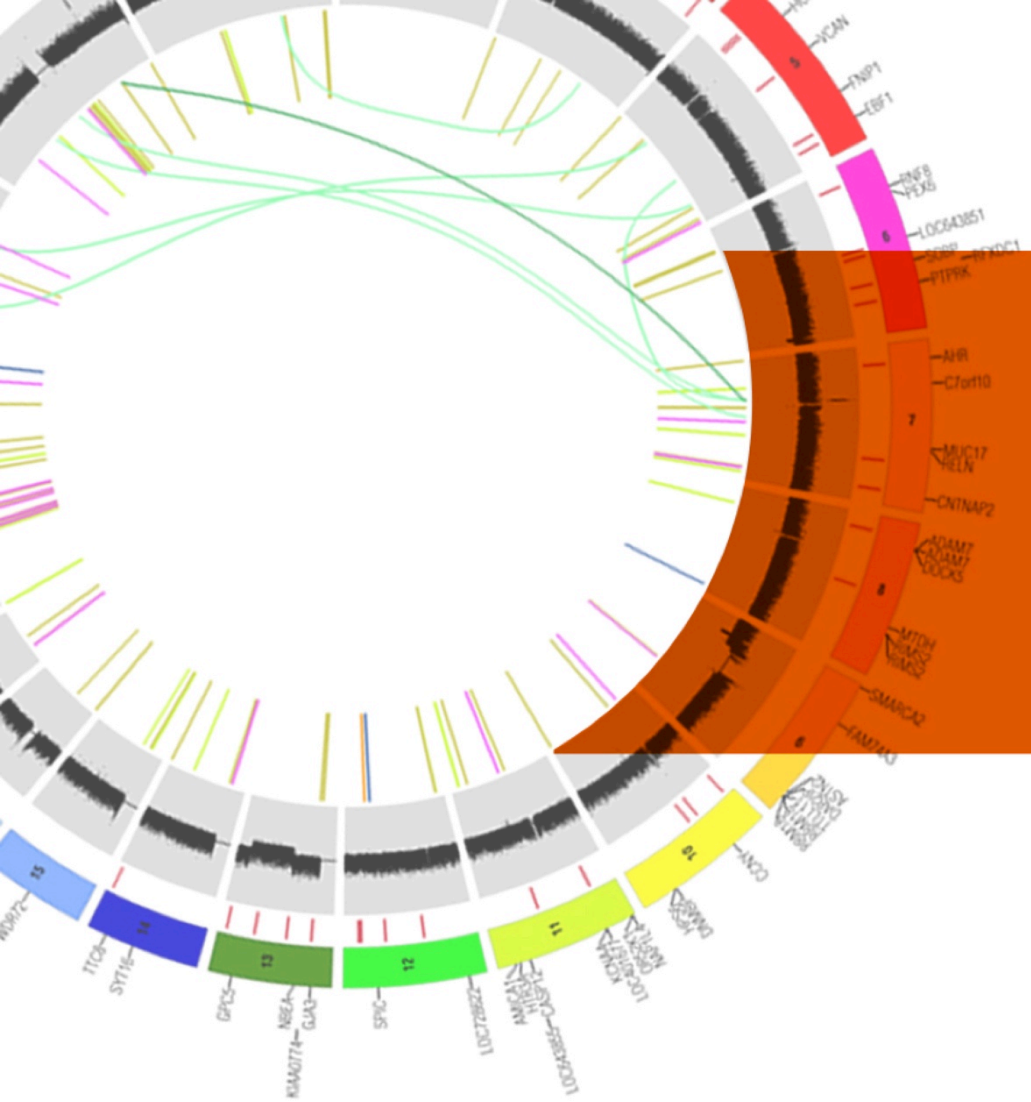
Analysis of formalin-fixed paraffin-embedded biopsies



Decreased cost of whole genome sequencing

NCI Center for Cancer Genomics: Future Initiatives

- Define the molecular basis for clinical phenotypes
  - Analyze completed clinical trials of NCI cooperative groups
    - Colorectal cancer
    - Lung adenocarcinoma
    - RFP to be announced to NCTN for genomic analysis of trial samples
  - Alchemist trial in lung adenocarcinoma
  - Exceptional responders initiatives
- Define the “full” set of genetic drivers in cancer
  - Pilot projects in colorectal, lung adeno, and ovarian cancer
- Next generation cancer models for functional genomics
- Develop NCI Genomics Data Commons (GDC)

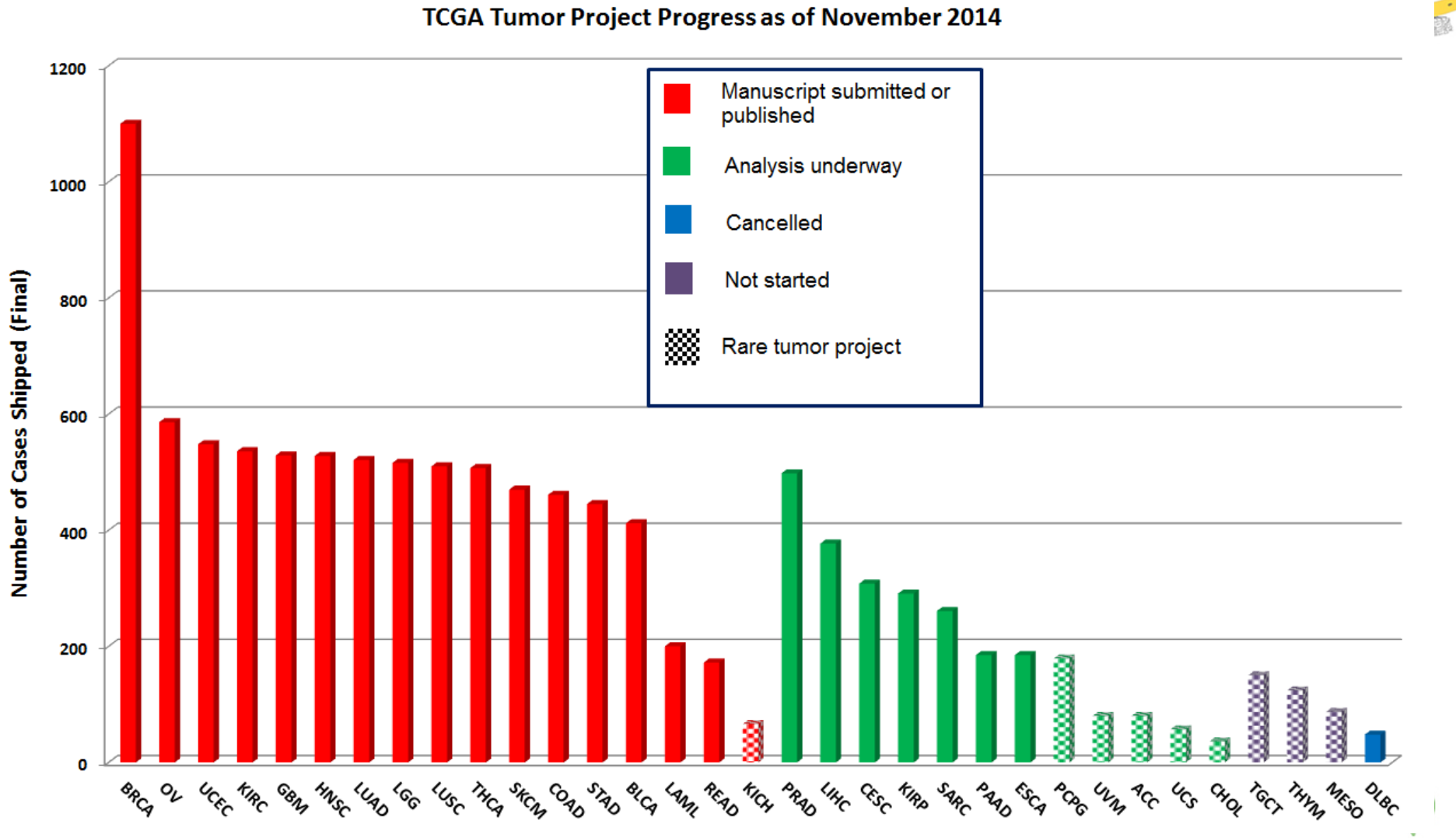


The Cancer Genome Atlas

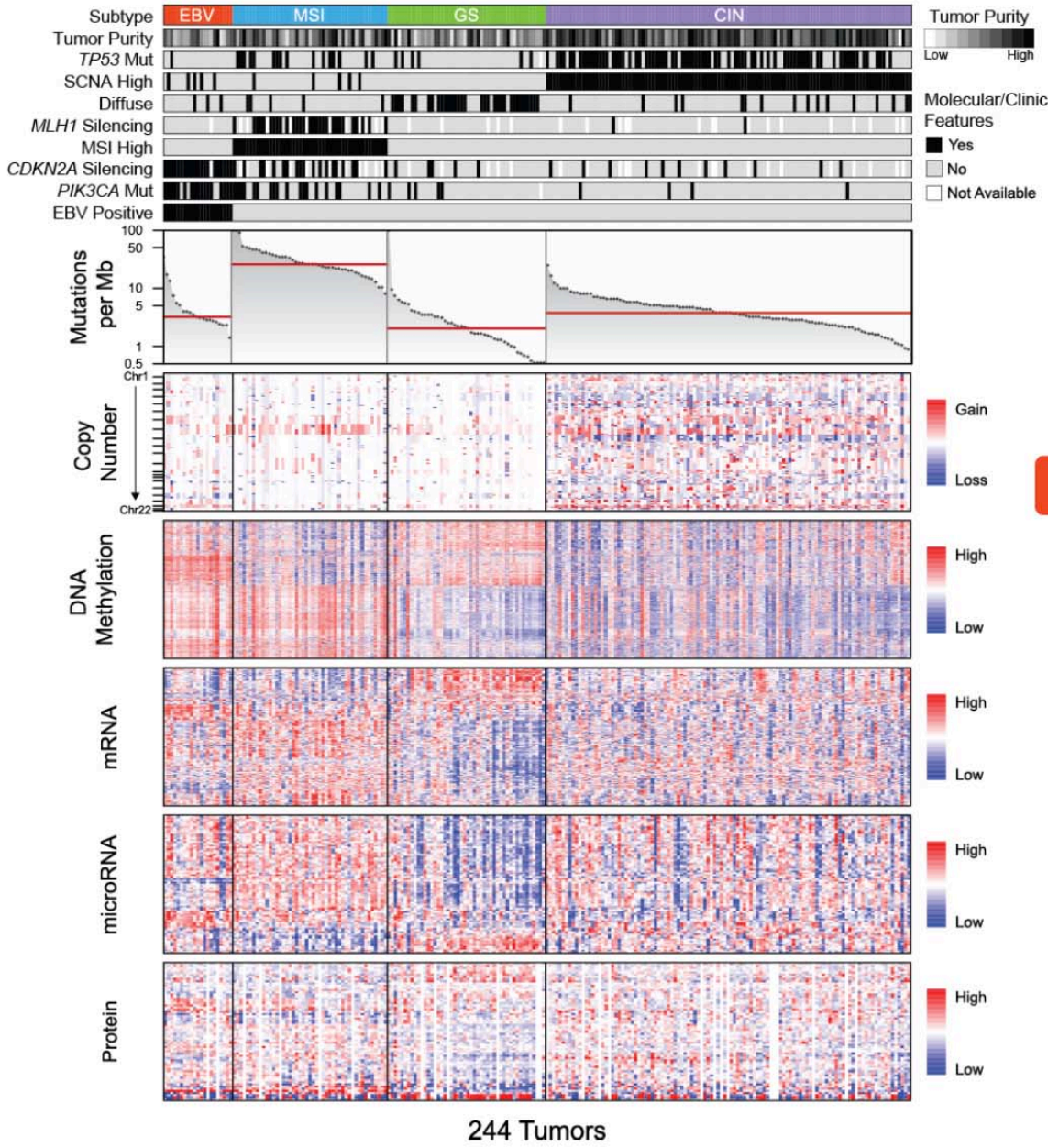
TCGA

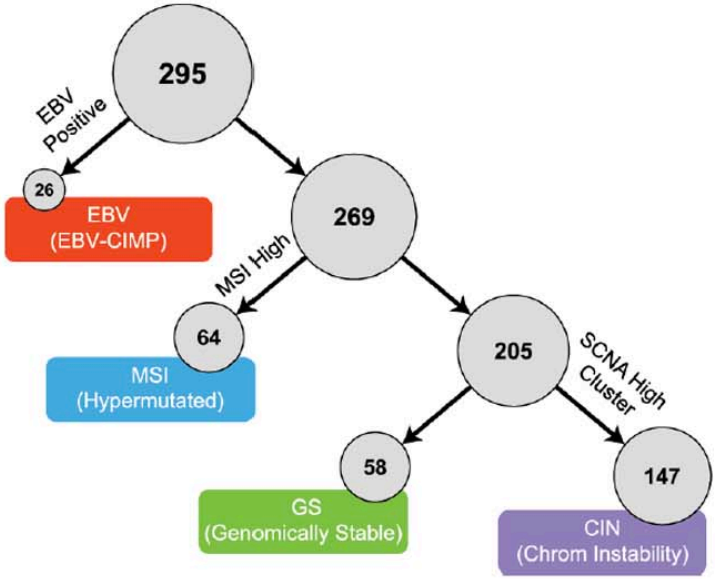
Jean Claude Zenklusen, Ph.D.
Director
TCGA Program Office
National Cancer Institute

Case Accrual and Analysis Status

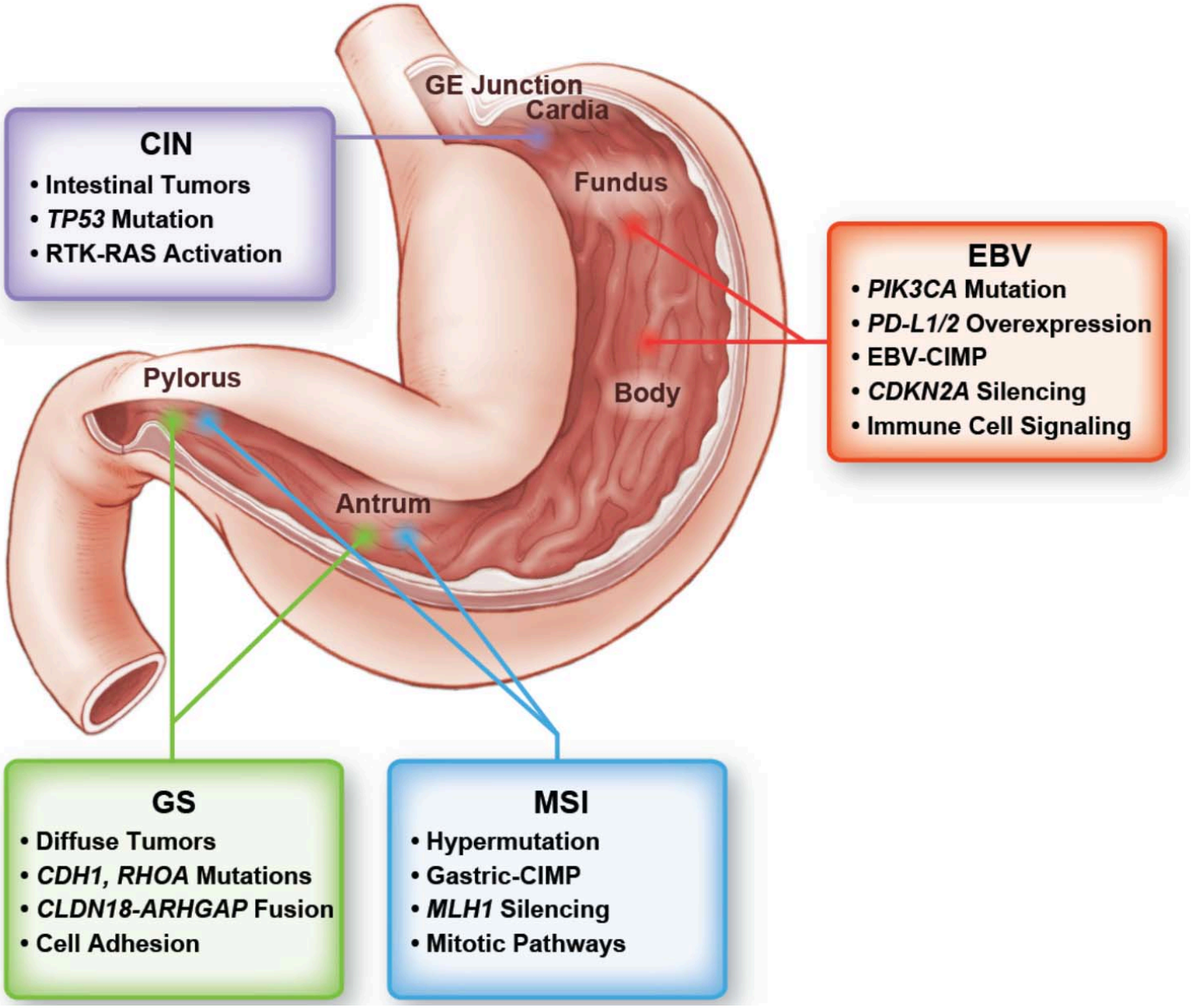


TCGA Gastric Cancer Project – The Power of Integrative Analysis





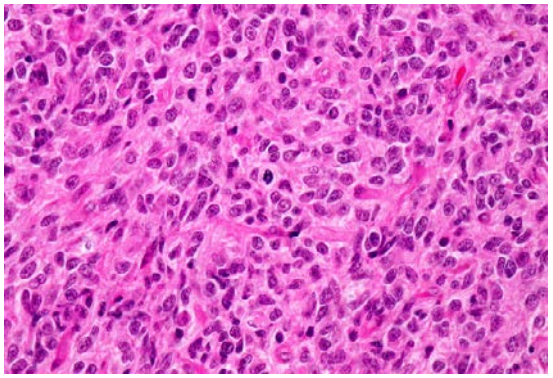
TCGA Gastric Cancer Project – The Power of Integrative Analysis



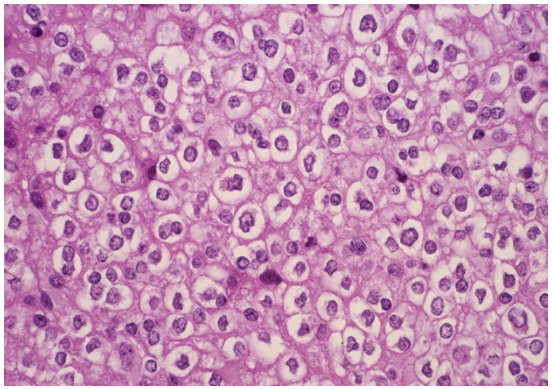
Histopathology of Gliomas

Low grade gliomas

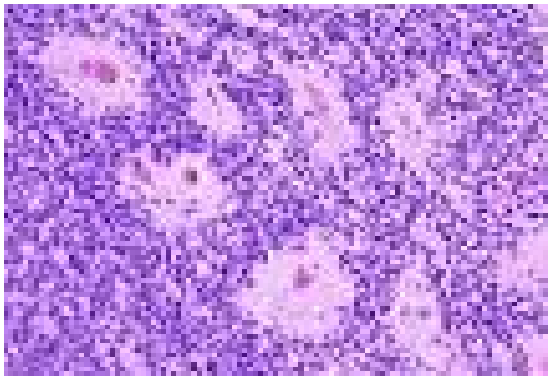
Astrocytoma

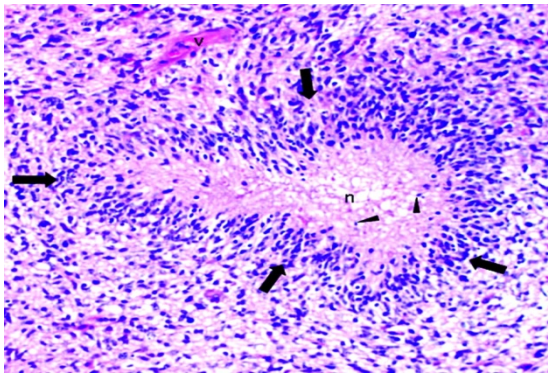


Oligodendroglioma

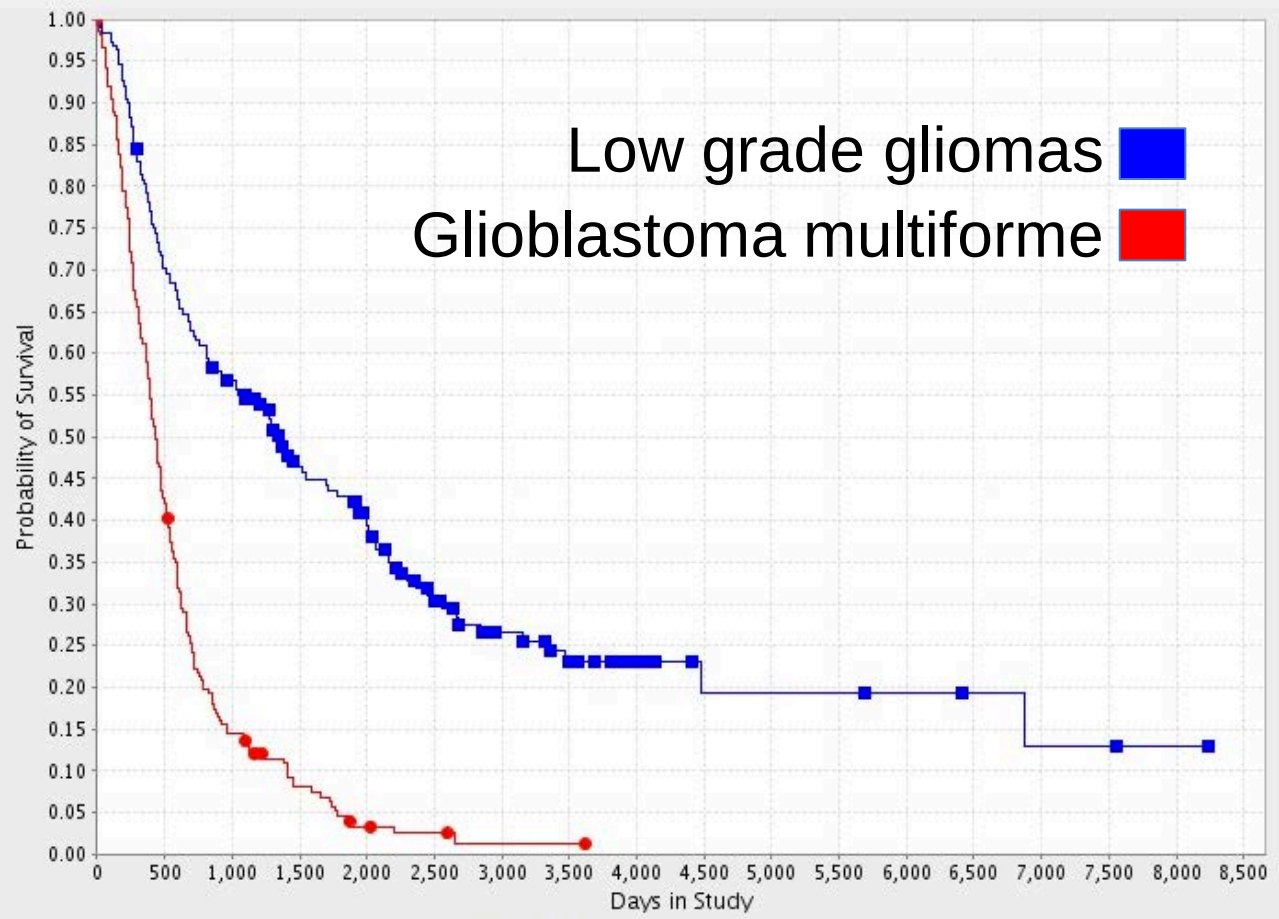


Glioblastoma Multiforme

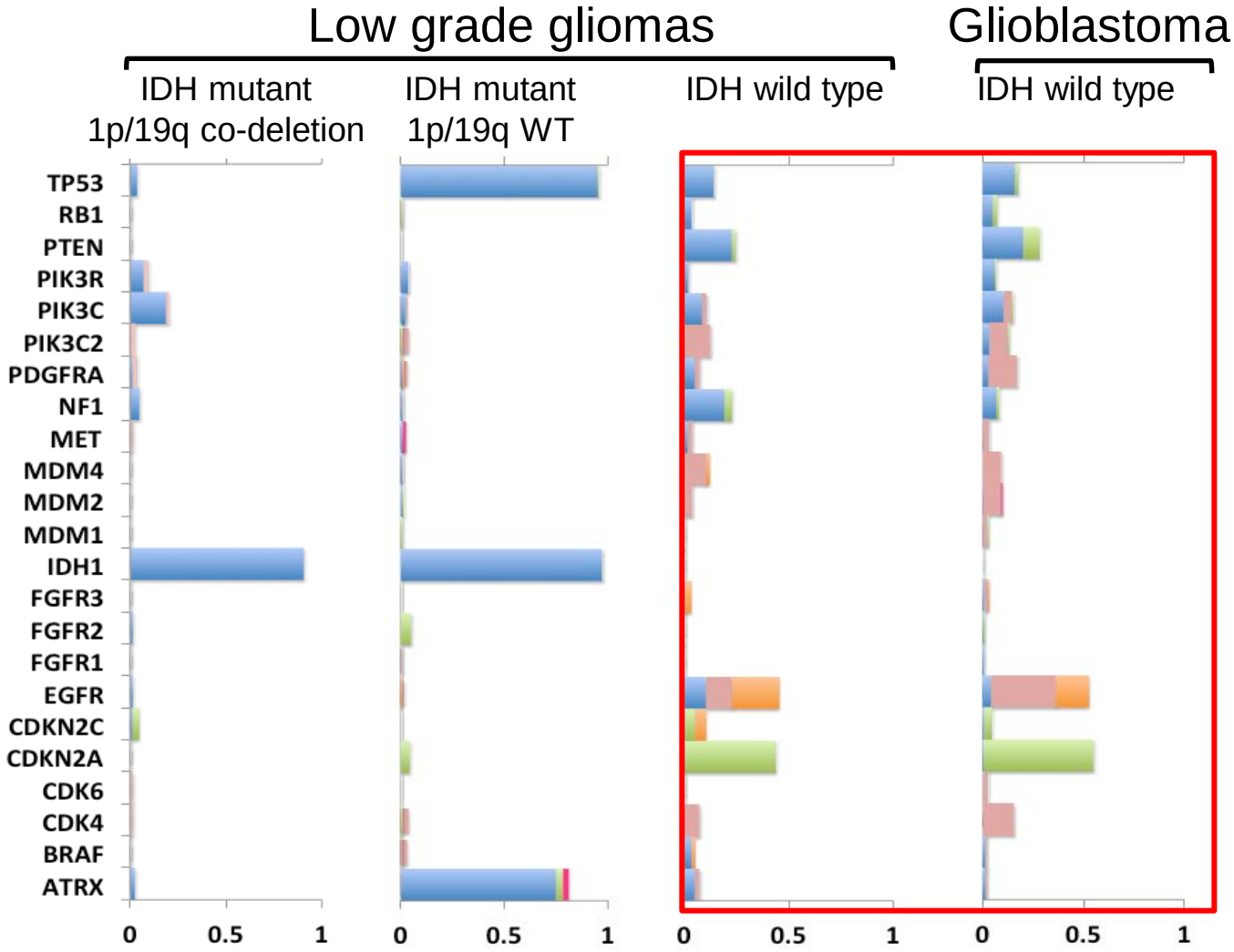




Survival With Glioblastoma Multiforme vs. Low Grade Glioma



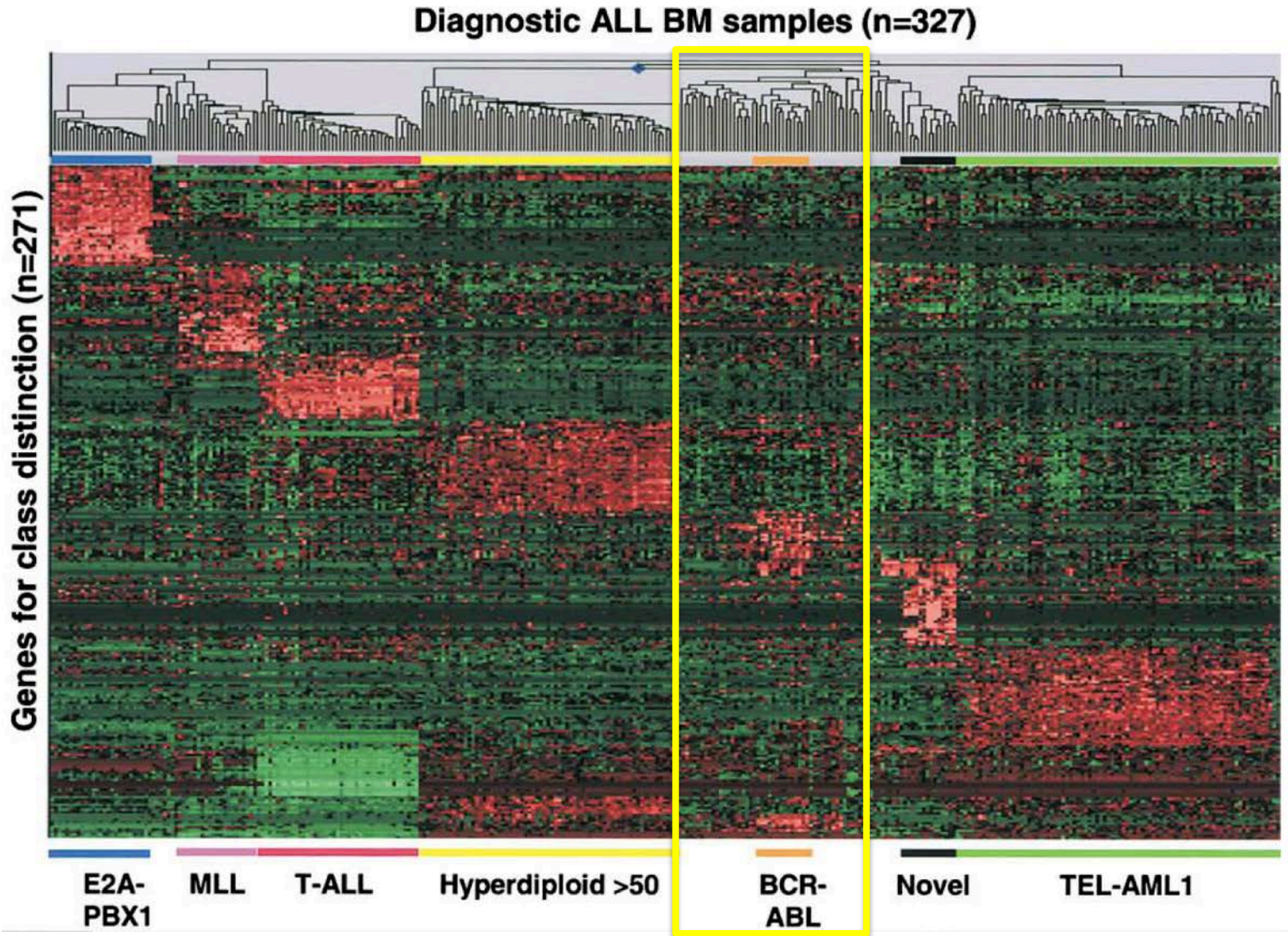
Common Genetic Profiles in Glioblastoma and a Subset of Low Grade Gliomas



The Cancer Genome Atlas

Daniela Gerhard, Ph.D.
Director
Office of Cancer Genomics
National Cancer Institute

The Ph-like subtype of B cell Acute Lymphoblastic Leukemia



Yeoh et al. Cancer Cell 1:133 (2002)

Kinase Fusions Discovered in Ph-like ALL

Kinase Gene	Tyrosine Kinase Inhibitor	Fusion Partners	Patients
		number	
ABL1	Dasatinib	6	14
ABL2	Dasatinib	3	7
CSF1R	Dasatinib	1	4
PDGFRB	Dasatinib	4	11
CRLF2	JAK2 inhibitor	2	30
JAK2	JAK2 inhibitor	10	19
EPOR	JAK2 inhibitor	2	9
DGKH	Unknown	1	1
IL2RB	JAK1 inhibitor, JAK3 inhibitor, or both	1	1
NTRK3	Crizotinib	1	1
PTK2B	FAK inhibitor	2	1
TSLP	JAK2 inhibitor	1	1
TYK2	TYK2 inhibitor	1	1

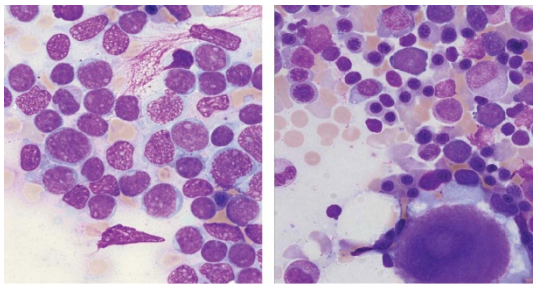
Roberts et al. *Cancer Cell* 2012;22:153
Roberts et al. N Engl J Med 2014;371:1005-1015

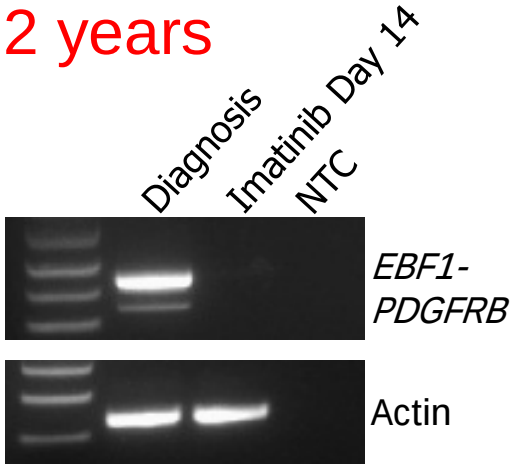
Response of Pediatric B-ALL With a EBF1-PDGFRB Translocation to Imatinib

- 10 year old male with refractory B-ALL – 70% blasts at day 29
- Cytogenetics: 5q alteration
  => interstitial deletion by array CGH disrupting EBF1 and PDGFRB genes
- *EBF1-PDGFRB* fusion translocation detected by RT-PCR

- Commenced imatinib
- Immediate clinical improvement
- 1 week: morphological remission
- 2 weeks: MRD 0.017%
- Consolidation chemotherapy added

=> Patient remains in CR > 2 years





B Weston et al. J Clin Oncol. 2013

Identification and Treatment of Ph-Like ALL

Plans for COG AALL1131 in 2015

Identify Ph-like ALL by LDA Card

↓

Candidate testing

Fusions: RT-PCR
CRLF2 alterations: FISH/PCR
JAK/IL7RA/SH2B3 mutation

↓

Kinome Capture and RNA-seq

If candidate screens negative

↓

WGS

If above negative

ABL1/ABL2/PDGRFB/CSF1R fusion positive: Add dasatinib in prospective phase and compare outcome to that of pts from retrospective phase

Important Open Questions in Cancer Structural Genomics

What is the molecular basis of clinical phenotypes?

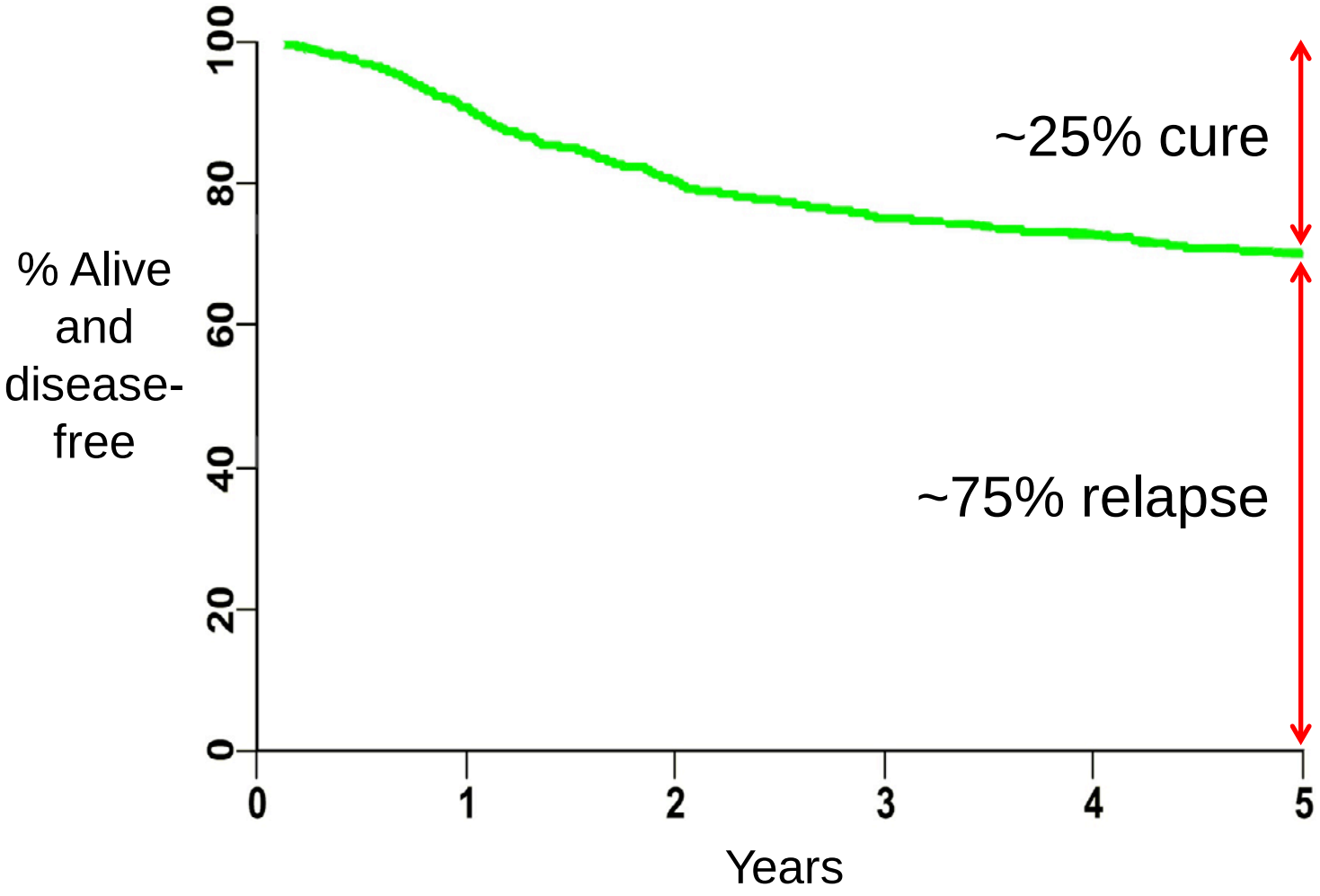
- Aggressive vs. indolent disease
- Metastatic vs. localized disease
- Response to therapy
- Mechanisms of resistance

Important Open Questions in Cancer Structural Genomics

What is the molecular basis for cure vs. relapse following adjuvant chemotherapy?

Opportunities in colorectal cancer and lung adenocarcinoma

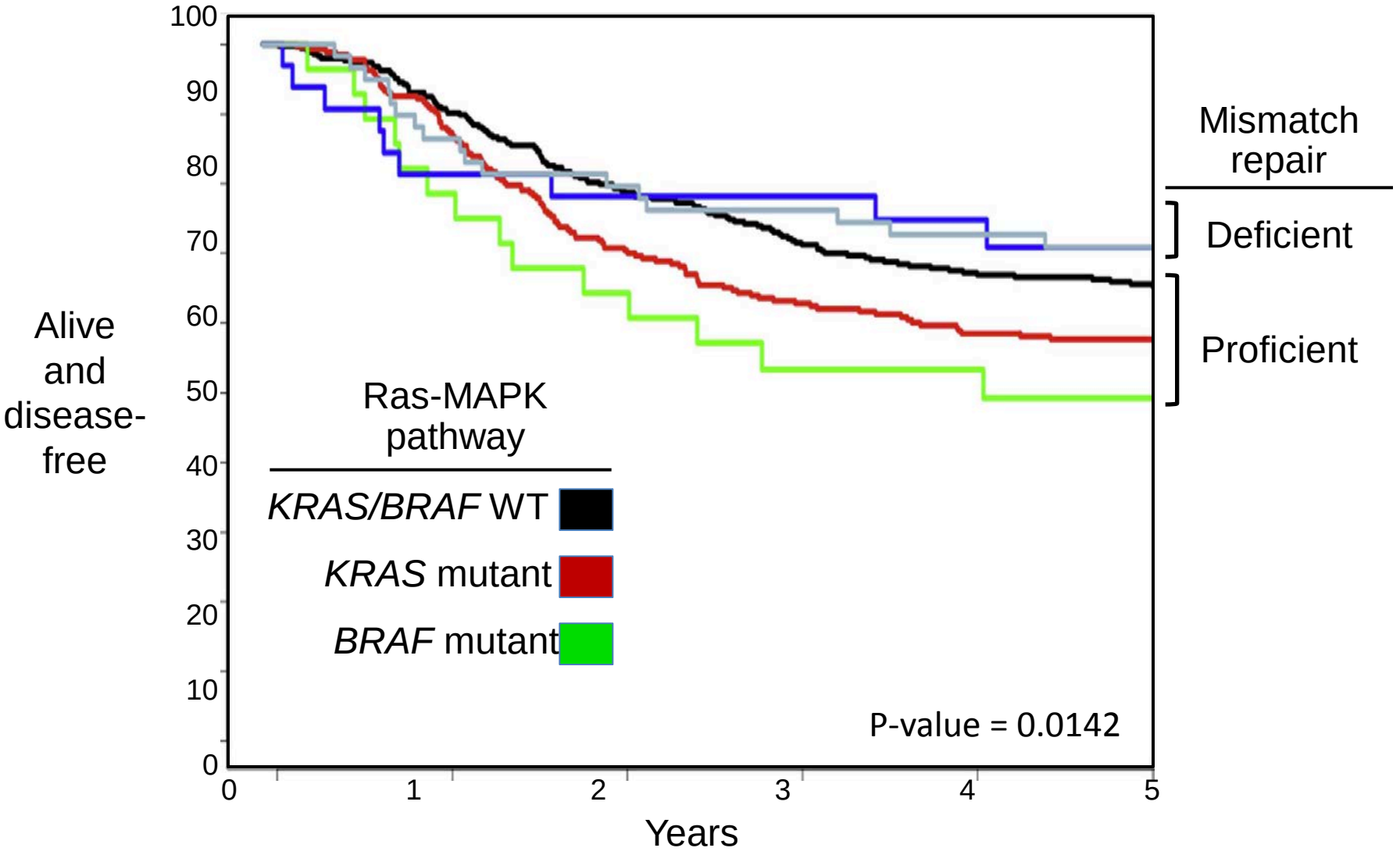
Disease-free Survival in Stage 2-3 Colorectal Cancer Treated with Adjuvant FOLFOX Chemotherapy



Is there a molecular basis for this clinical difference?

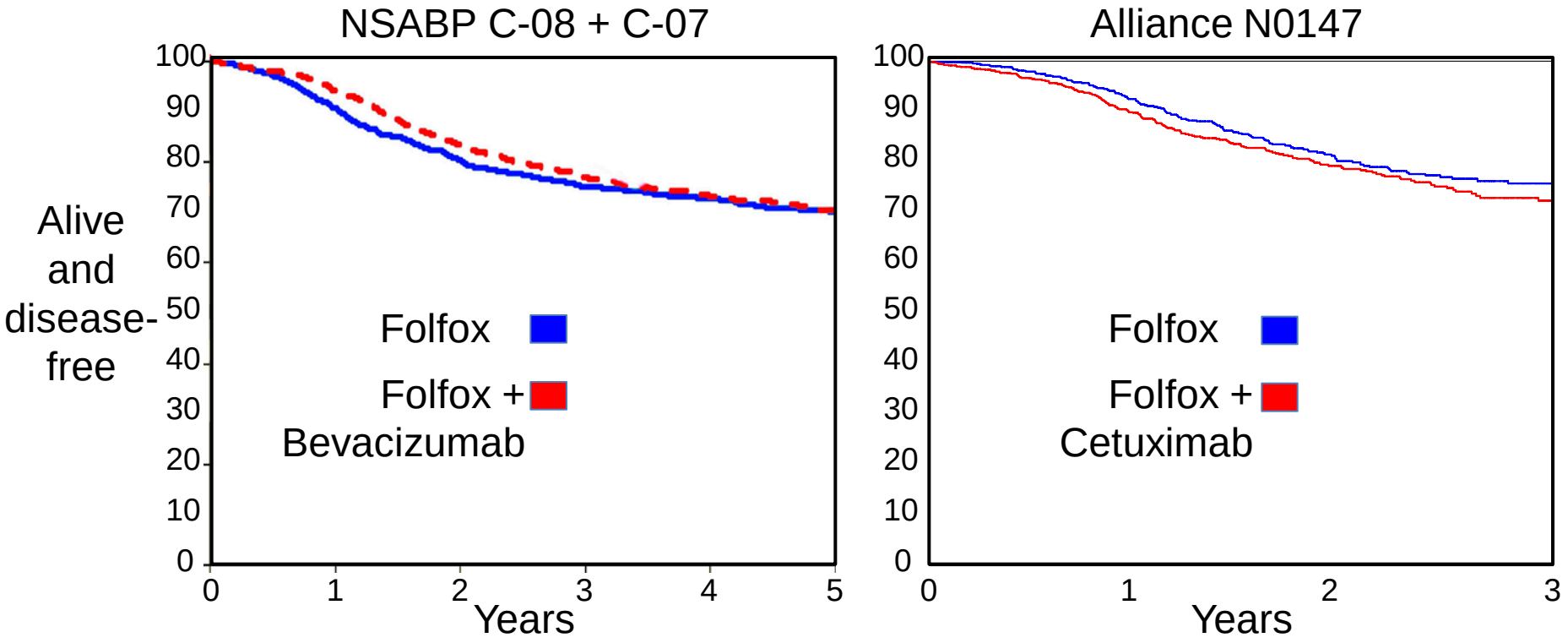
NSABP C-08

Influence of Tumor Genetics on Progression-free Survival in Colorectal Cancer Treated With Adjuvant Chemotherapy



Sinicrope et al. Gastroenterology 2014, in press

Opportunity: Completed NCI Adjuvant Trials in Colorectal Ca

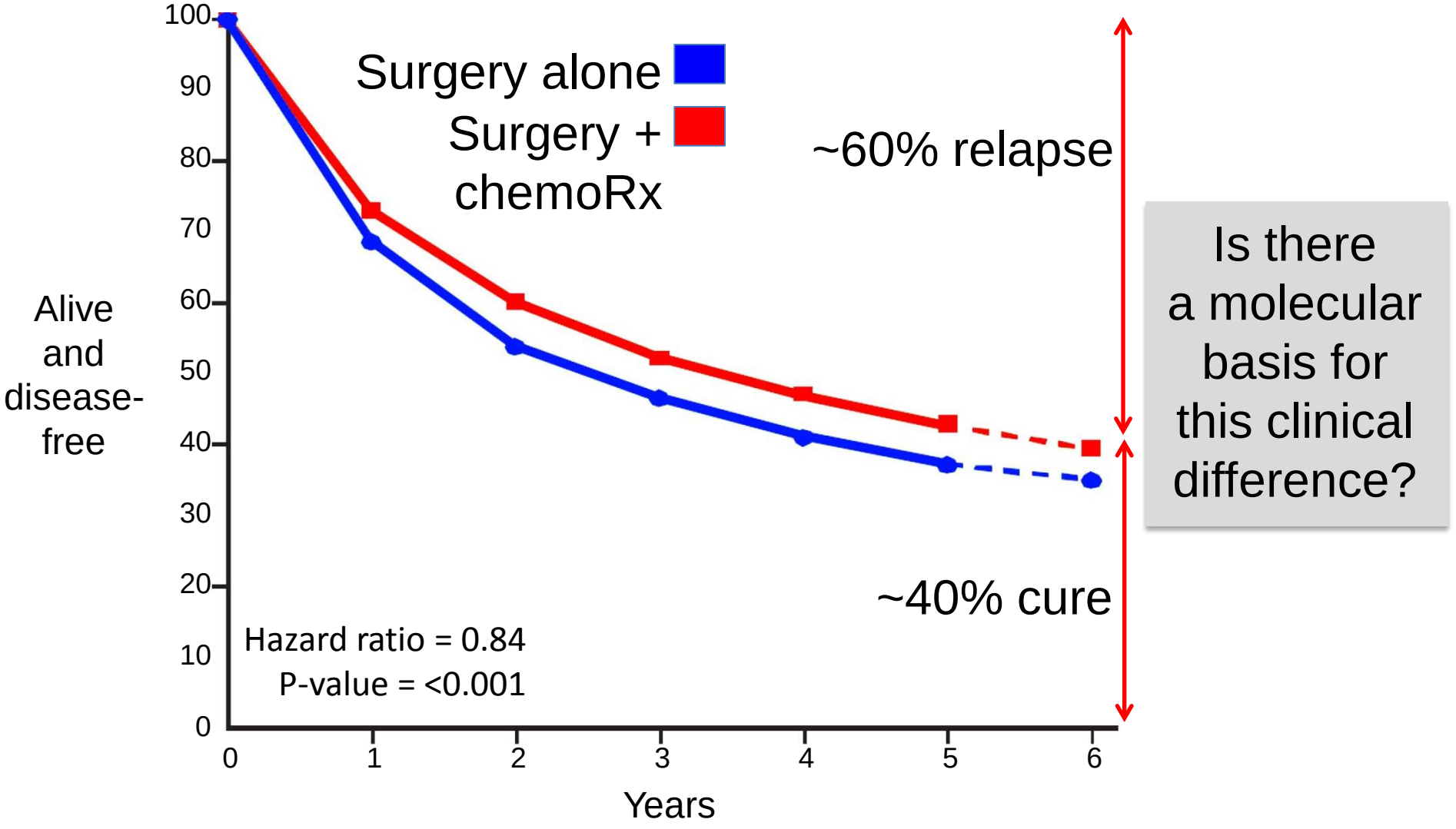


Question: Can tumor genomics at diagnosis predict outcome to adjuvant therapy?

Plan: Whole exome/genome sequencing + transcriptome sequencing
Compared equal #s of biopsies from cured vs. relapsed cases
Identify genetic or gene expression predictors of survival
Use training and test set paradigm to validate predictor

Promise: A molecular predictor could reduce the frequency/duration of surveillance
=> Decreased anxiety for patient and decreased healthcare costs

Benefit of Adjuvant Chemotherapy in Stage 1-3 Non-small Cell Lung Carcinoma

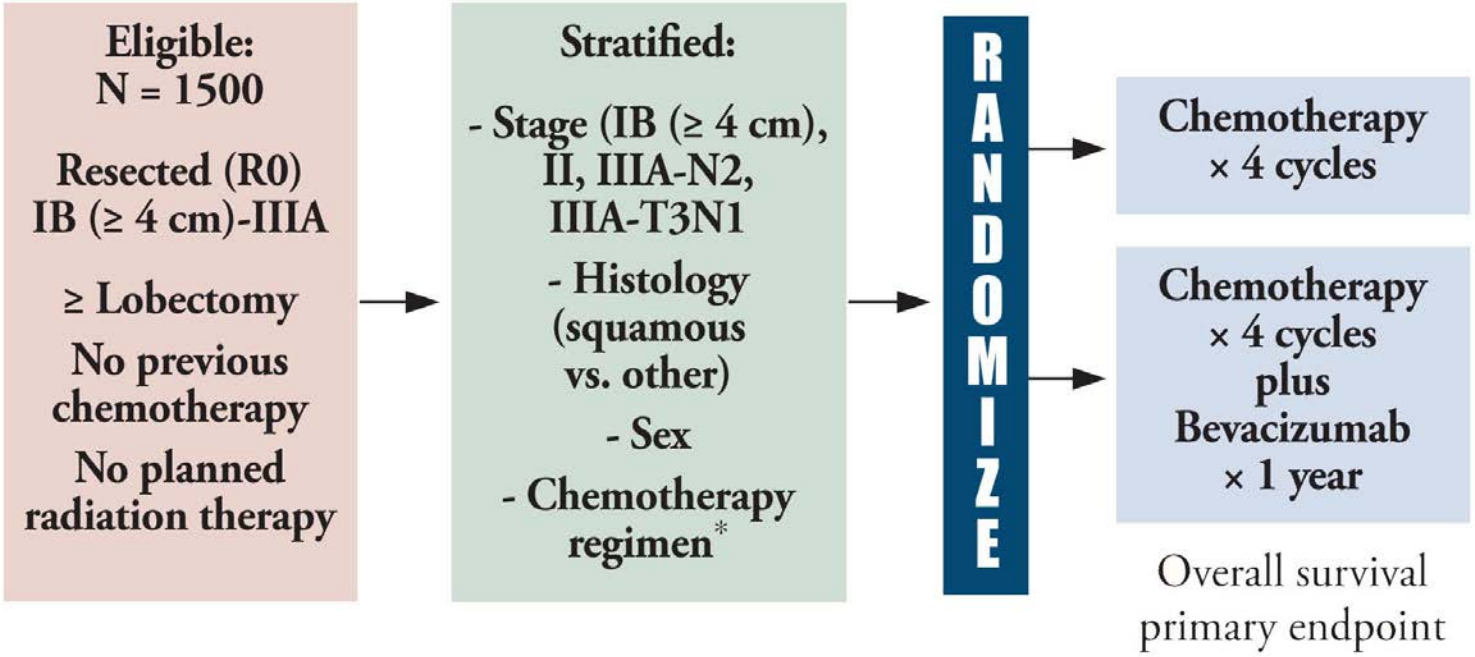


Is there a molecular basis for this clinical difference?

Pignon et al. J Clin Oncol. 2008 26:3552

Opportunity: Completed NCI Adjuvant Trial in NSCLC

ECOG 1505 (~1000 adenocarcinoma biopsy samples)



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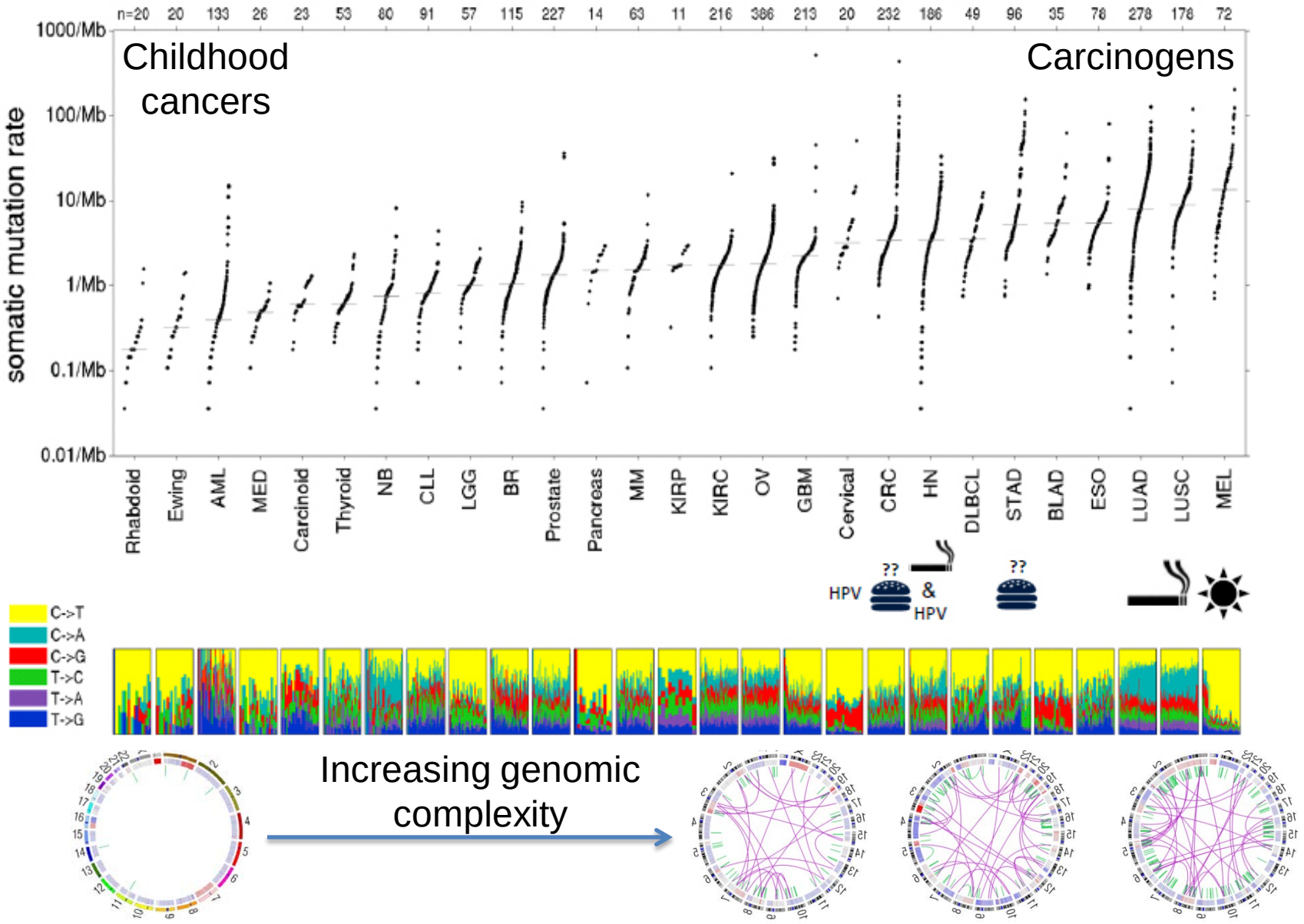
Important Open Questions in Cancer Structural Genomics

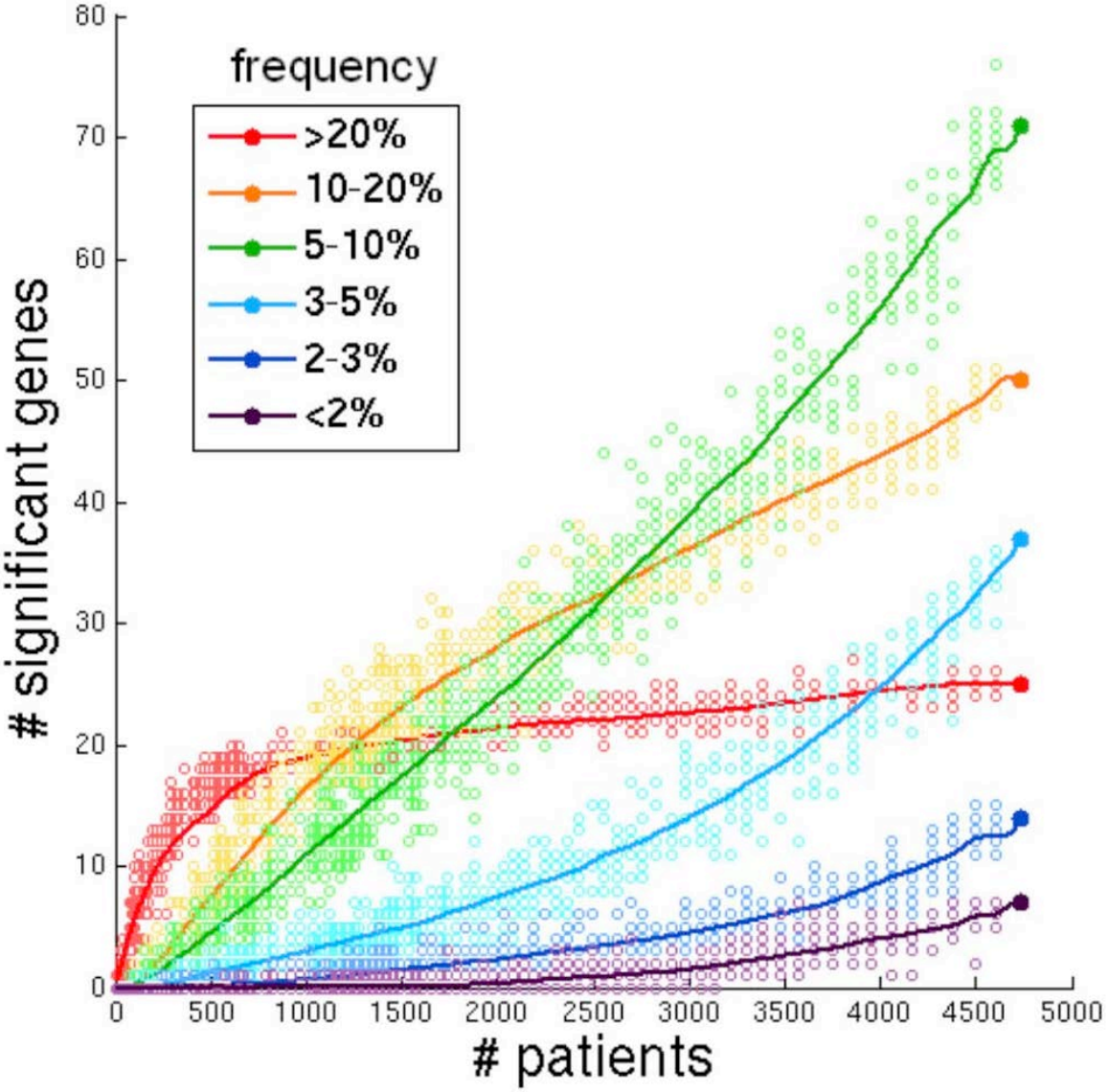
- What is the “full” extent of genetic drivers in cancer?
  - Can we define genetic events occurring in >2% of patients?
  - Which genetic events co-occur and which are mutually exclusive? => Define genetic pathways to cancer
  - Will whole genome sequencing discover non-coding driver mutations and cryptic chromosomal rearrangements?

The Mutational Burden of Human Cancer



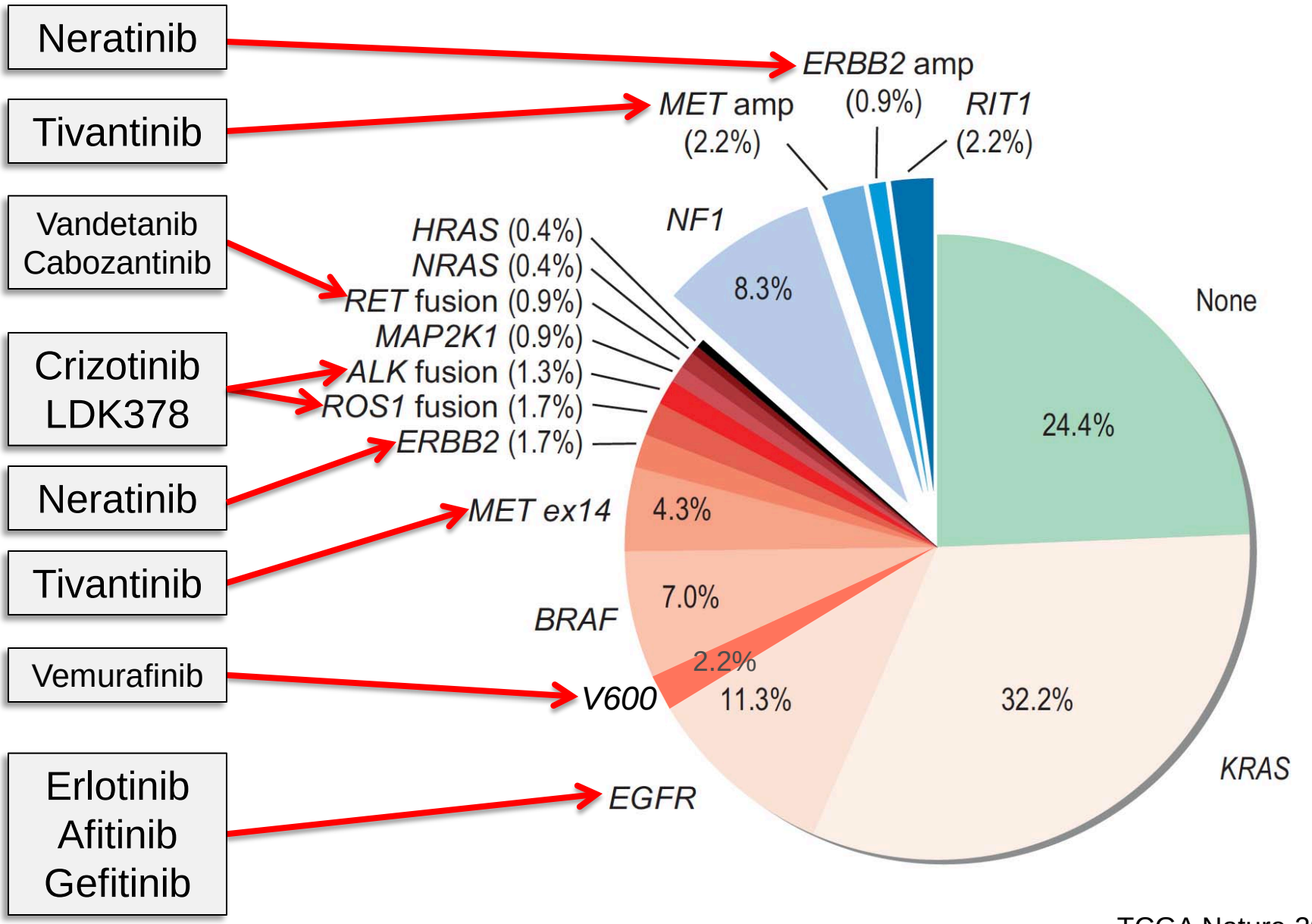
Mike Lawrence and Gaddy Getz

Many Cancer Drivers With <20% Prevalence Remain Undiscovered



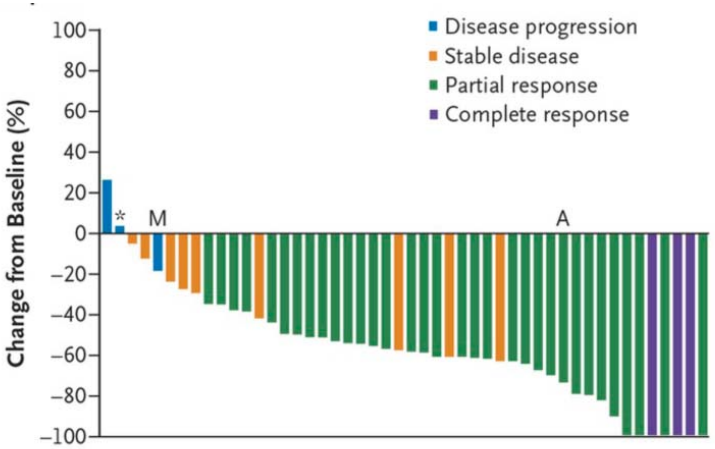
Lawrence et al, Nature 2014

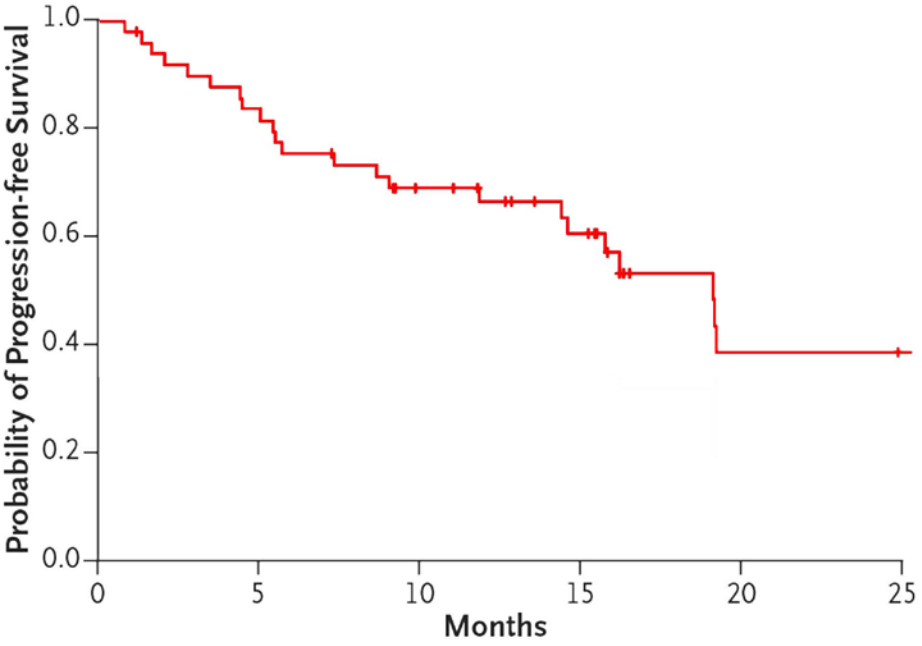
Driver Genes in Lung Adenocarcinoma



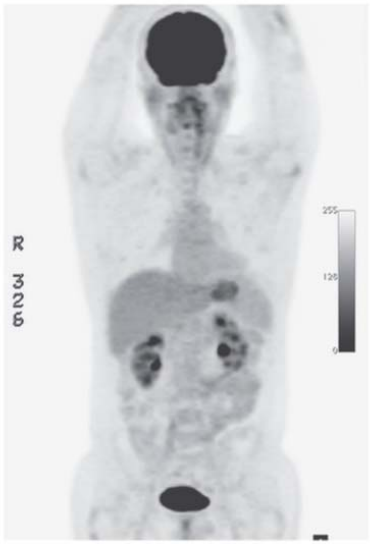
TCGA Nature 2014

Crizotinib Produces Prolonged Objective Responses in Lung Adenocarcinoma with ROS1 translocation





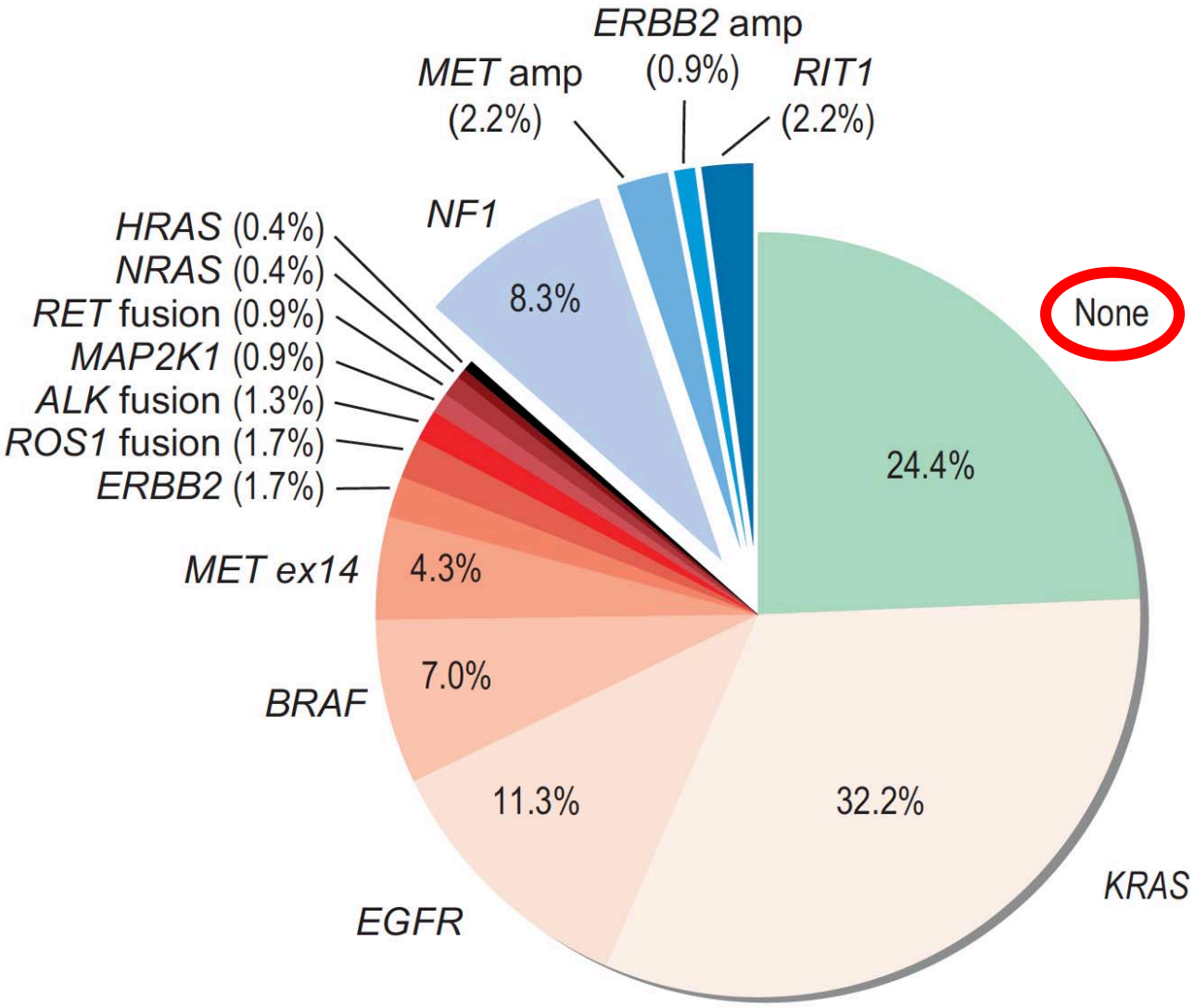
Baseline



After 7 Weeks

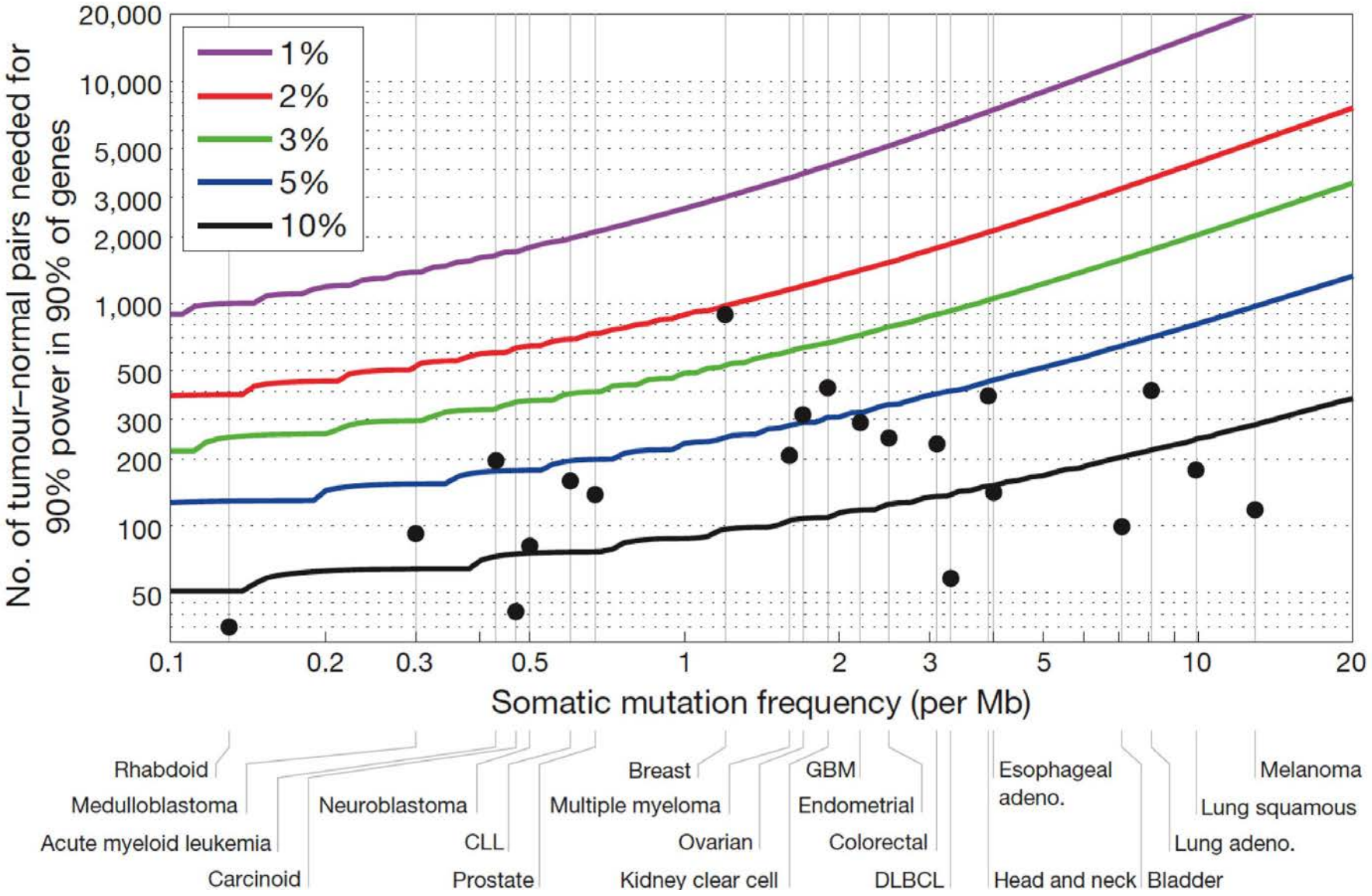
Shaw et al. NEJM 371:1965 (2014)

Driver Genes in Lung Adenocarcinoma



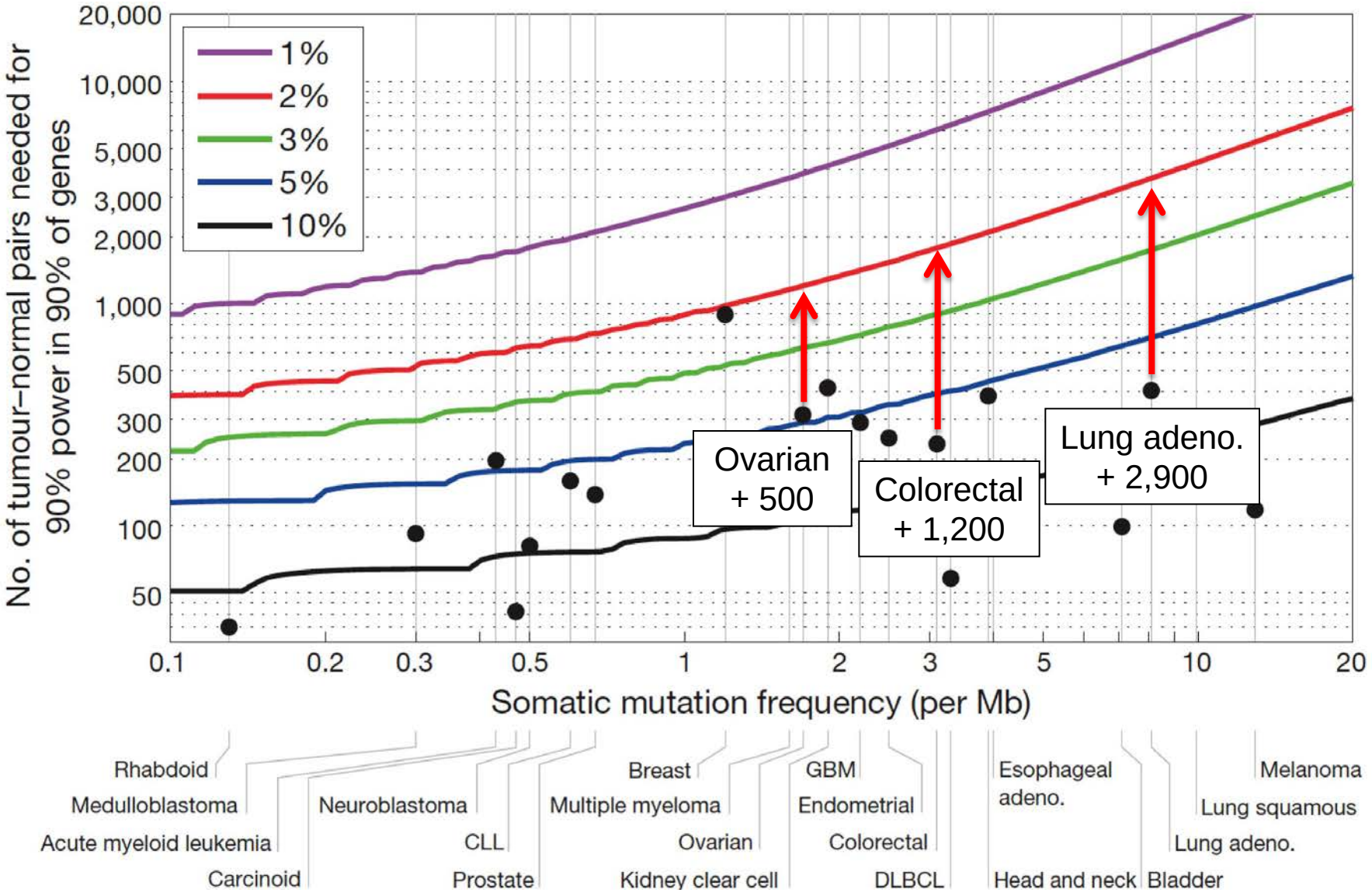
TCGA Nature 2014

Power Calculation for Cancer Driver Discovery

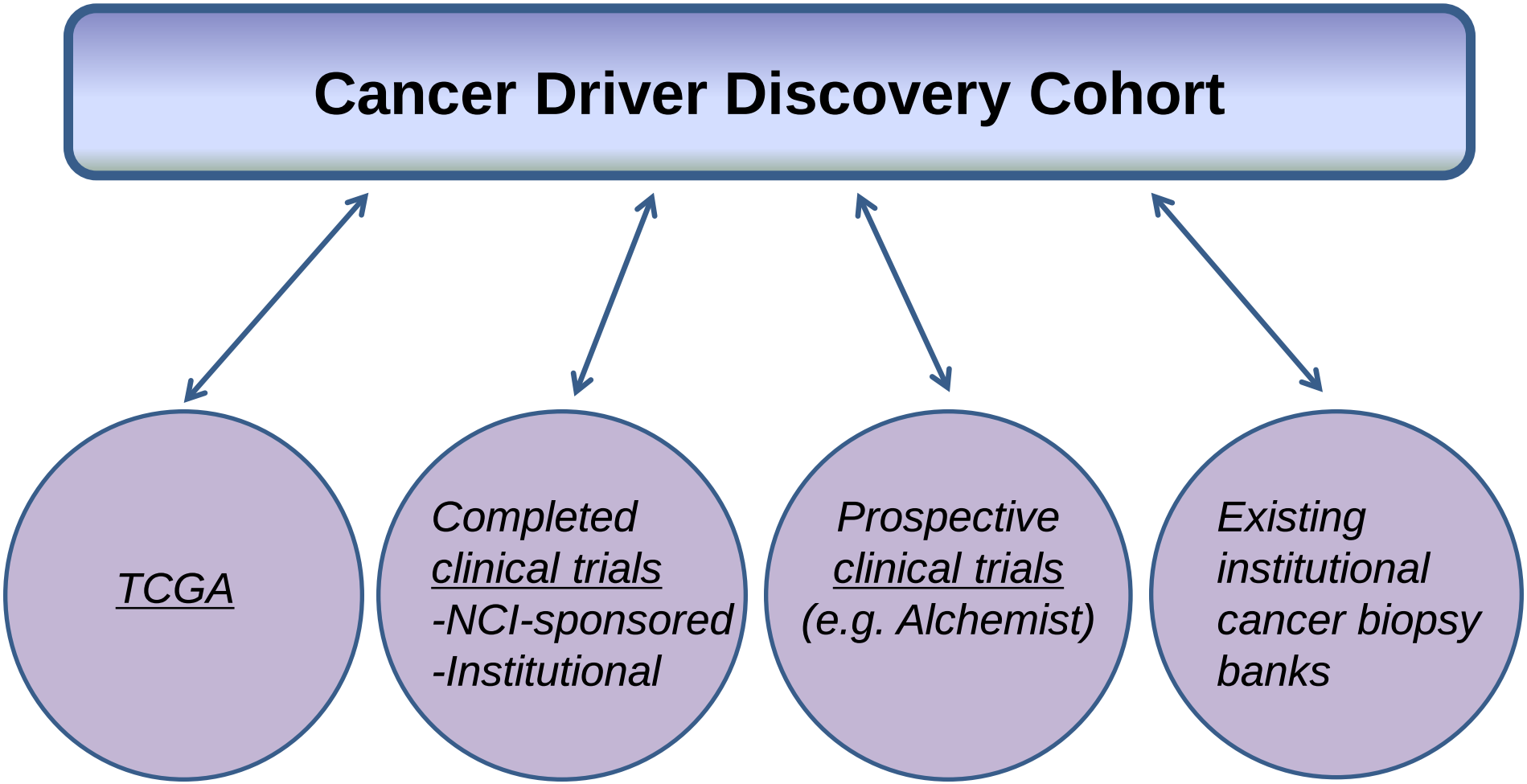


Lawrence et al, Nature 2014

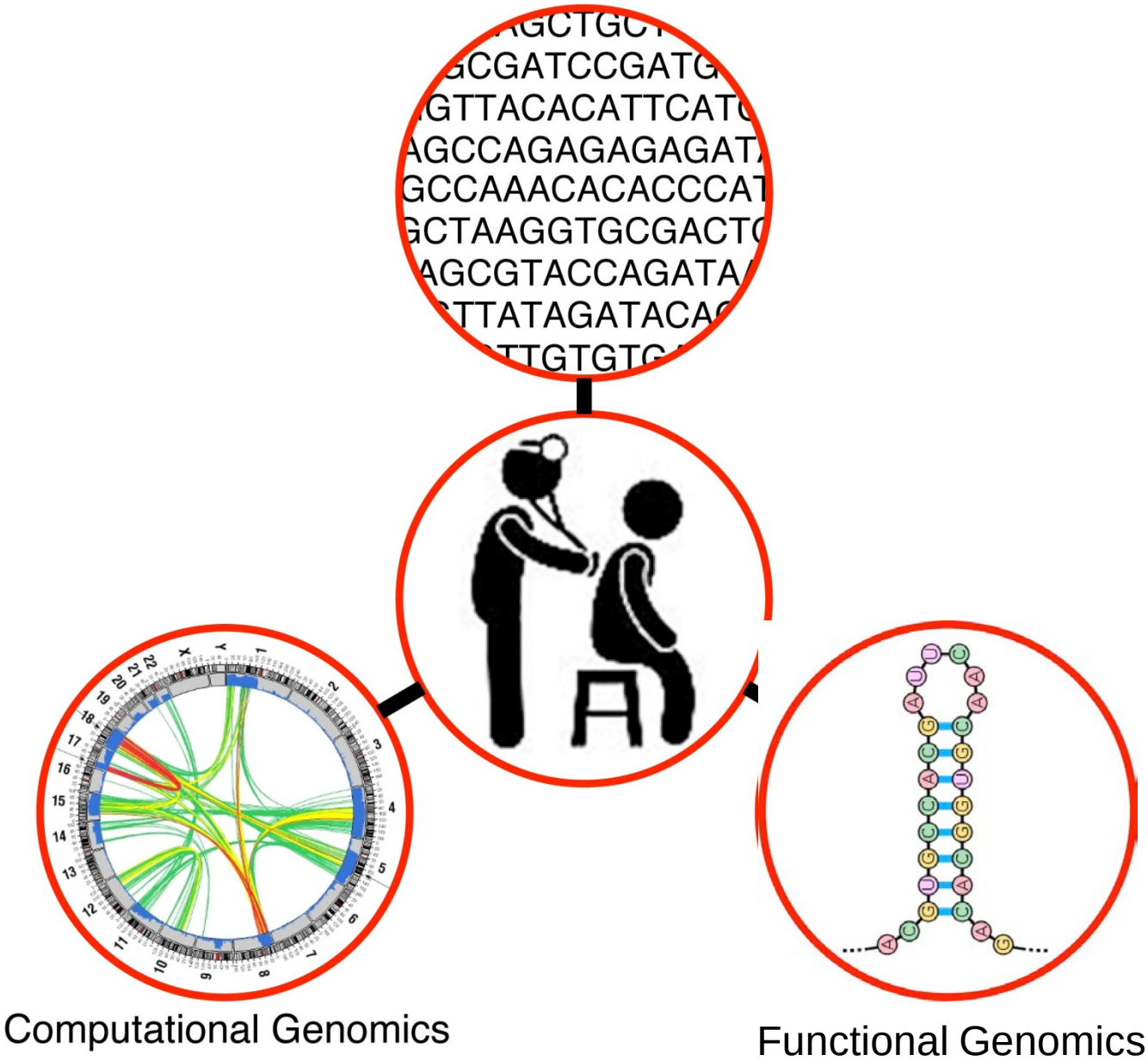
Discovery of Cancer Drivers With 2% Prevalence



Lawrence et al, Nature 2014


Cancer Driver Discovery Cohort
TCGA
Completed clinical trials -NCI-sponsored -Institutional
Prospective clinical trials (e.g. Alchemist)
Existing institutional cancer biopsy banks

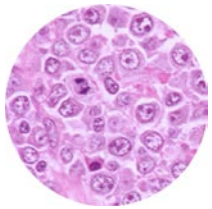
Prospects in Cancer Functional Genomics



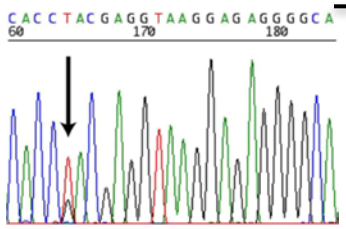
Integration of Functional Genomics and Structural Genomics is Required to Identify Essential Cancer Pathways

Structural genomics

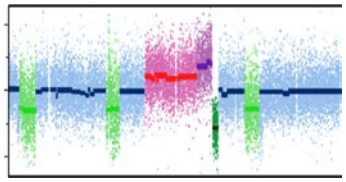
Functional genomics



Cancer biopsy



Sequence



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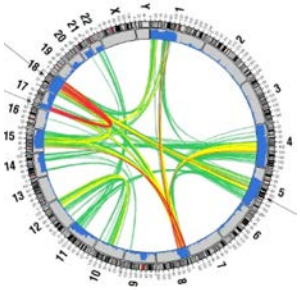
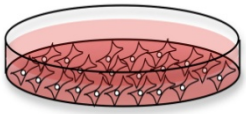
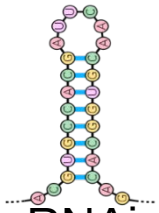


Rearrangements

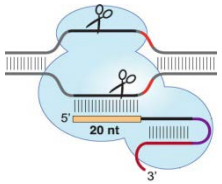
Putative driver genes



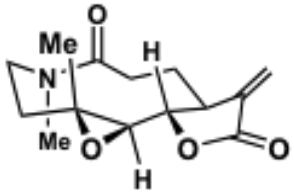
Develop relevant cancer model



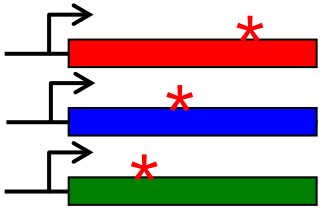
RNAi



CRISPR

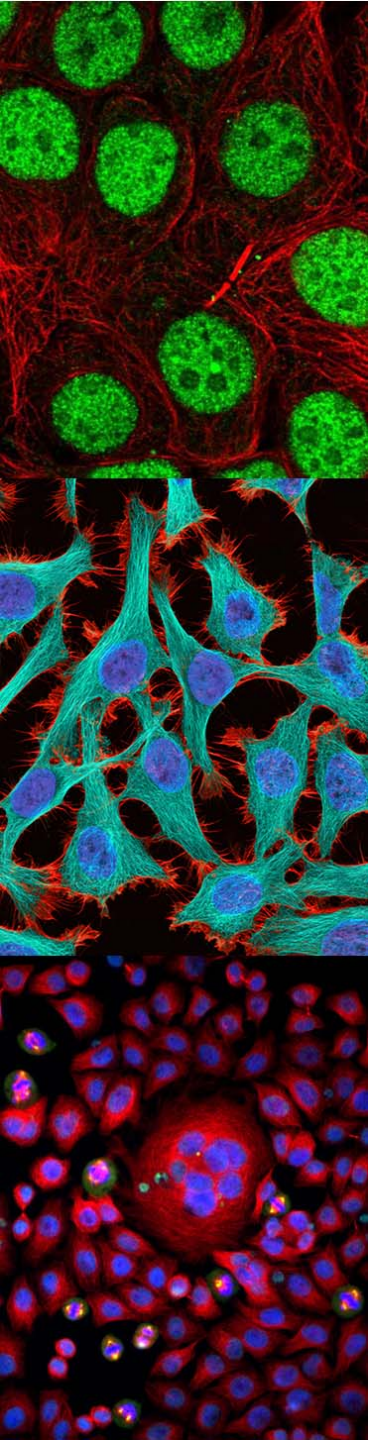


Small molecules



Mutant ORFs

Essential cancer pathways

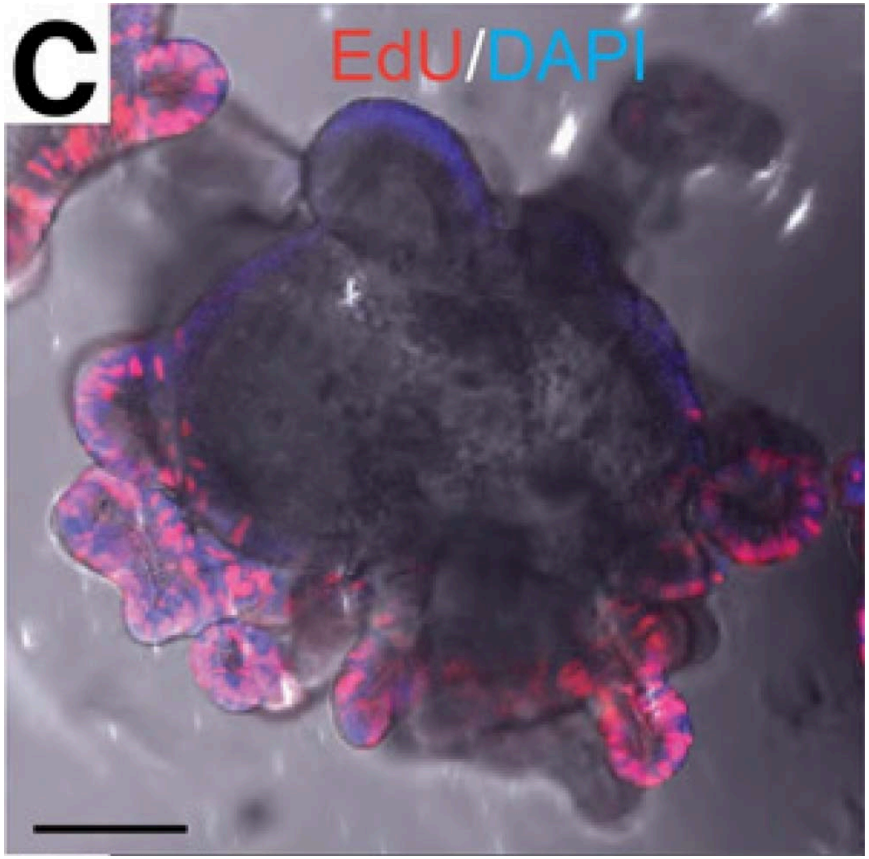


Modeling the Diversity of Human Cancer: An Unmet Need

- Genetic analysis has identified recurrent genetic lesions in cancer that range in frequency from 1% - >50% of cases.
- Most cancer cell lines have not been directly compared to the primary tumor using current genomic methods.
- Existing cell line models of common cancer types are suspect biologically and genetically (e.g. prostate CA)
- Models of rare cancer subtypes may be nonexistent or underrepresented
- Models do not exist for many recurrent genetic lesions in human cancer, and for common combinations of lesions
- Existing models do not recapitulate hierarchical relationships of tumor subpopulations (i.e. tumor propagating cells, stroma)

Next Generation Models of Epithelial Cancers

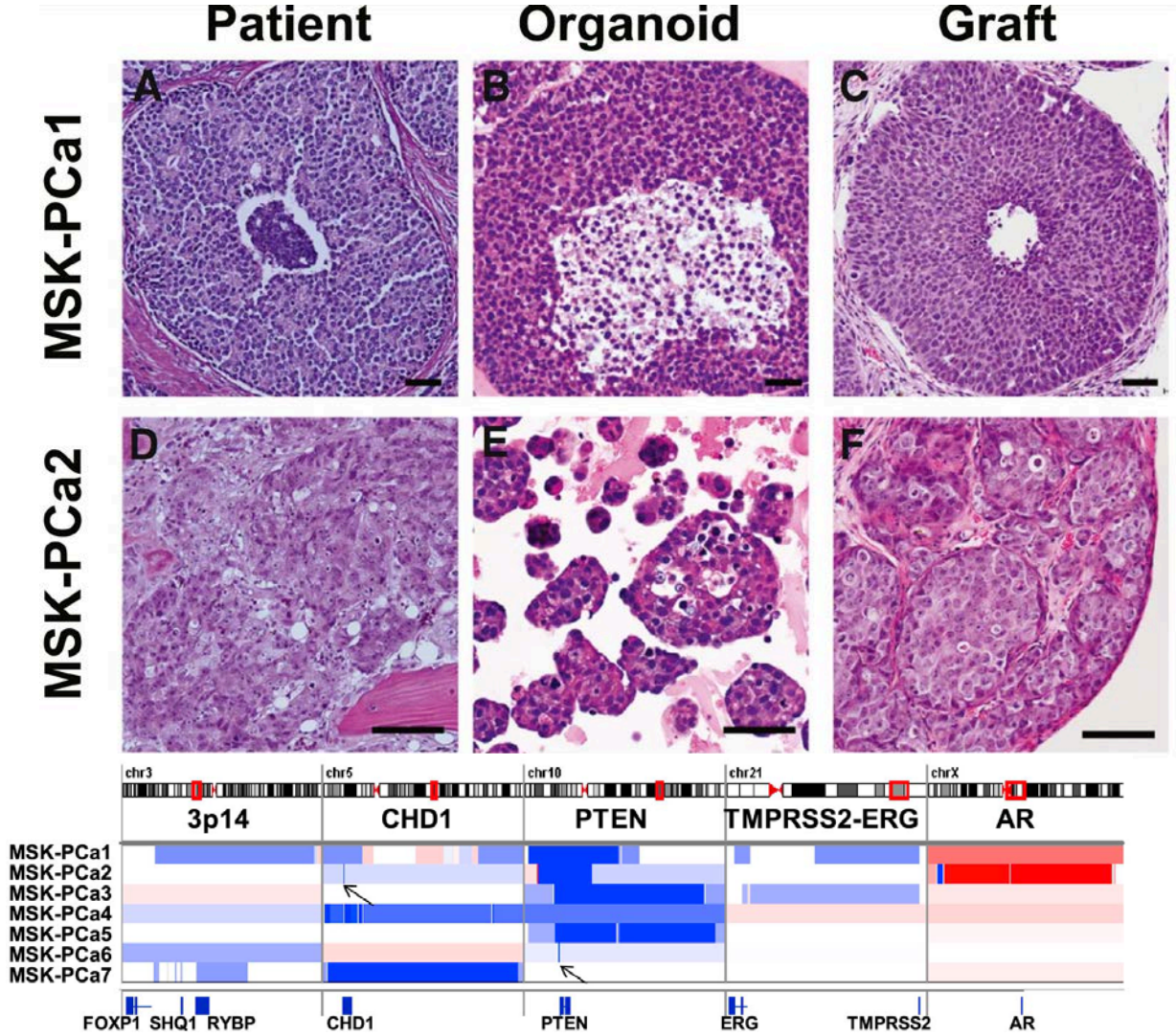
Organoid cultures



Clevers laboratory
Sato et al. Gastroenterology 2011 141:1762

Next Generation Models of Epithelial Cancers

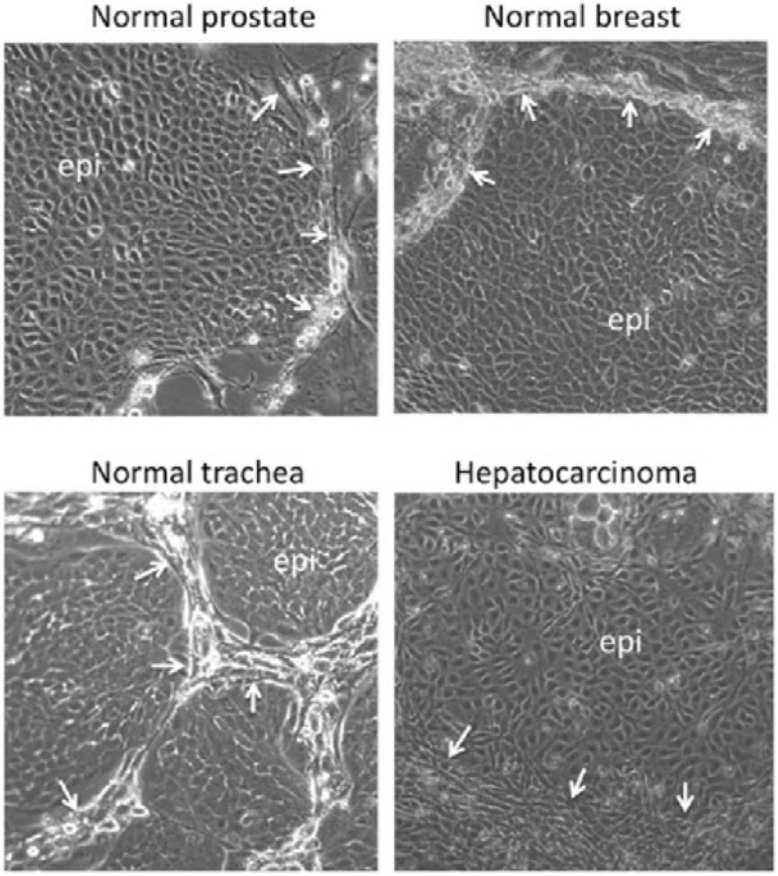
Organoid cultures



Chen, Sawyers laboratory
Gao et al. Cell 2014 159:176

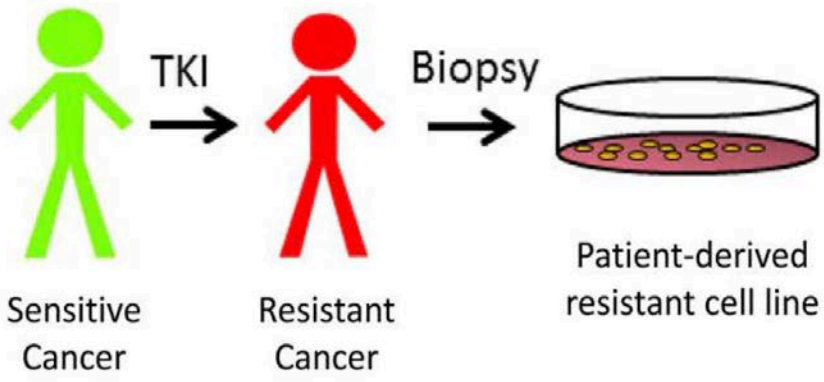
Next Generation Models of Epithelial Cancers

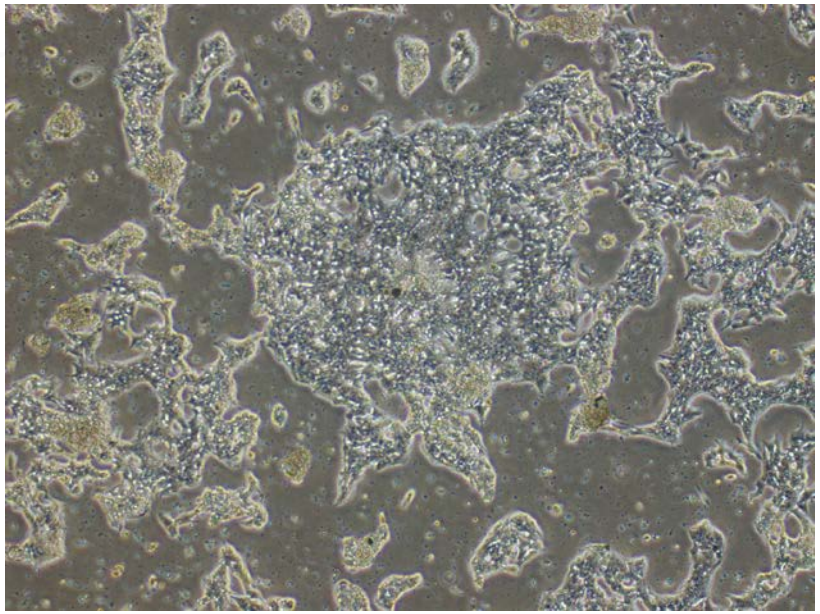
Conditionally reprogrammed cells

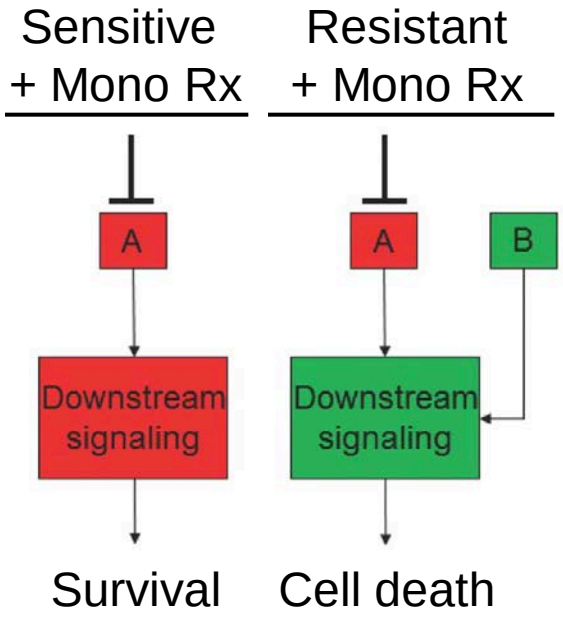


Schlegel laboratory
Liu et al. Amer J Pathol 2012 180:599

Using Next Generation Cancer Models to Develop Therapies

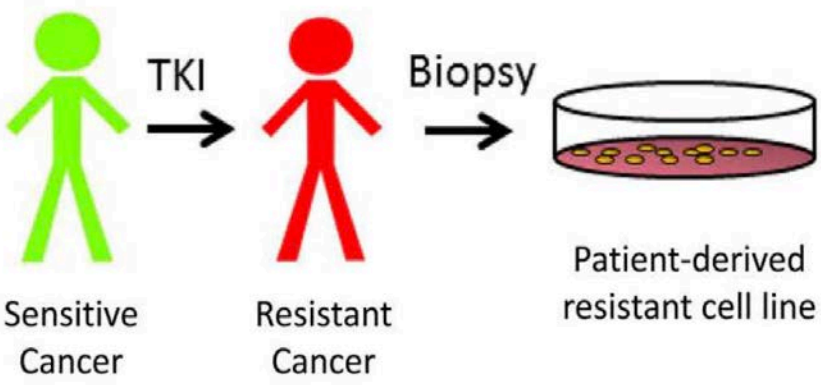


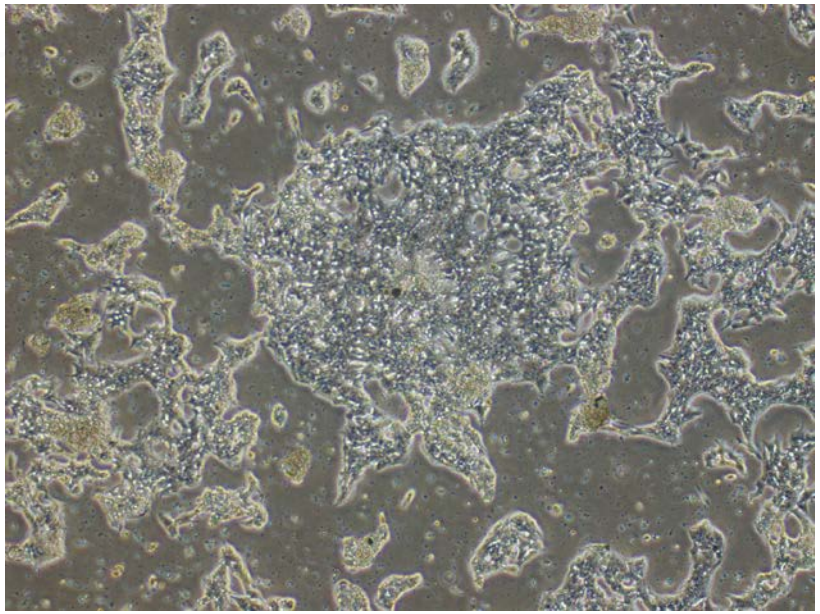




Engelman lab
Crystal et al. Science 2014, in press

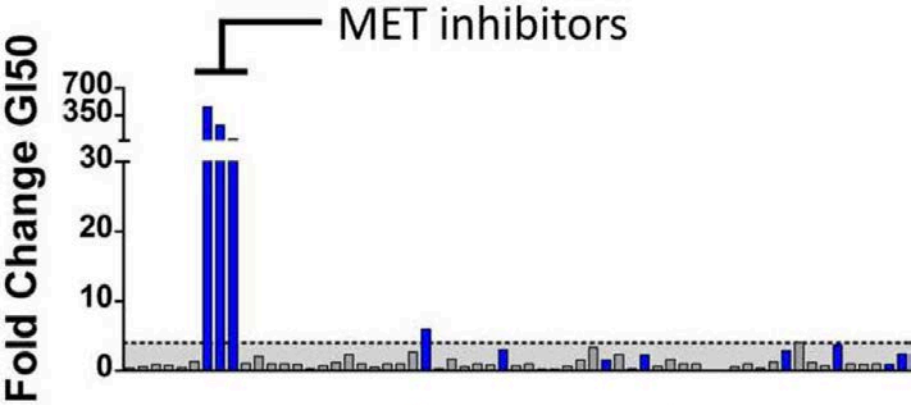
Using Next Generation Cancer Models to Develop Therapies

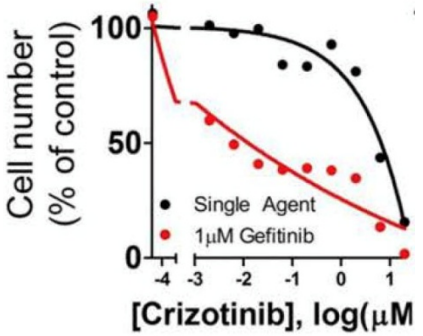




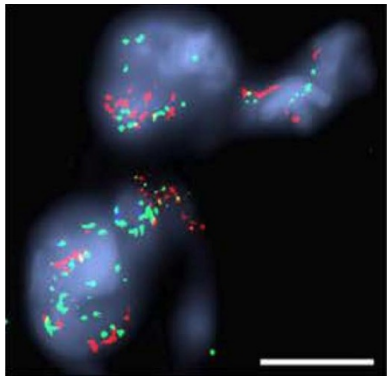
Engelman lab
Crystal et al. Science 2014, in press

Combo drug screen with Gefitinib

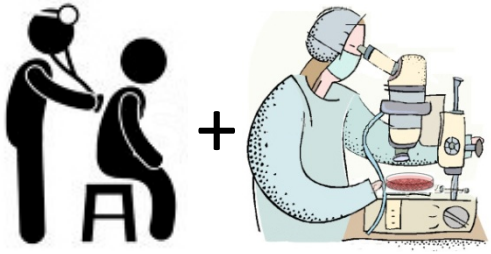




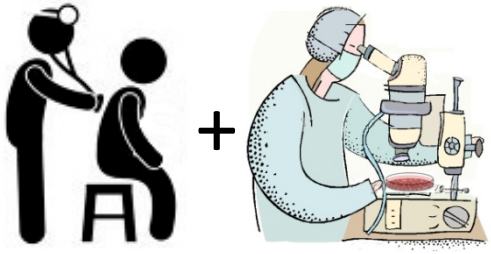
High level MET amp



A Next Generation Cancer Model Network



Site 1



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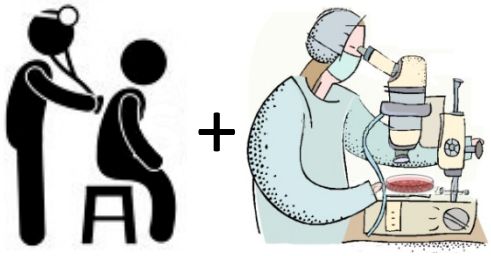
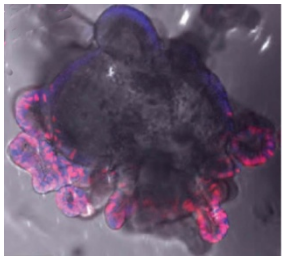


Site 3

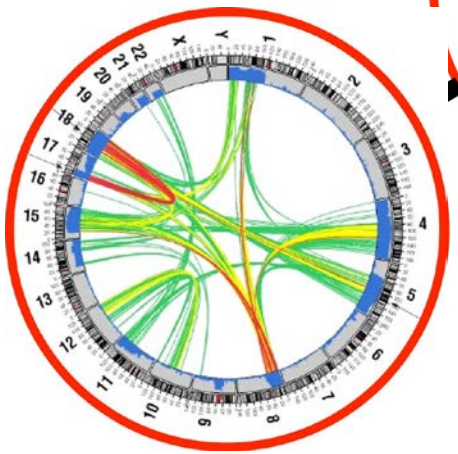


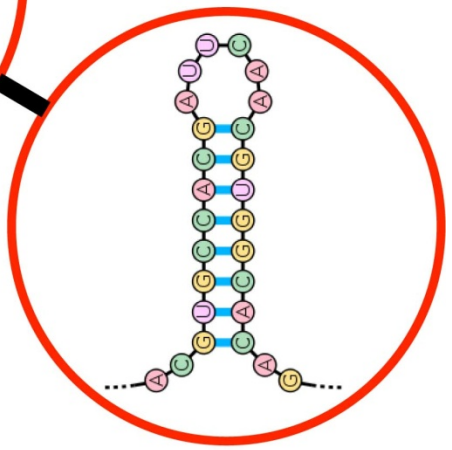
Human Cancer Models

Genomic data

Wide distribution to cancer researchers

Goals for Cancer Computational Genomics

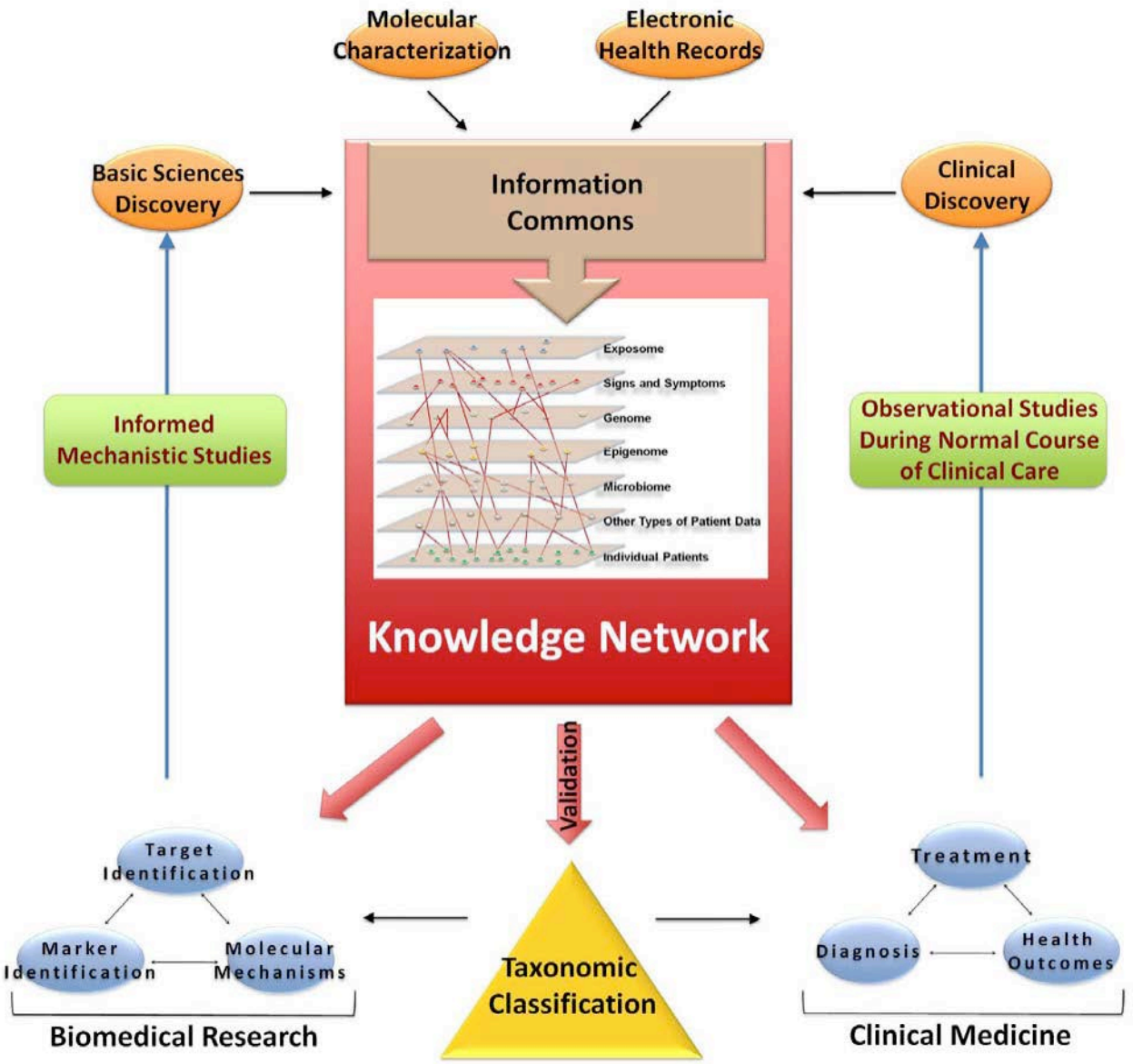




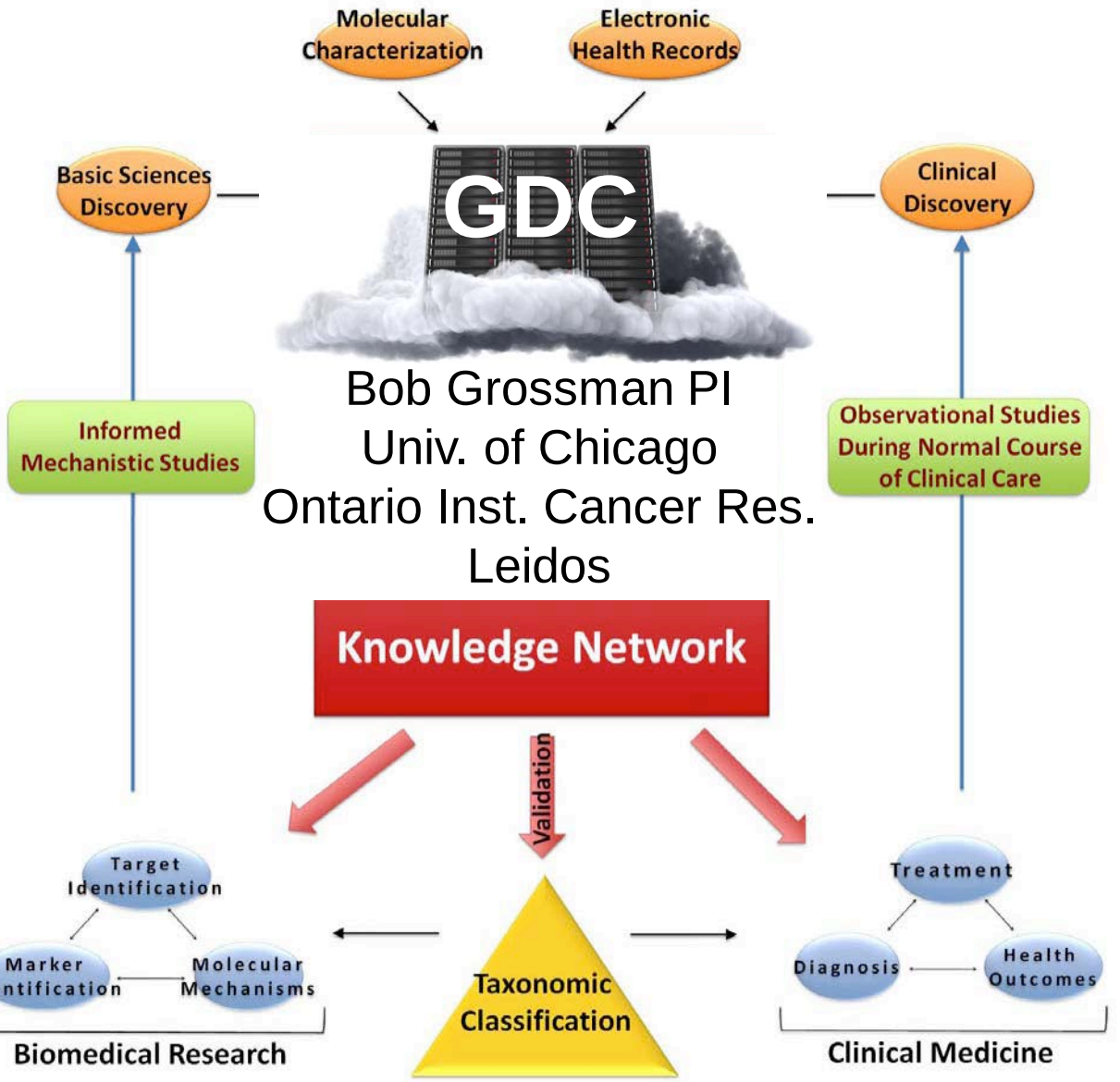
Computational Genomics

Functional Genomics

IOM Report on Precision Medicine Envisioned a Knowledge Network of Disease



Development of the NCI Genomics Data Commons (GDC) To Foster the Molecular Diagnosis and Treatment of Cancer



NCI Genomics Data Commons (GDC) Functionality

Genomic/ clinical data

NCI Genomics Data Commons

1. Import and standardize genomic and clinical data from legacy programs
2. Harmonize mapping of sequence data to the genome / transcriptome
3. Implement state-of-art methods for derived data:
   - mutation calls
   - copy number
   - structural variants
   - digital gene expression
4. Maintain data security and manage authorized access
5. Provide data for download or computation on a co-localized compute cluster
6. Open GDC for upload of new genomic data for comparison with existing data and shared access

Utility of a Cancer Knowledge System

Questions?