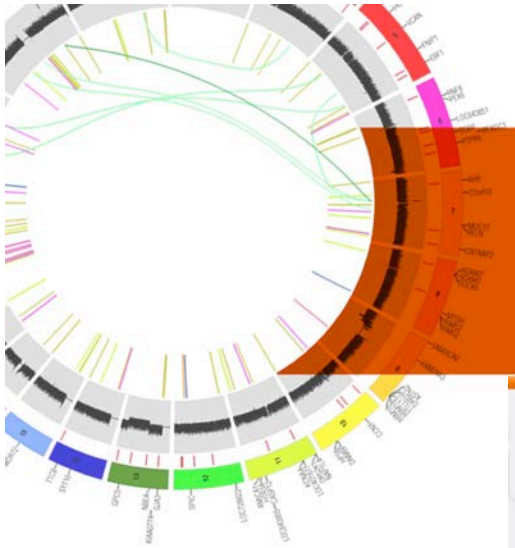
What is the NCI Center for Cancer Genomics (CCG)?

NCI Center for Cancer Genomics Programs



The Cancer Genome Atlas

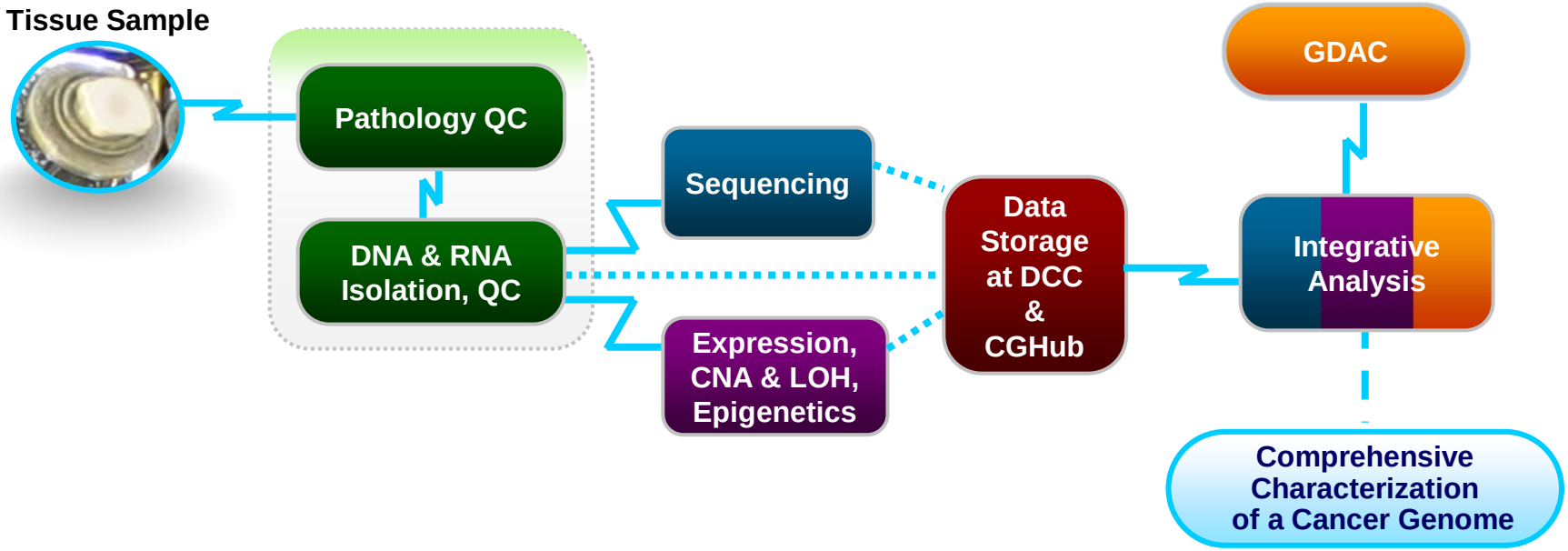
TCGA

TARGET

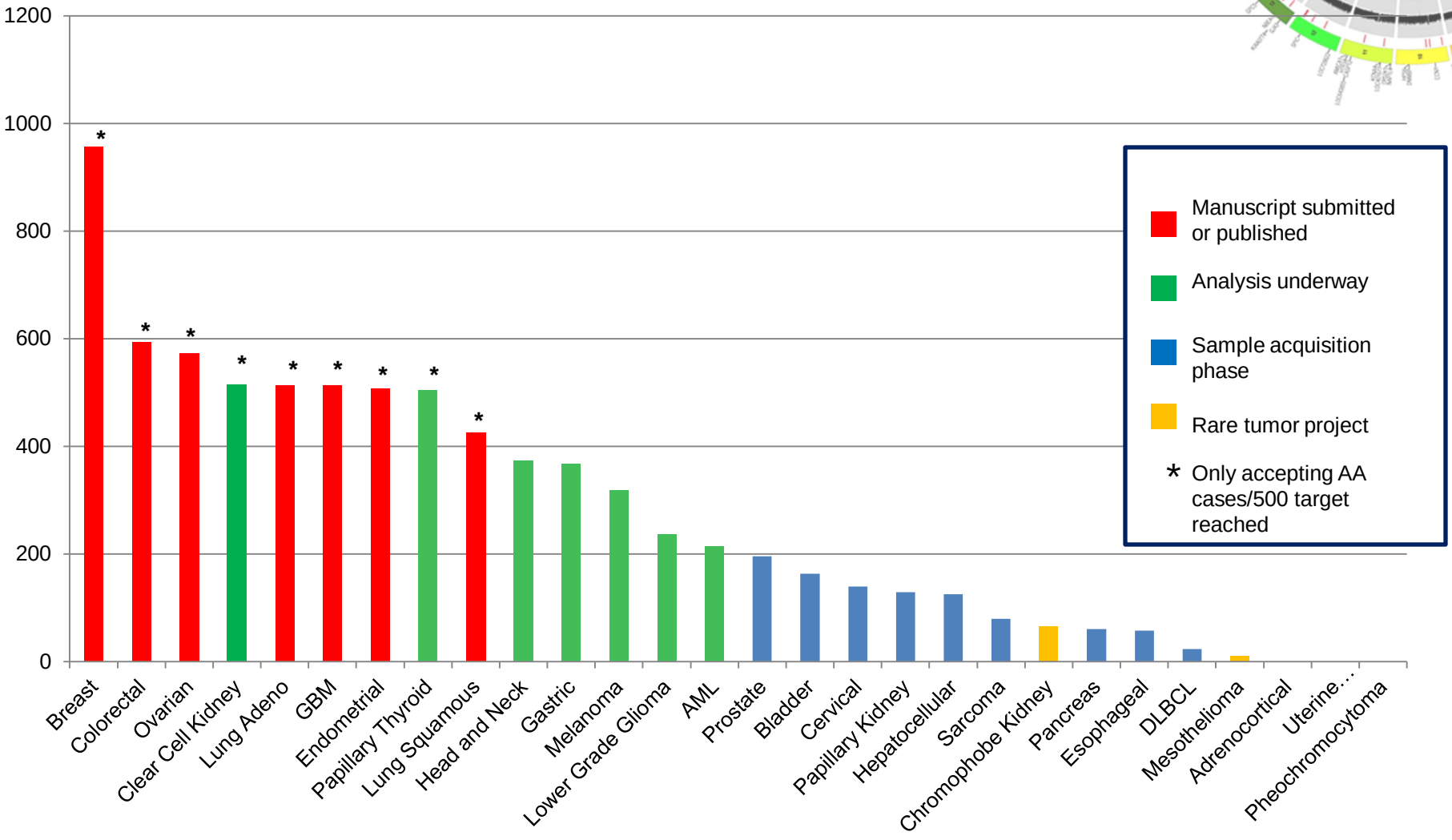
Therapeutically Applicable Research to Generate Effective Treatments

CTD²: A Bridge from Genomics to Cancer Therapeutics

TCGA: The Pipeline for Comprehensive Characterization of the Tumor Genome



TCGA Tumor Project Progress



The Cancer Genome Atlas

Whither the NCI Center for Cancer Genomics (CCG)?

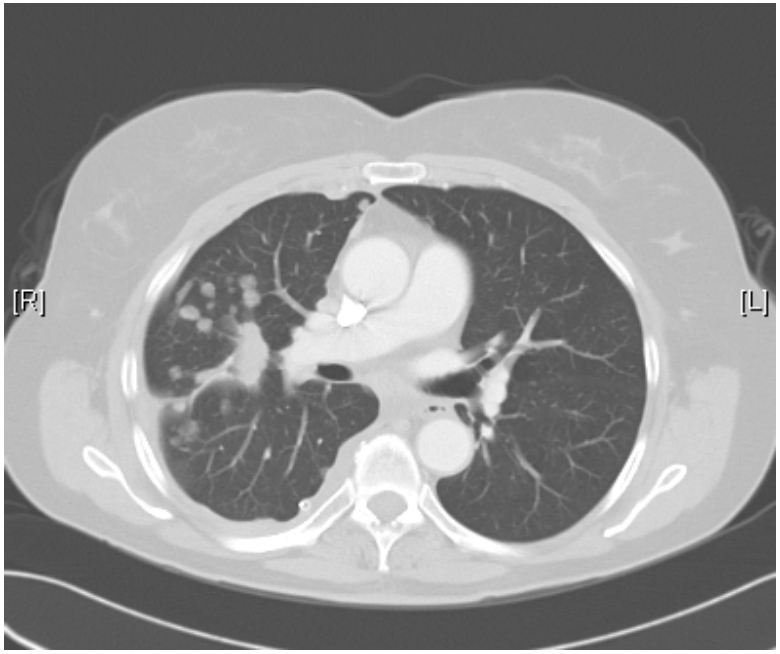
Open Questions in Cancer Genomics

- What is the full extent of driver mutations and genetic pathways in cancer?
- What is the contribution of intratumor genetic heterogeneity to progression and treatment response?
- What is the genetic basis of metastasis?

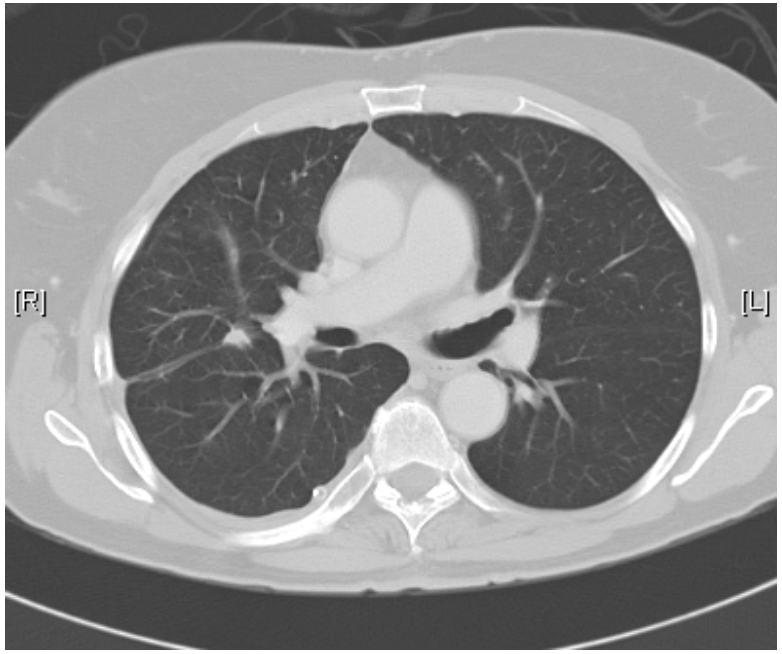
The 10K Concept

Targeted Therapy of Lung Adenocarcinoma From Cancer Genomics

Lung adenocarcinoma with *EGFR* deletion mutant in exon 19

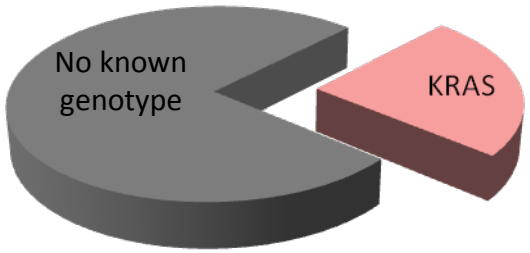


Before treatment

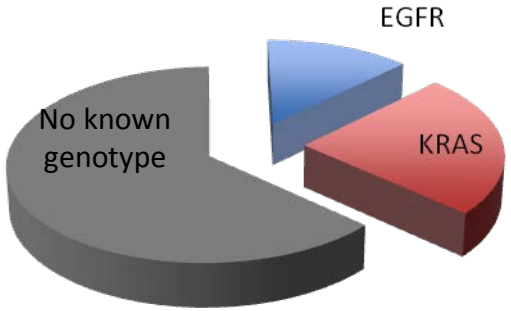


Erlotinib treatment (2 months)

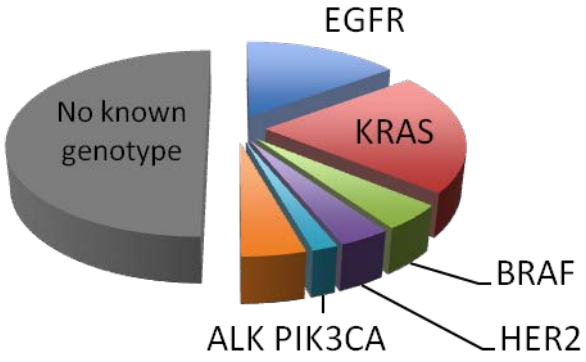
Identifying Novel Genomic Targets in Lung adenocarcinoma



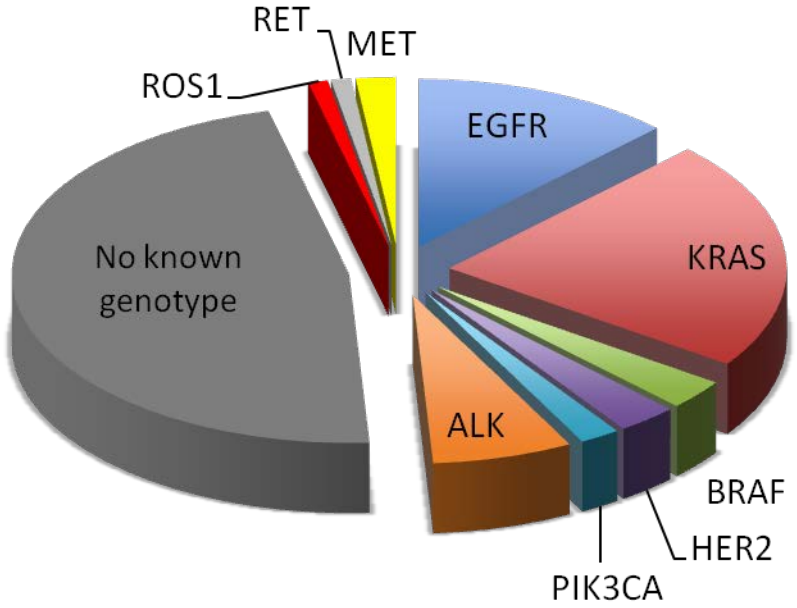
1984 - 2003



2004



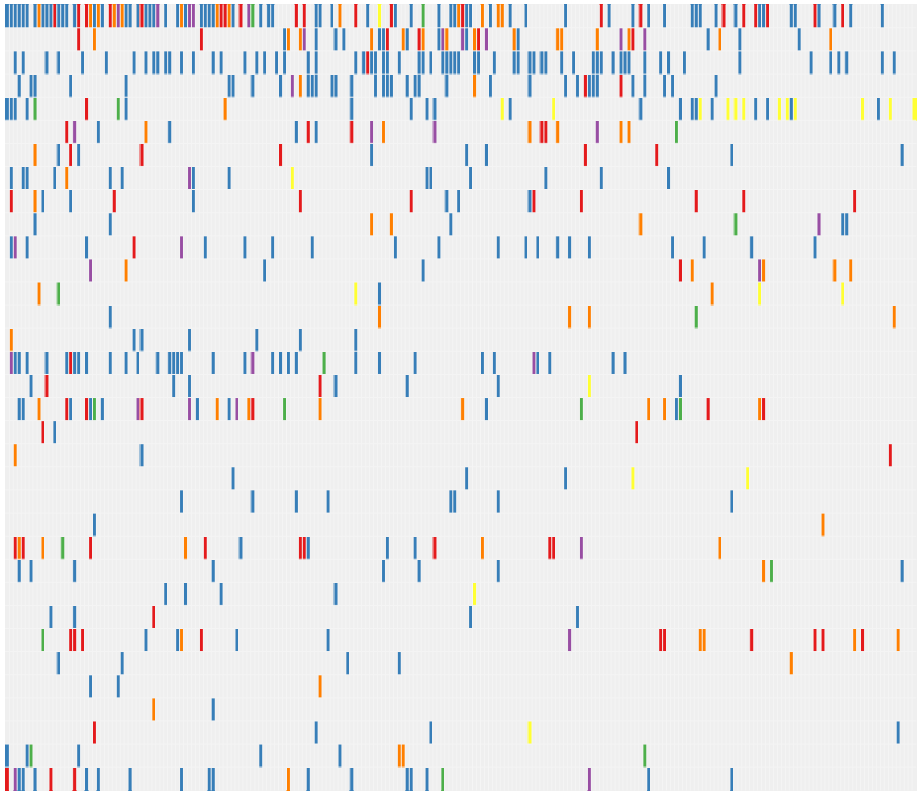
2009



2012

Matt Meyerson

Significantly mutated genes in 230 lung adenocarcinomas



Mostly known genes

Mixture of novel significant genes and false positives

Juliann Chmielecki, Mara Rosenberg, Matt Meyerson

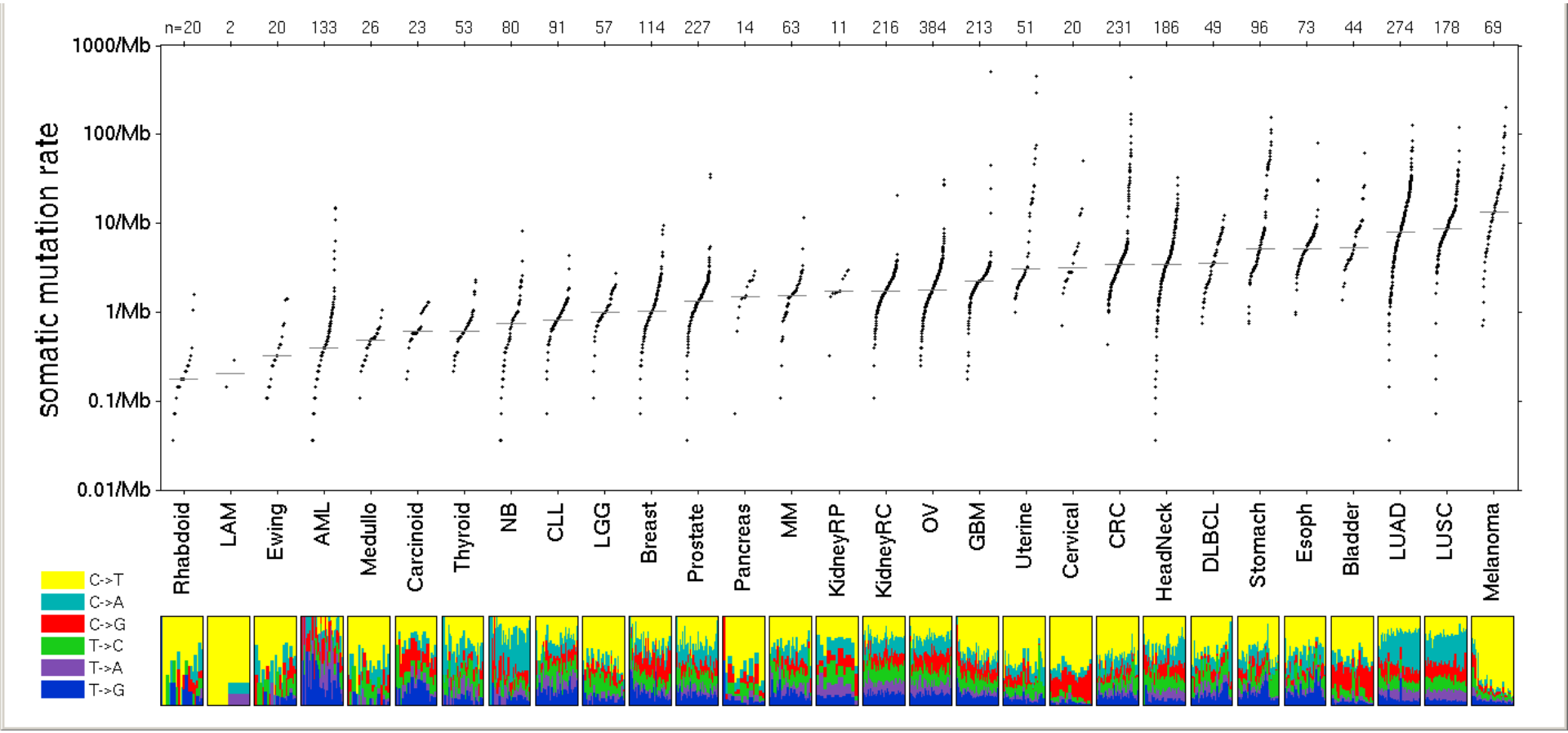
High lung cancer mutation rates pose a major problem in identifying significantly mutated genes

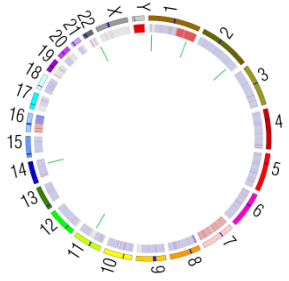
- Genes near statistical threshold may be true positives (oncogenes or tumor suppressors), or false positives
- Known recurrently mutated genes (e.g. *ERBB2*, *CTNNB1*) aren't detected as significant regardless of method used
- In the end, a much larger sample size will be required to elucidate "all" causative mutations in lung adenocarcinoma

10K Goals

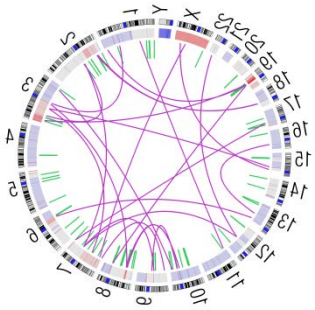
- Oncogenes and Tumor Suppressors
  Define comprehensive set of driver genes with ≥ 1% frequency in a particular cancer subtype
- Genetic Pathways
  Identify epistatic or cooperative relationships between cancer genes that are altered in ≥ 1% cases
- Interactions
  Investigate relationship of somatic alterations to germline variations & exposures (e.g. tobacco)
- Clinical Implications
  Correlate genetics to clinical outcomes (e.g. local growth vs. 1° / 2° metastasis) and treatment response

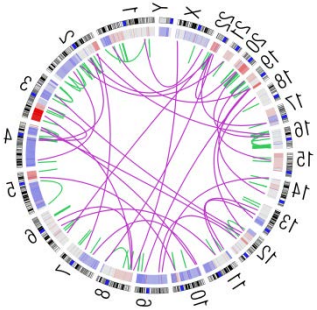
The Problem: High Background Mutation Rate in Cancer

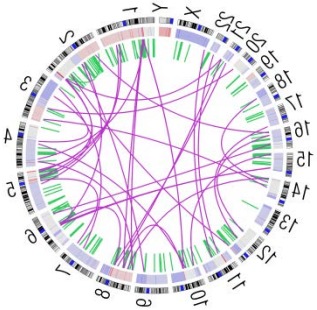




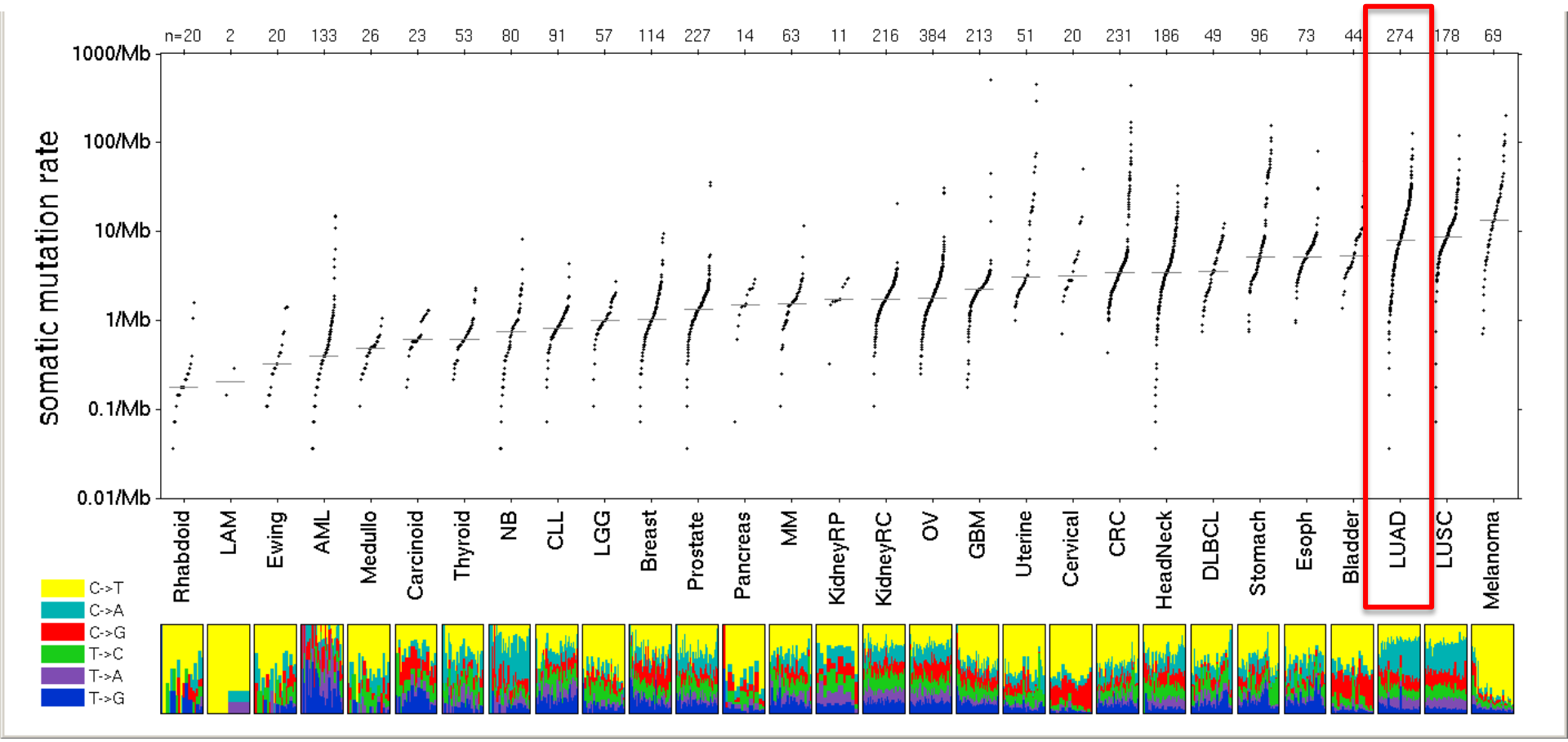
Mike Lawrence and Gaddy Getz

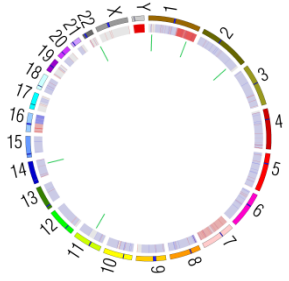




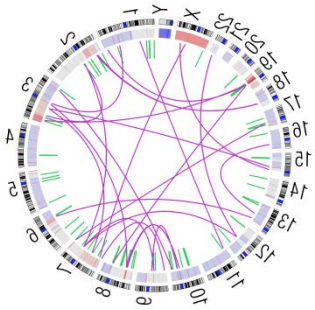


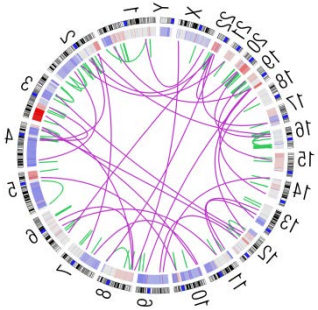
Lung Adenocarcinoma has Extensive Genetic Damage

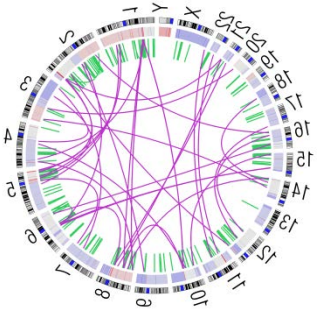




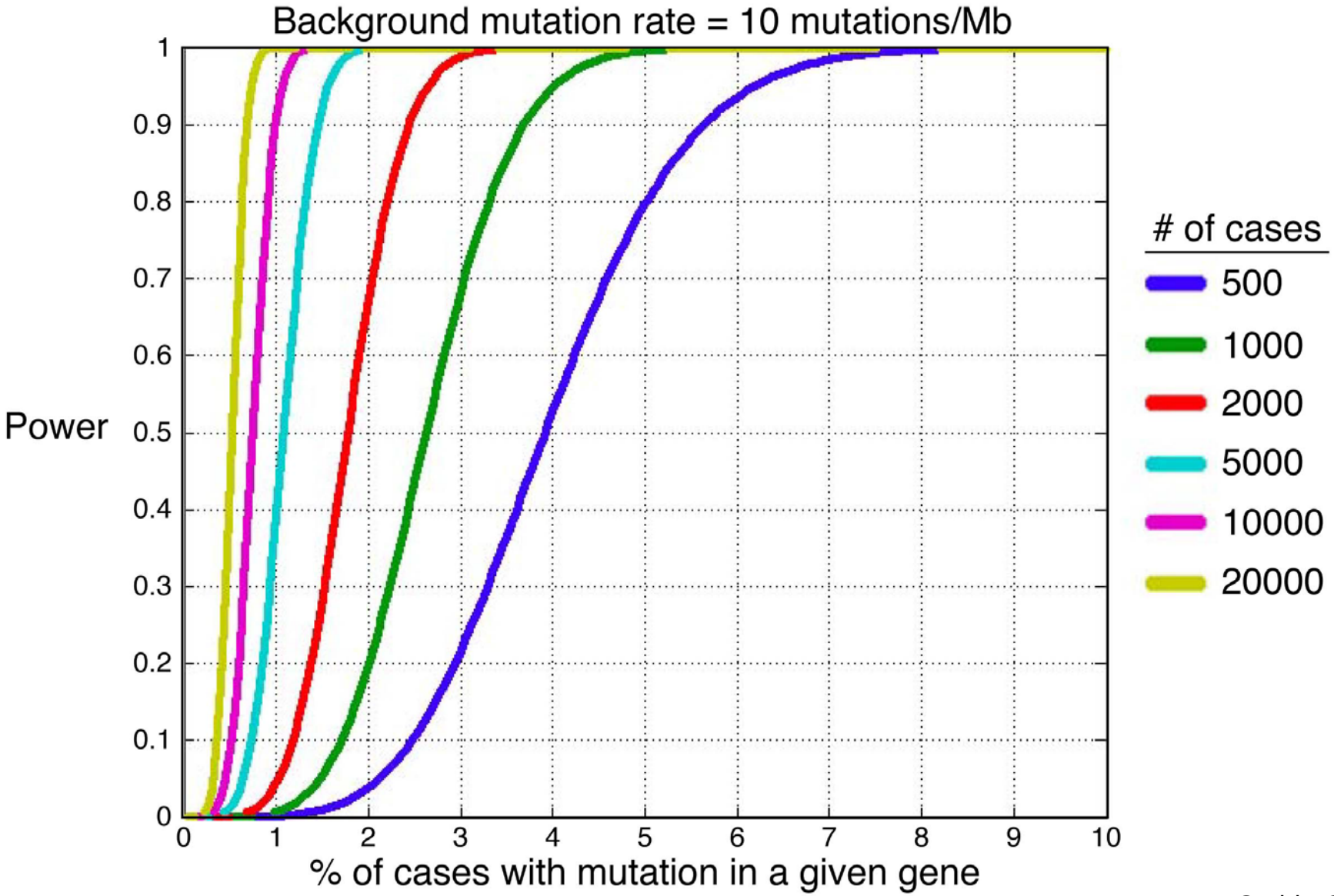
Mike Lawrence and Gaddy Getz





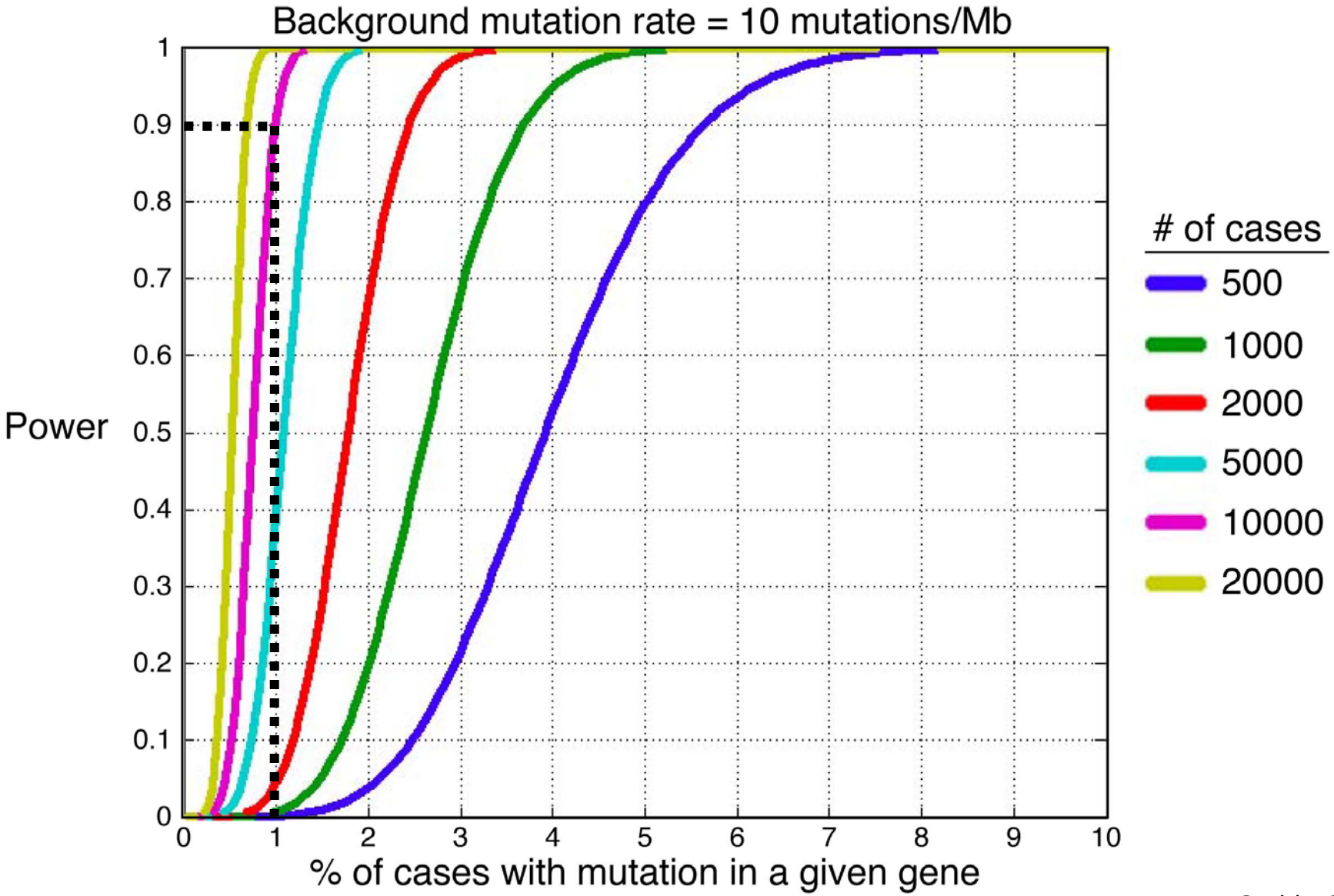


Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



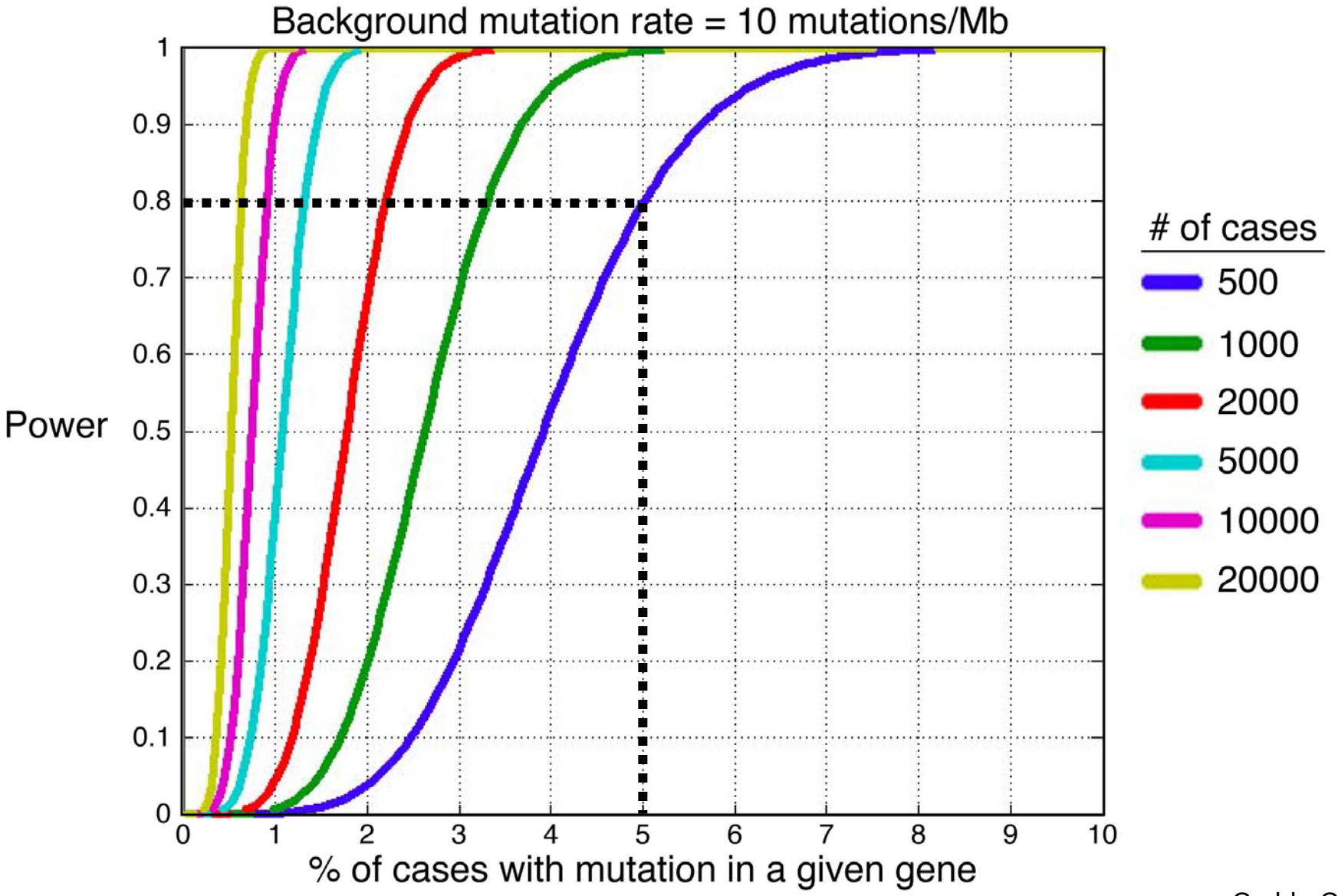
Gaddy Getz

Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



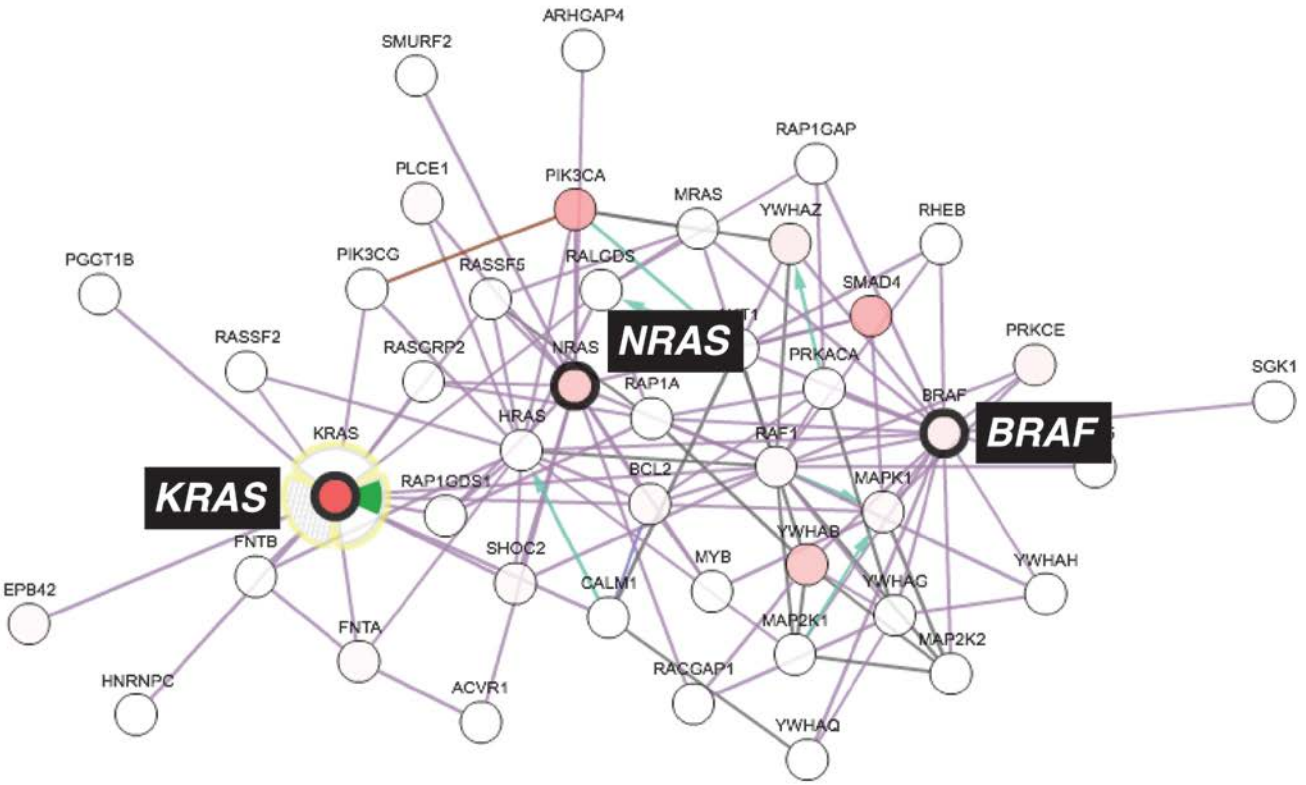
Gaddy Getz

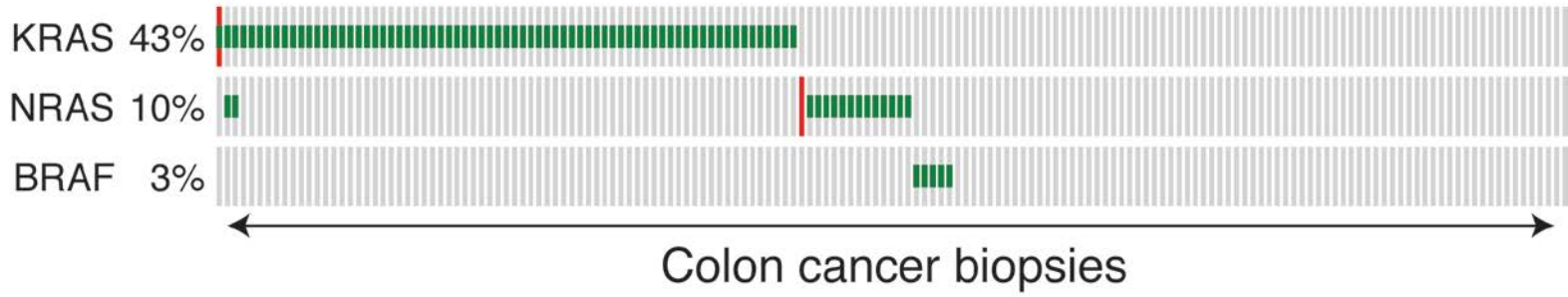
Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



Gaddy Getz

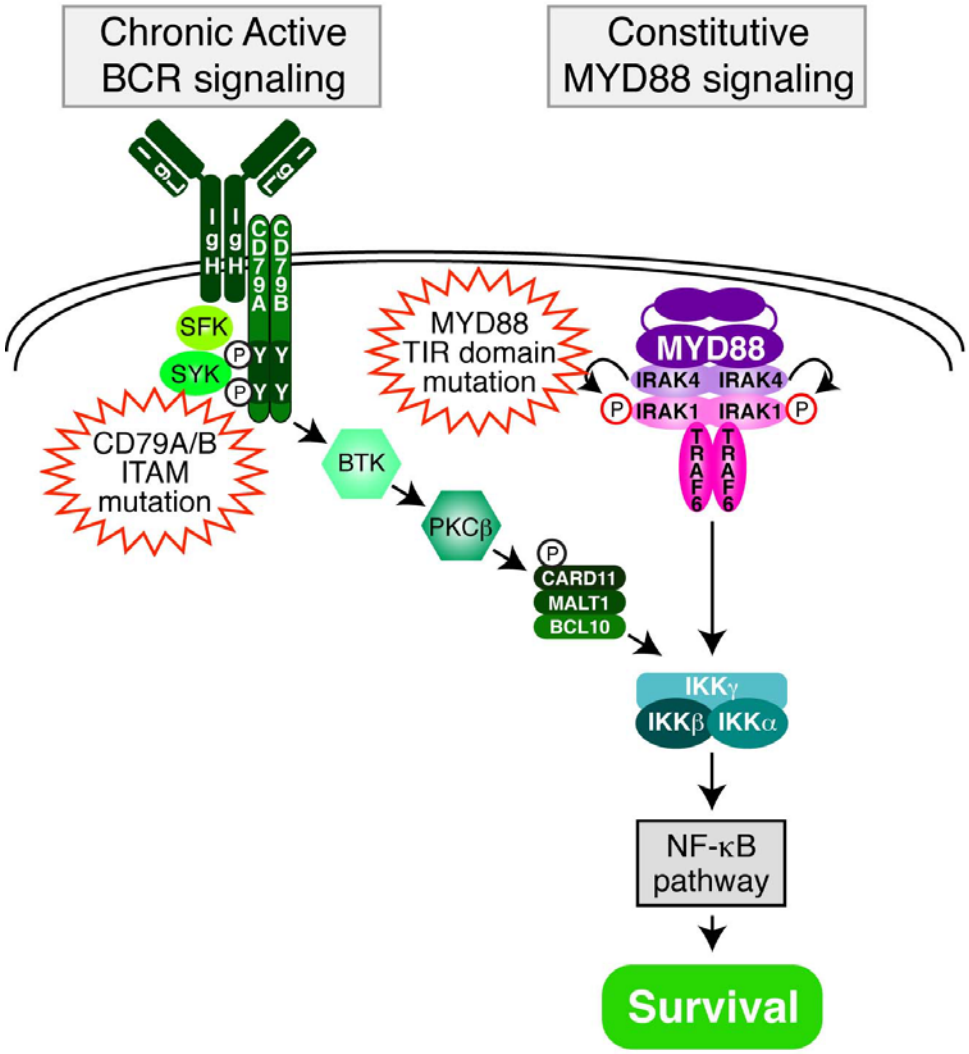
Mutual Exclusion of Genetic Aberrations Defines Genetic Pathways in Cancer

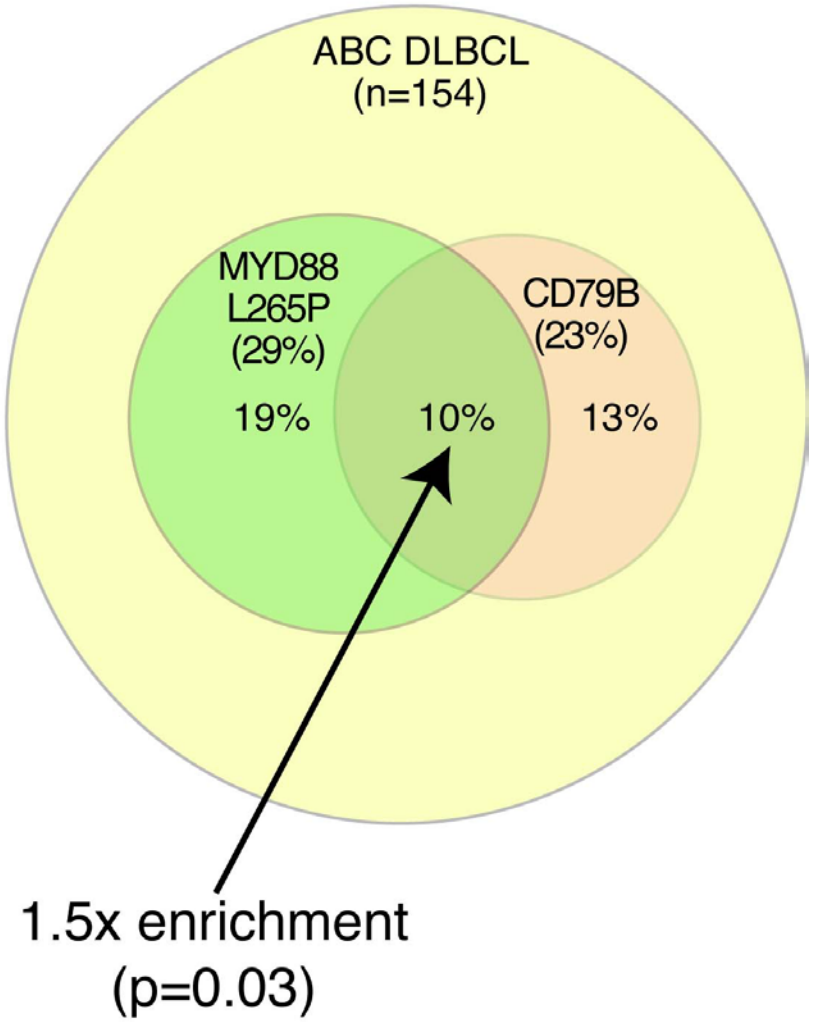




TCGA, *Nature* 2012 *487:330*

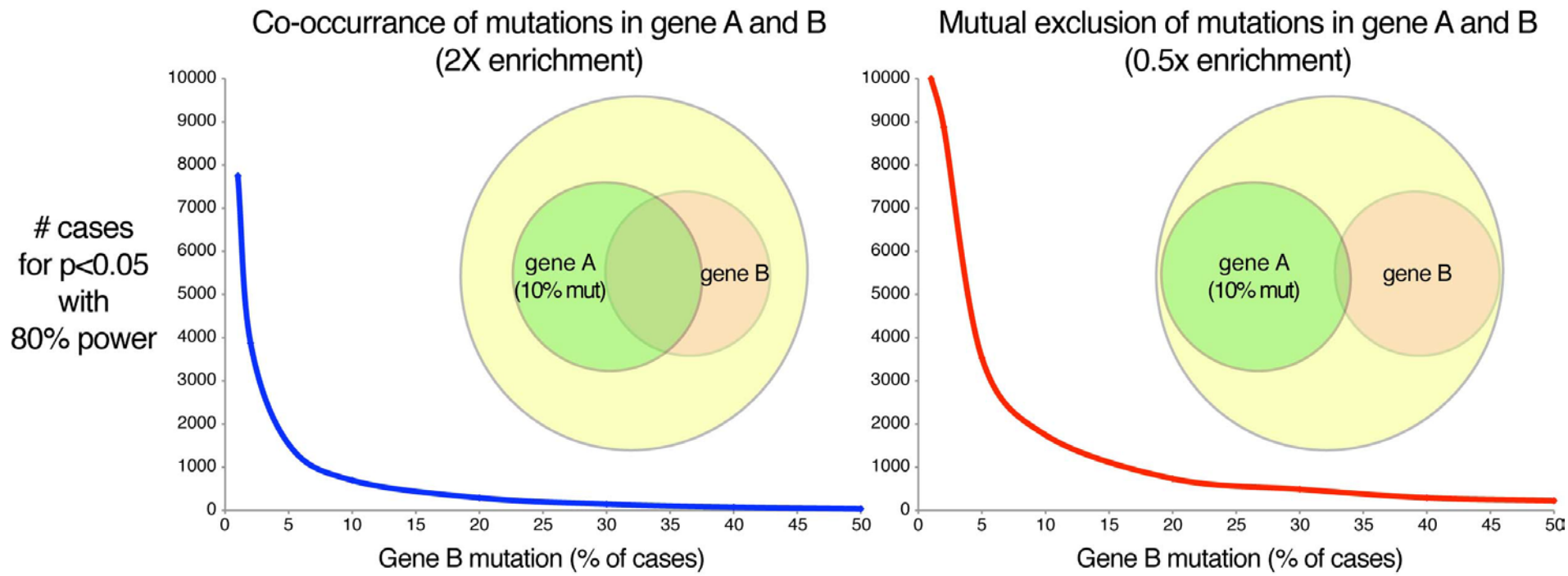
Co-occurrence of Genetic Aberrations Defines Genetic Pathways in Cancer





Ngo et al. Nature 2006 441:106

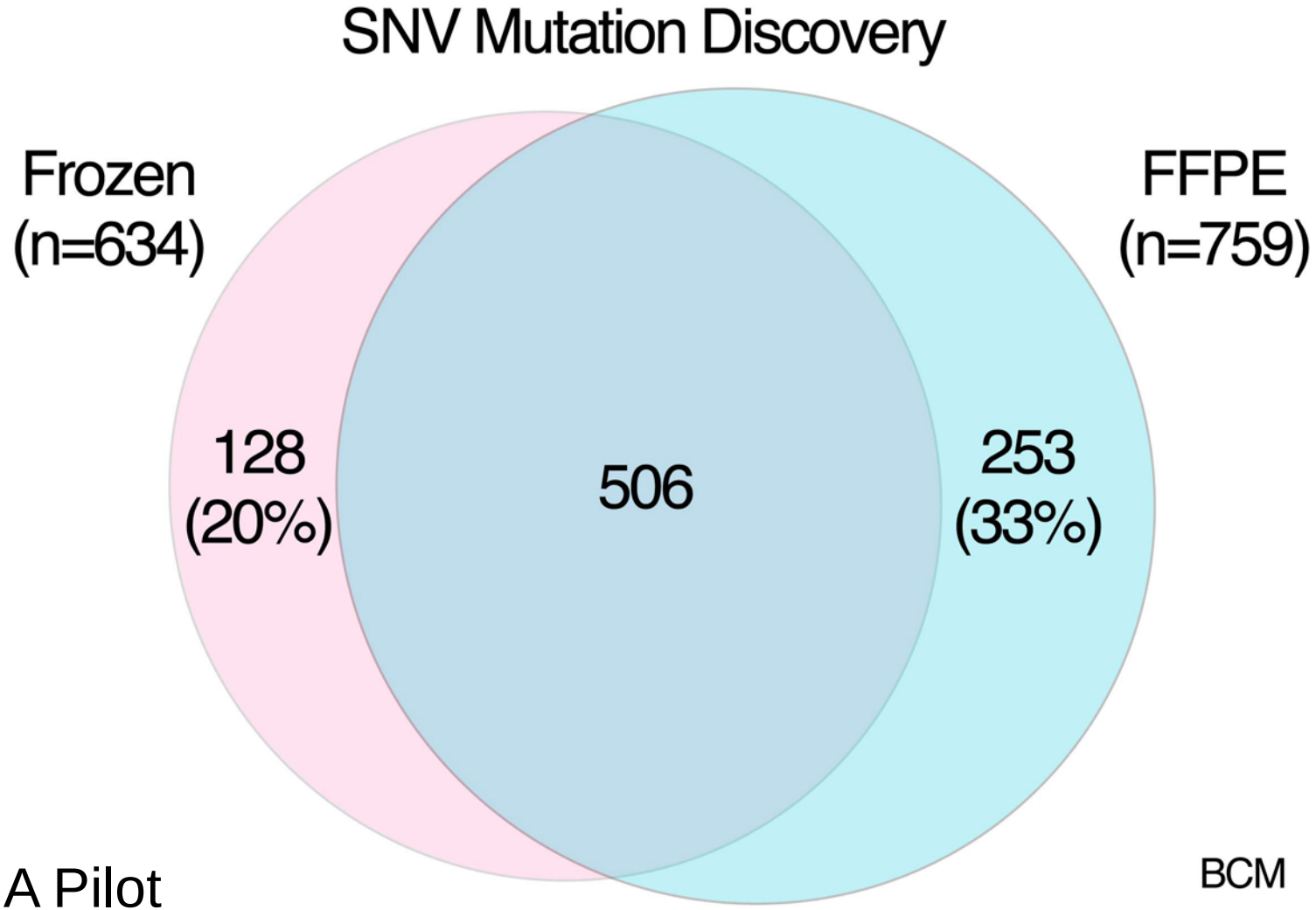
Large Case Numbers Needed to Assign Less Common Cancer Genes to Genetic Pathways



George Wright

How to find 10K tumor biopsies?

Genomic Analysis of FFPE Biopsies: A Game Changer



TCGA Pilot

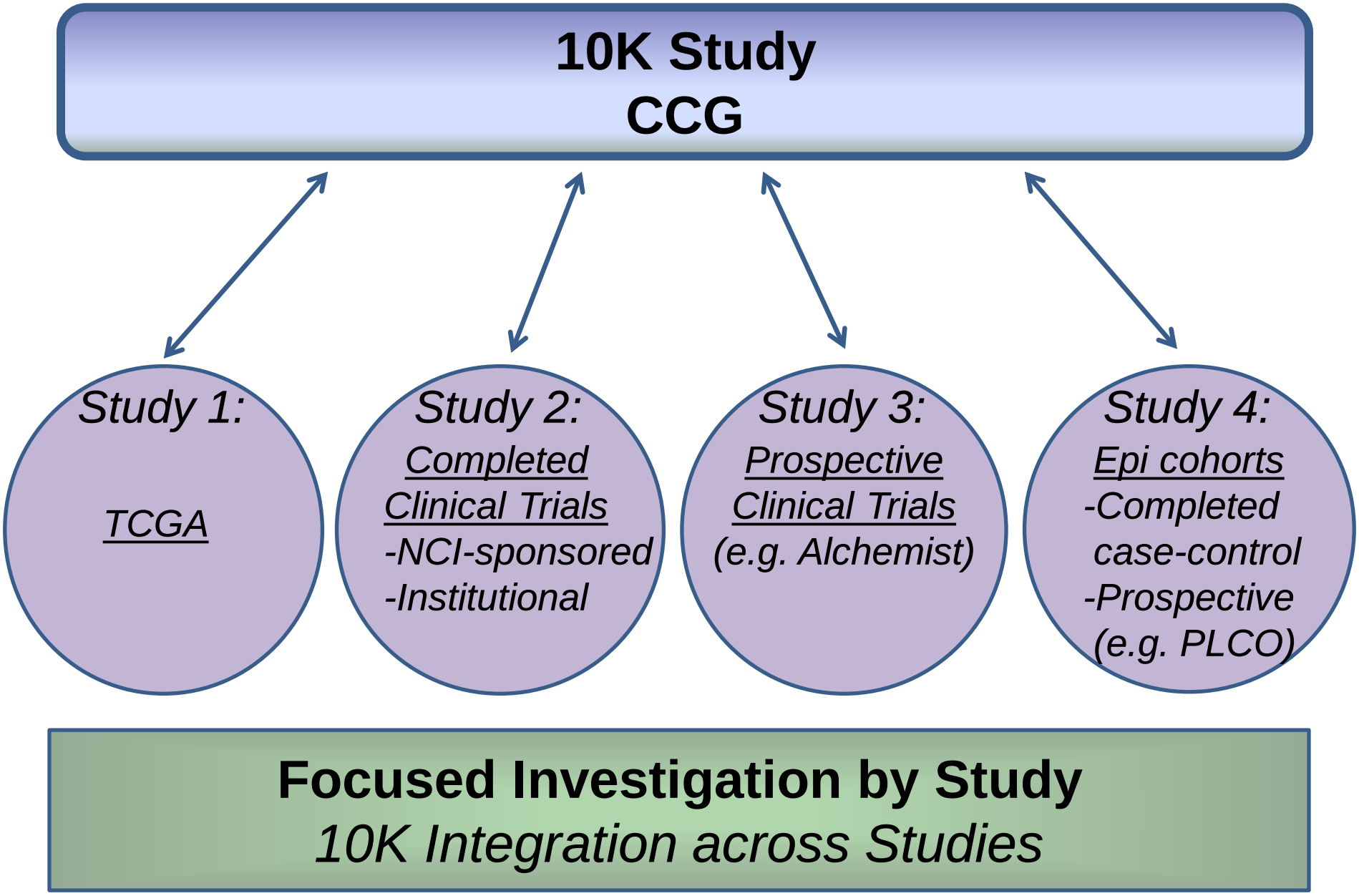
BCM

10K Tumor Biopsies

Sample criteria

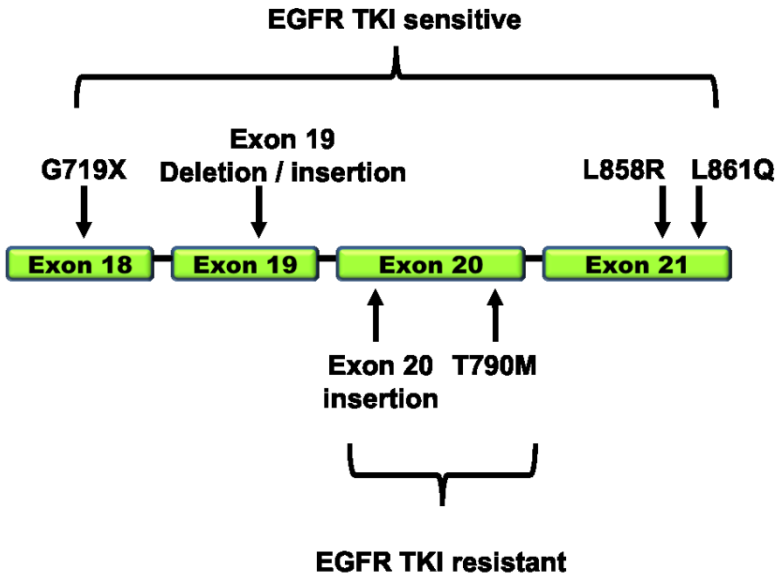
- FFPE or frozen biopsy samples large enough for whole exome and RNA-seq analysis (i.e not FNAs)
- Clinical annotation and treatment response necessary
- Matched normal tissue in most (maybe not all) cases
- Consent for genomic analysis
- Likely focus on common cancers (lung, colon, breast, prostate etc.)

Building a 10K Study

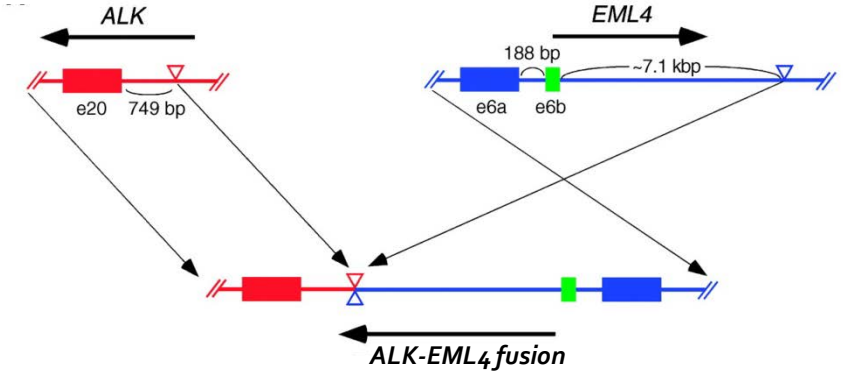


ALChEMIST
Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:
10% in Western population
Up to 50% in Asian population
Enriched in:
•females
•non-smokers
•younger patients
Multiple tests in clinical use
No FDA-approved clinical assay

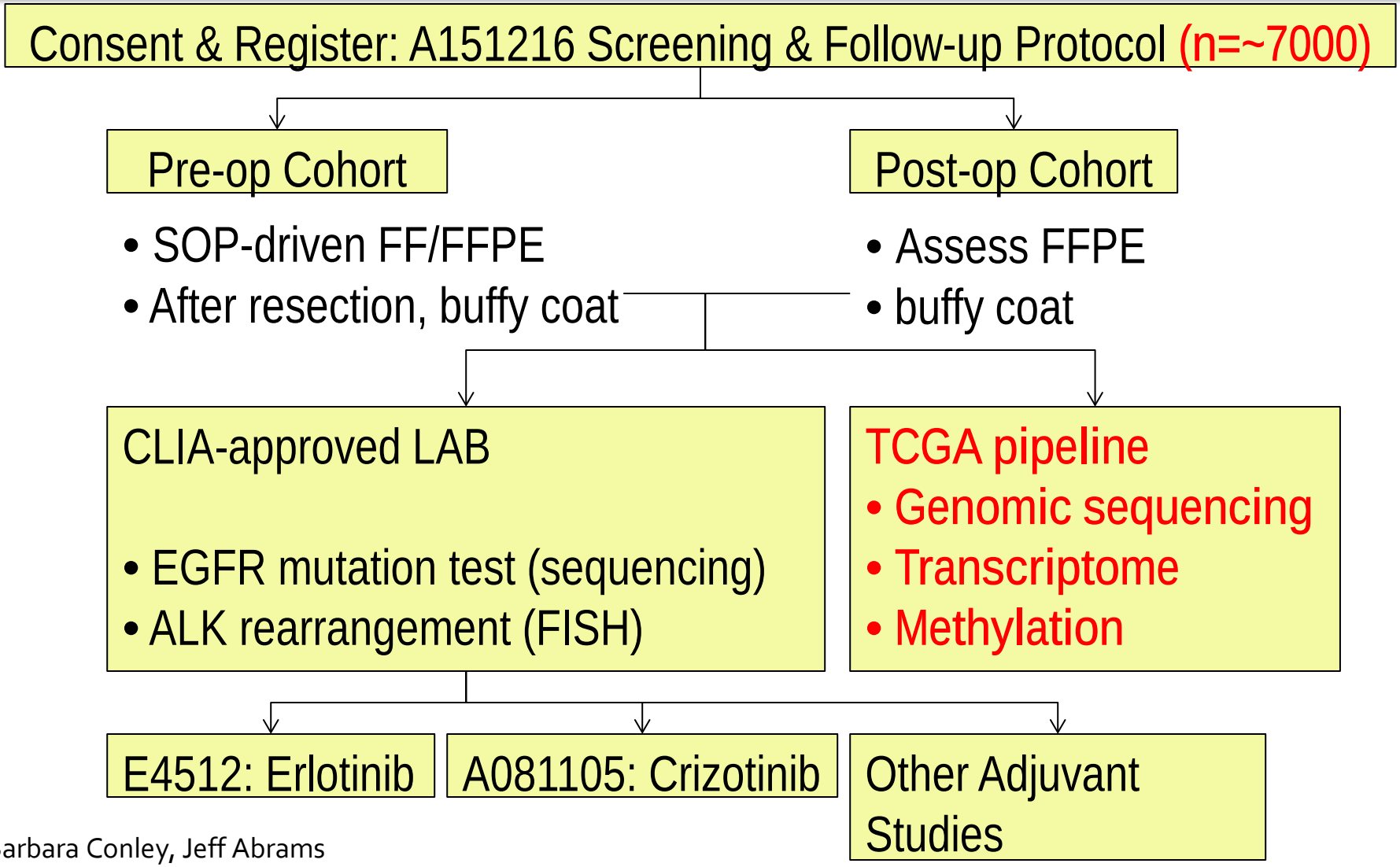


ALK Rearrangement
5-7% in Western population
FDA approved companion diagnostic:
Vysis Break Apart FISH probe



Barbara Conley, Jeff Abrams

ALChEMIST Tissue Flow



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ALChEMIST
Beyond Treatment Endpoints

- Molecular profiling studies on large cohort (~ 7000 pts)
- Ability to re-profile at relapse in about 50% of cases ("natural genomic history")
- Opportunity to collect epidemiologic info spanning tobacco, diet, alcohol and work exposures

Barbara Conley, Jeff Abrams

Questions?

Cost per Genome