Reclassifying Lung Cancer and Molecular Diagnostic(s)

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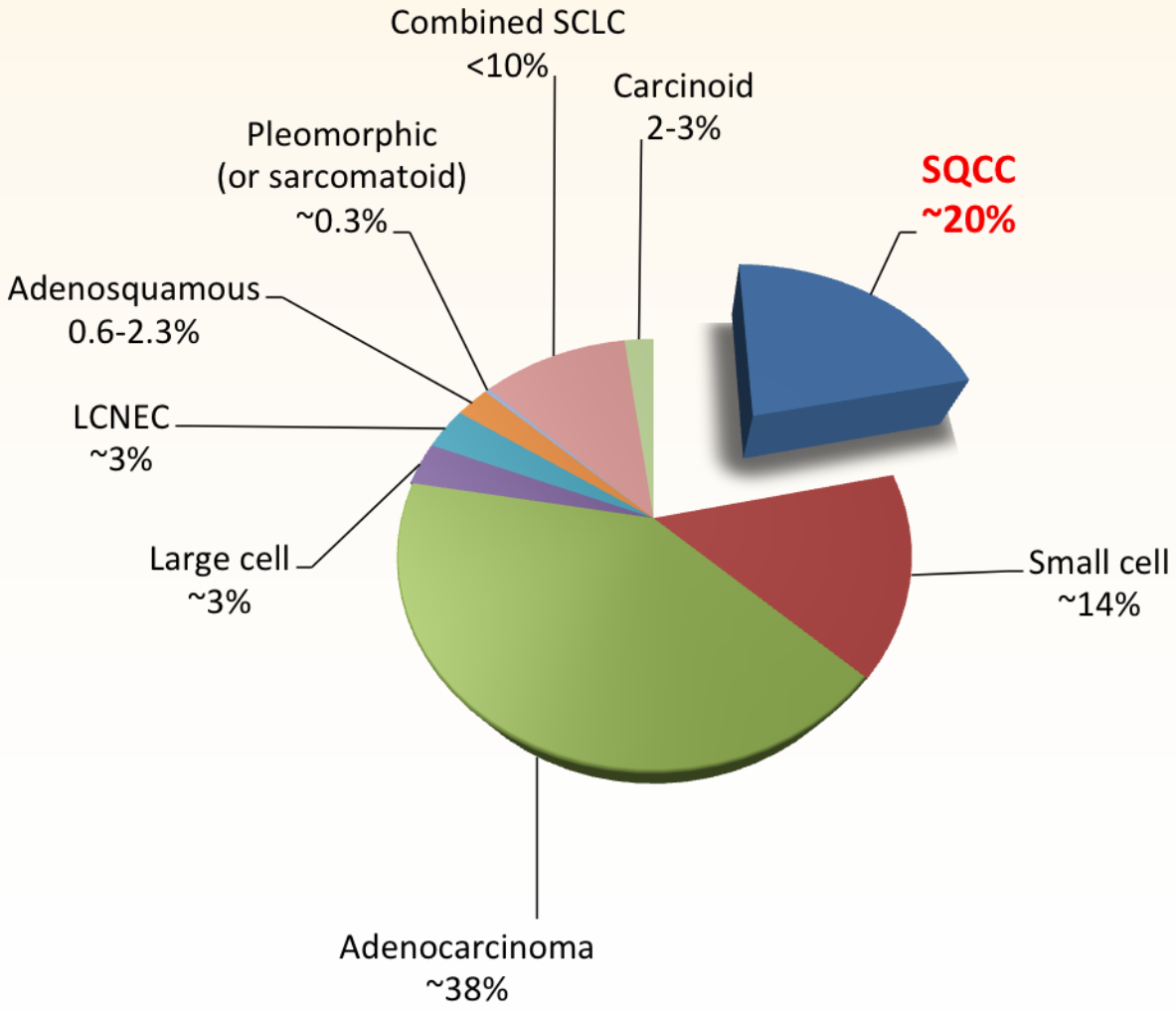
Disclosures

- No conflicts relevant to this presentation
- Consultant: BMS, BI, Pfizer, Mallinckrodt Medical, Genentech, Novartis, GSK
- Acknowledgement:
  - Sid Devarakonda, fellow, Washington University School of Medicine, St Louis, MO, USA
  - William Travis, Memorial Sloan Kettering

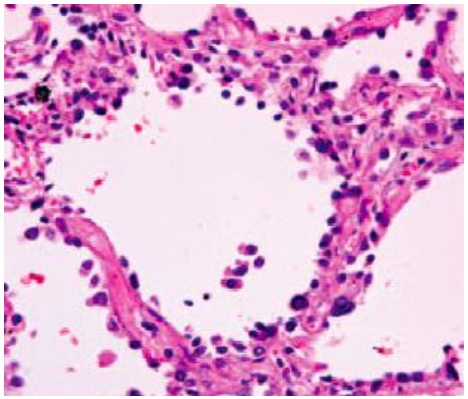
Histological distribution of lung cancer



Travis WD. Clin Chest Med 2011;32:669-92.

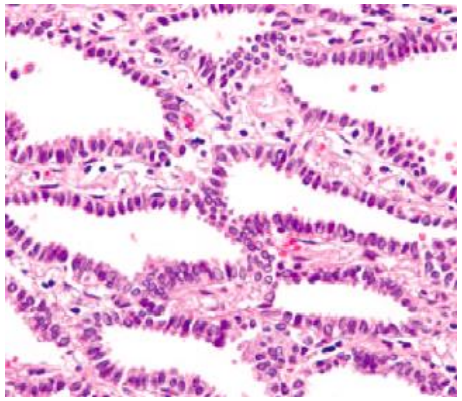
Histological re-classification of LUAD

Pre-invasive lesions

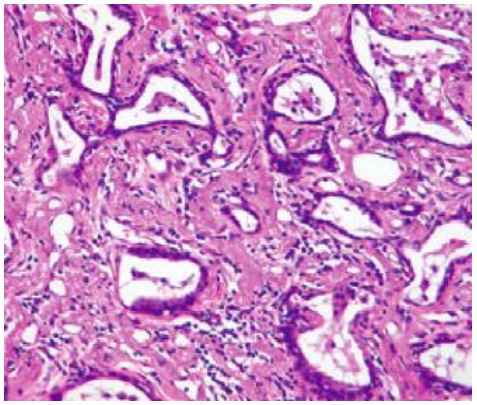


Atypical adenomatous hyperplasia

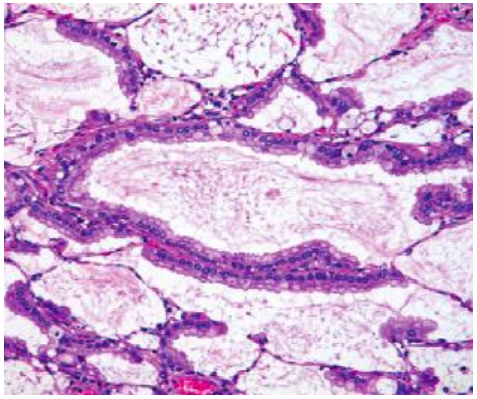
Non-mucinous

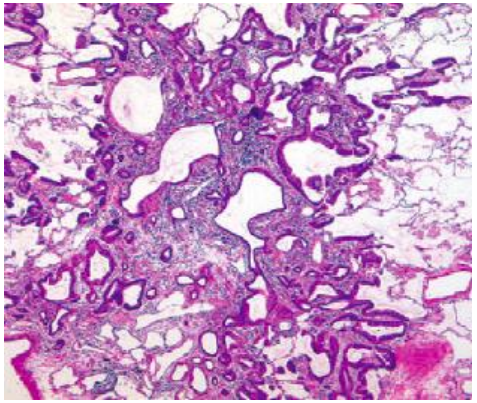


Adenocarcinoma-in-situ



Minimally invasive adenocarcinoma



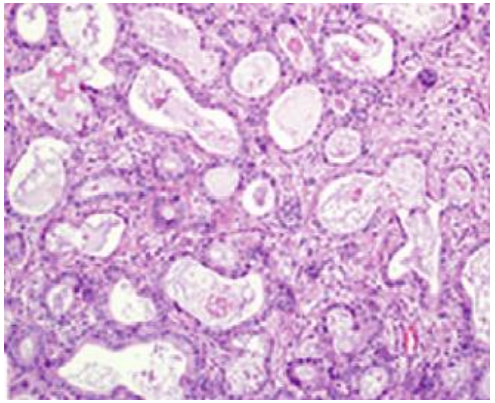


Mucinous

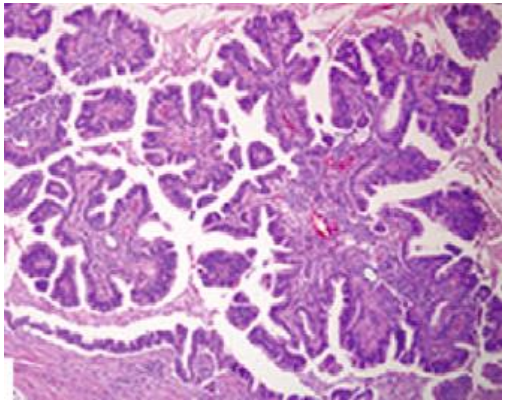
Image source: Travis et al., *J Thoracic Oncology* 2011;244-285.

Histological re-classification of LUAD

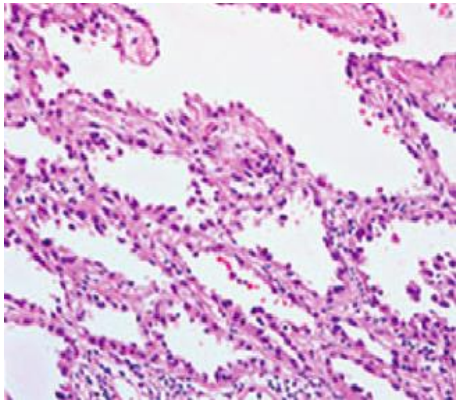
Invasive Adenocarcinoma



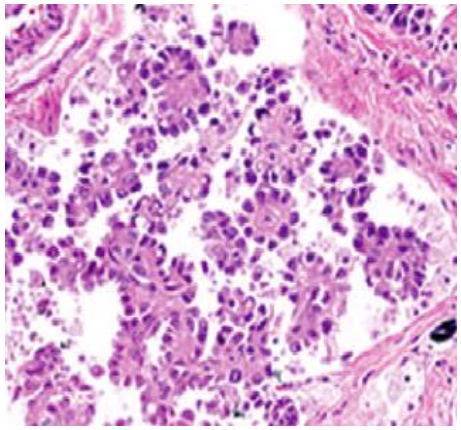
Acinar



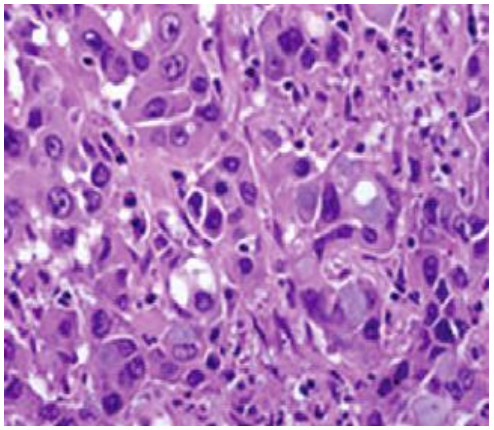
Papillary



Lepidic
(Non-mucinous with
BAC pattern)

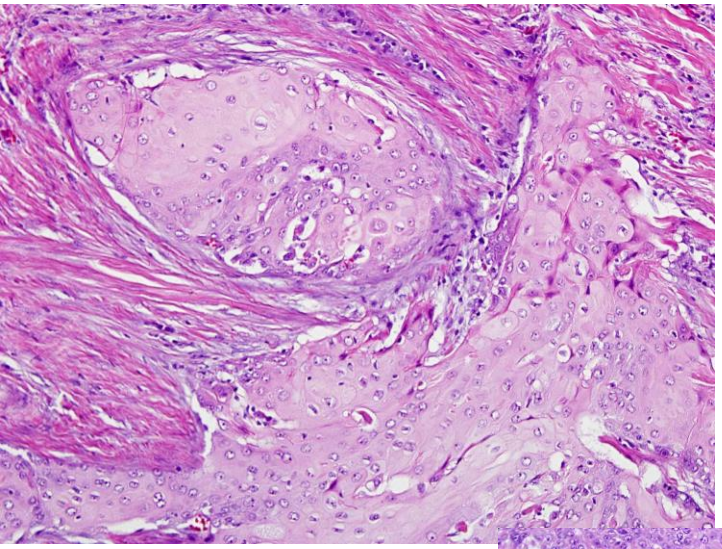


Micropapillary

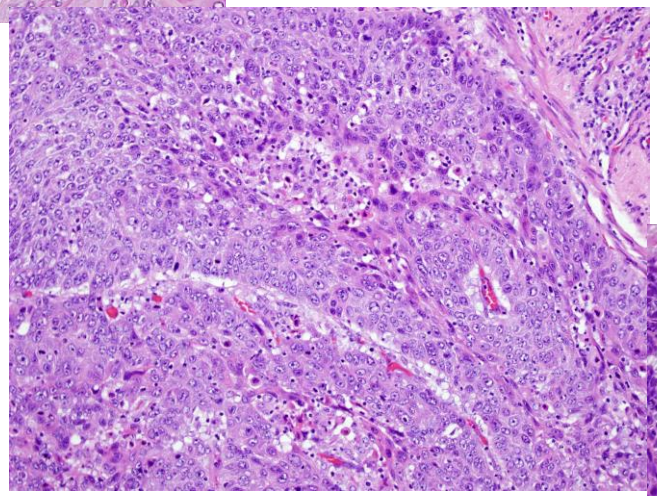


Solid predominant
with mucin

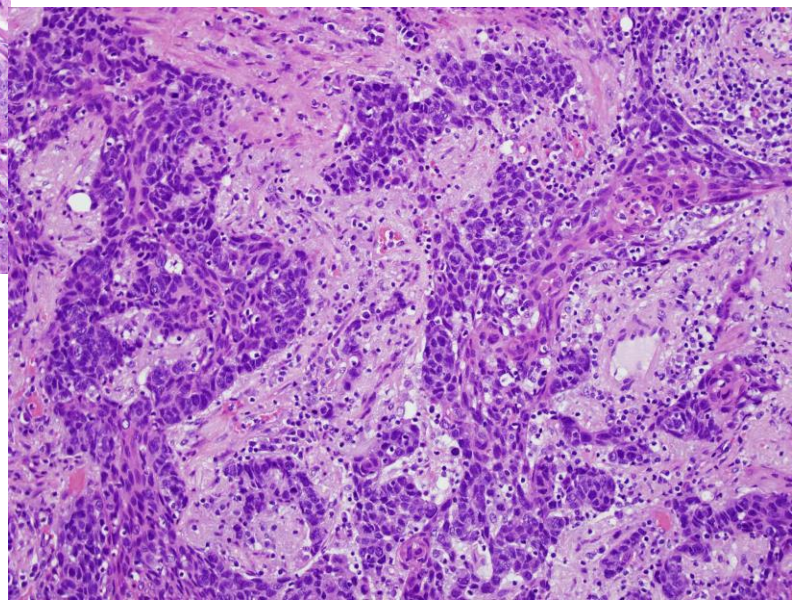
Image source: Travis et al., *J Thoracic Oncology* 2011;244-285.



Squamous cell lung cancer- Keratinizing



Squamous cell lung cancer- non-keratinizing



Squamous cell lung cancer- basaloid

Courtesy: Bill Travis MD

Expression subtypes: LUAD

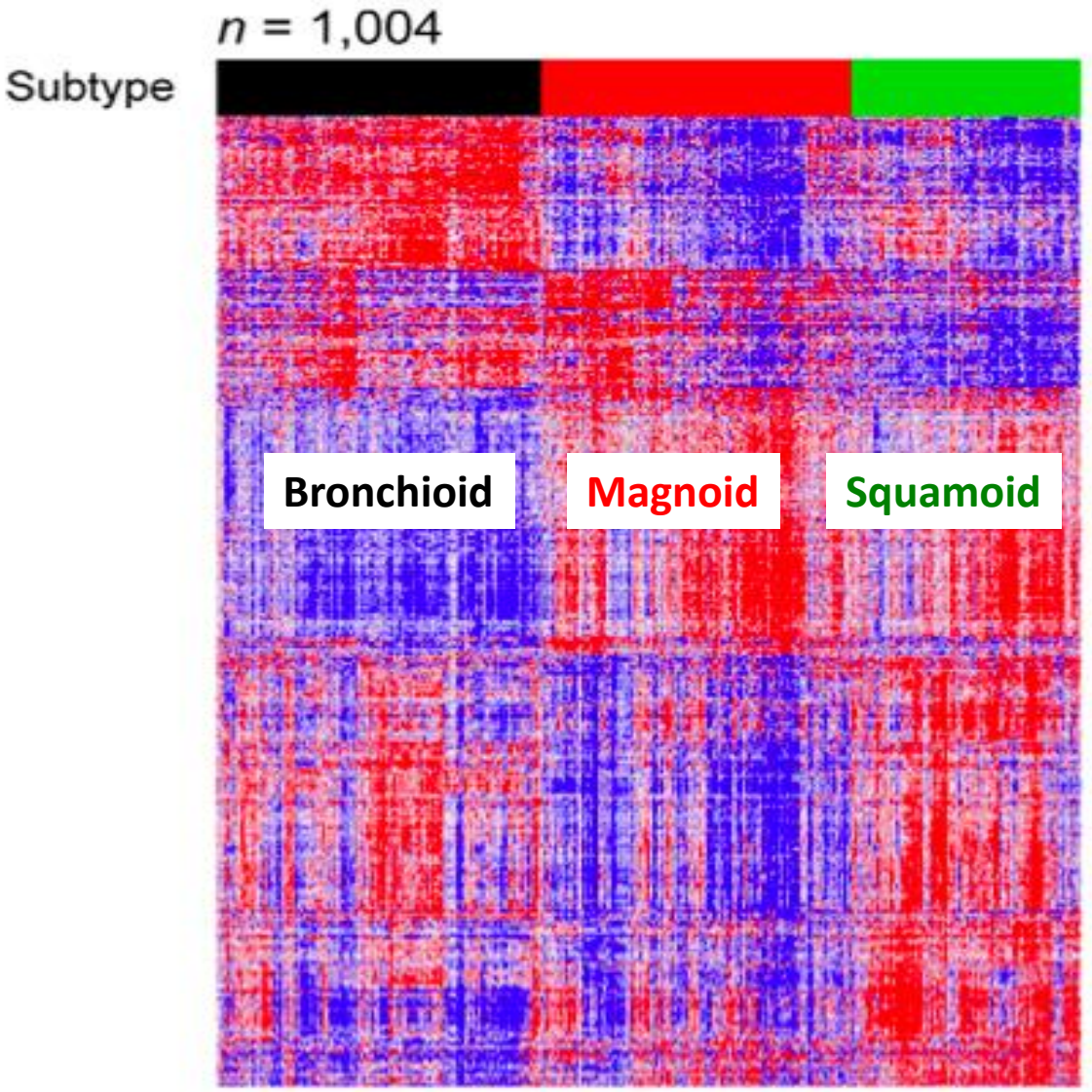


Image from Wilkerson et al, *PLoS One* 2012; 7(5):e36530

Expression subtypes: molecular features

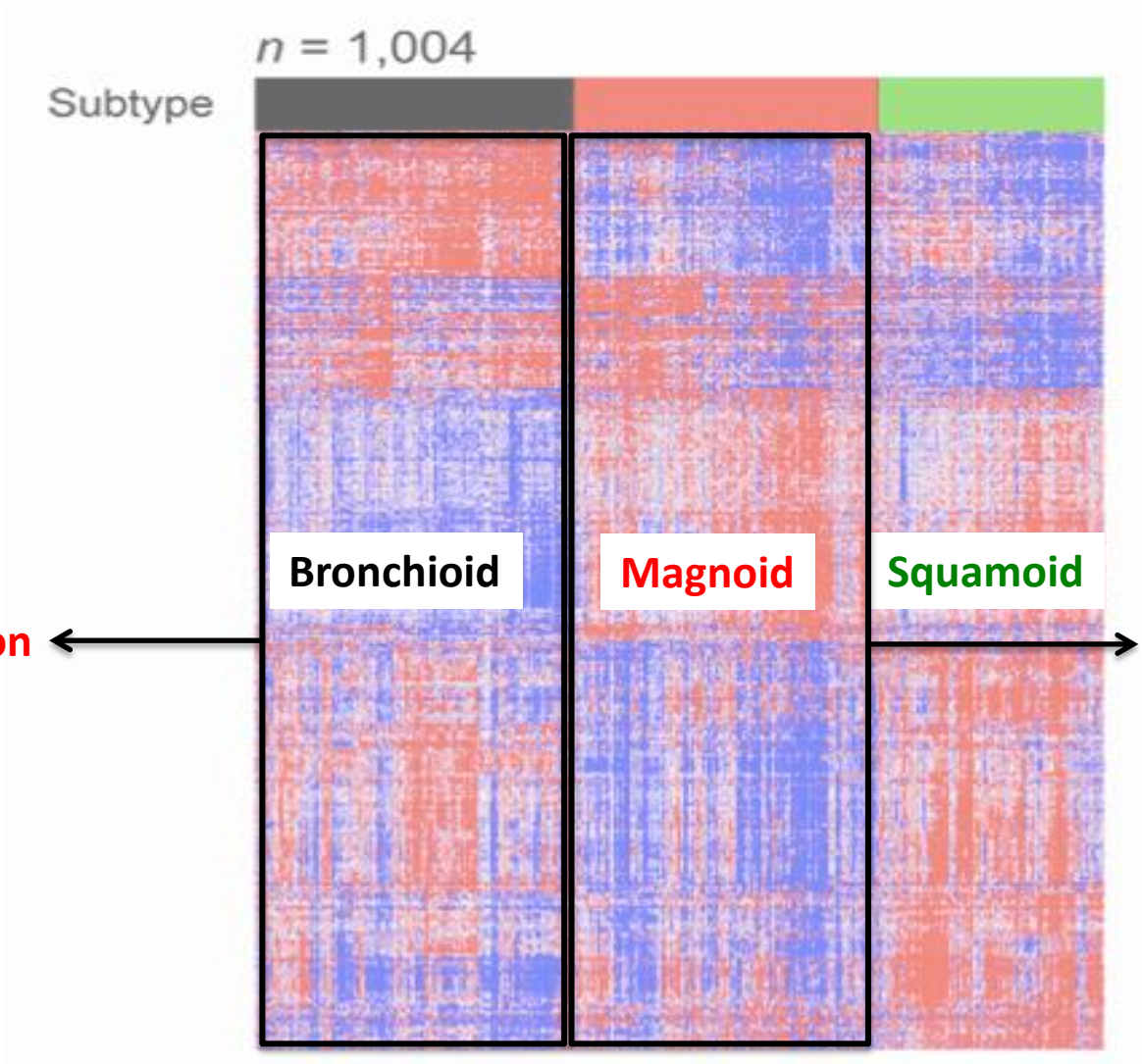


Image from Wilkerson et al, *PLoS One* 2012; 7(5):e36530

Expression subtypes: molecular features

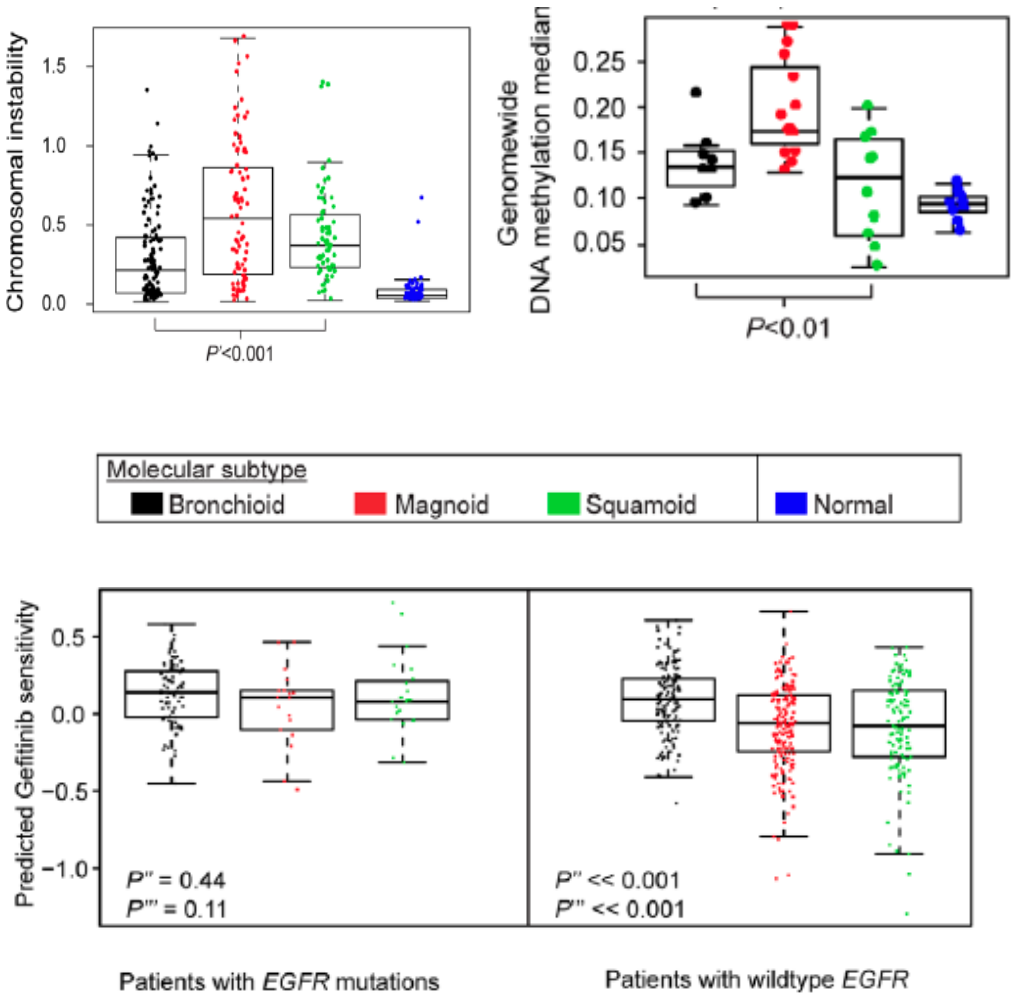
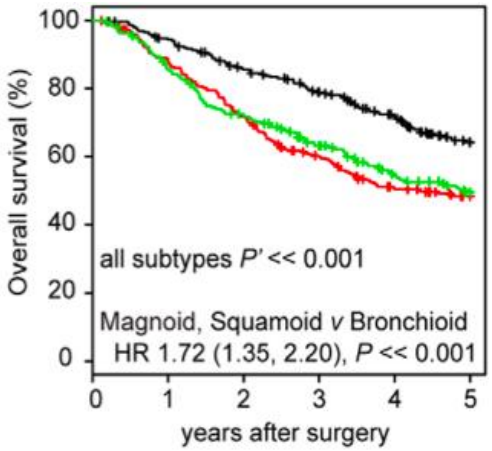
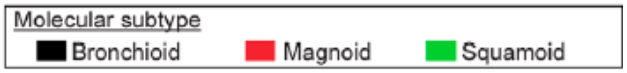
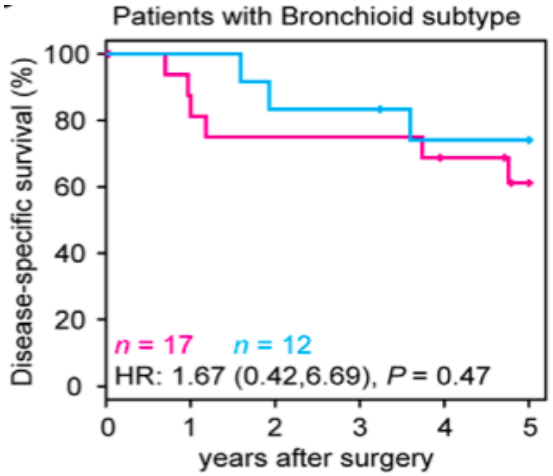


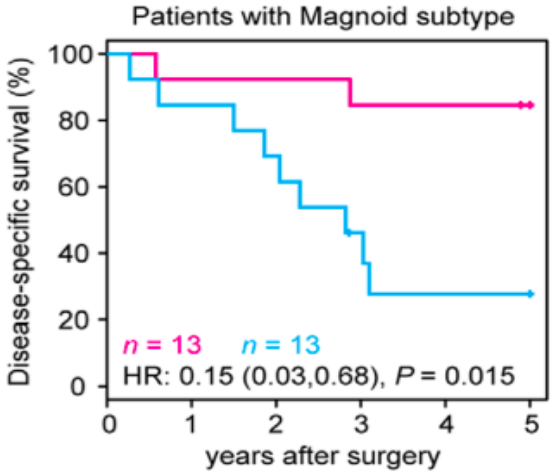
Image from Wilkerson et al, *PLoS One* 2012; 7(5):e36530

LUAD subtypes: prognostic significance









JBR 10 trial data

Adjuvant

Cisplatin + Vinorelbine

Observation

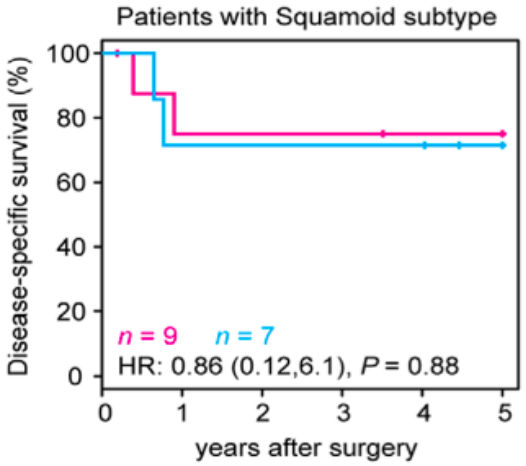
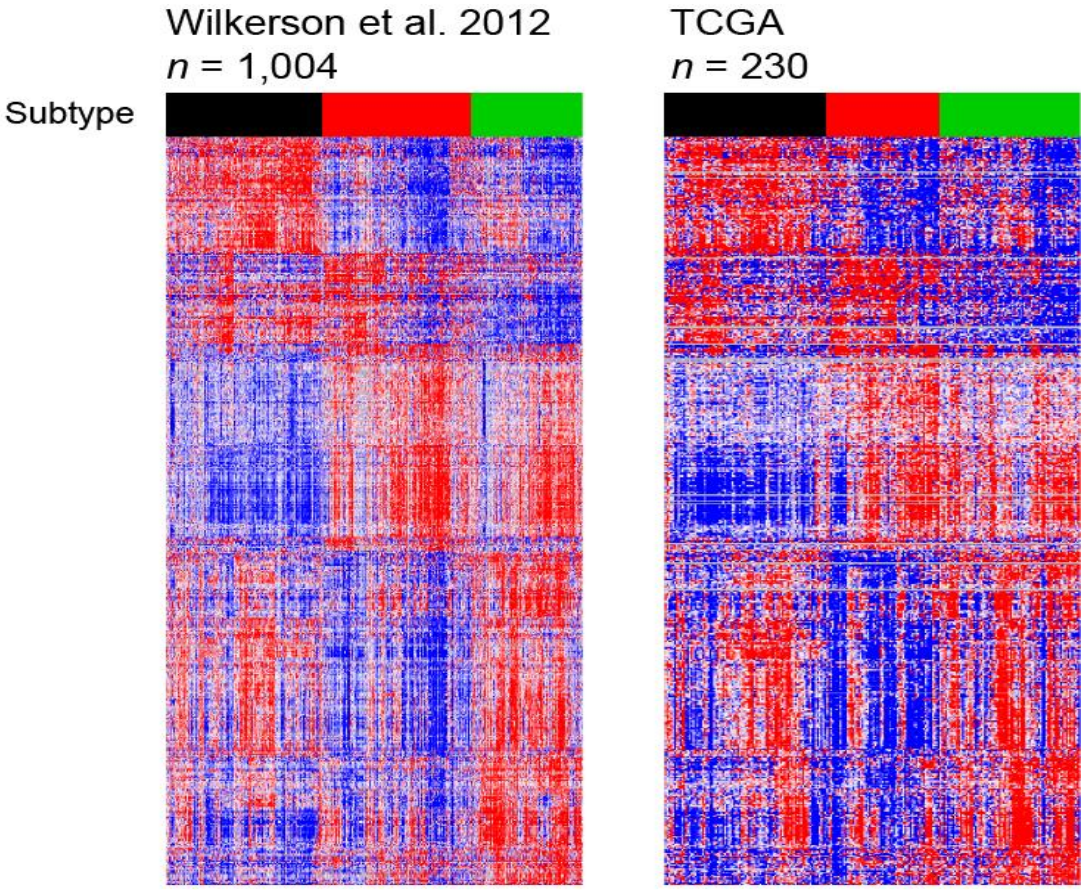


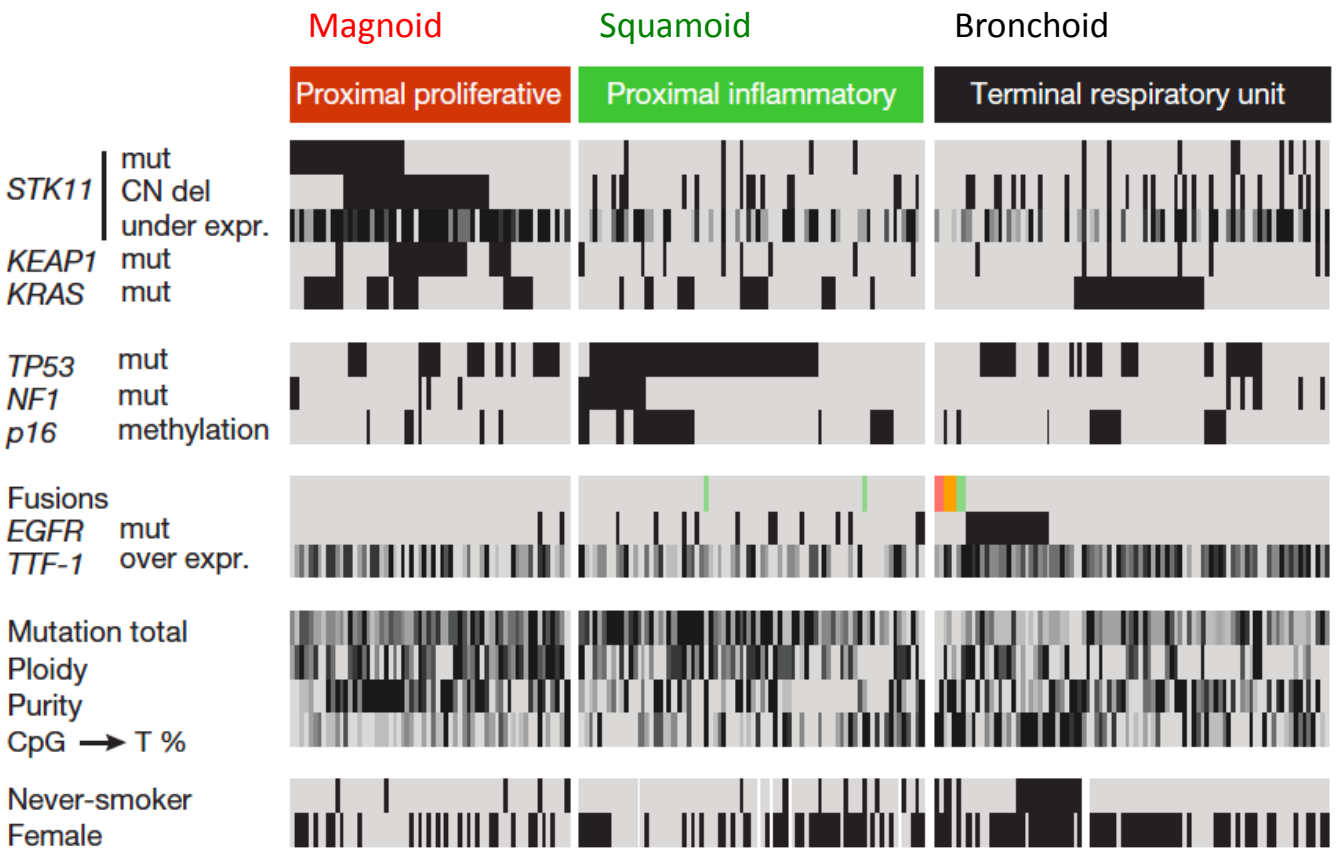
Image from Wilkerson et al, *PLoS One* 2012; 7(5):e36530

LUAD subtypes: TCGA



TCGA, *Nature 2014;* **511**, 543–550.

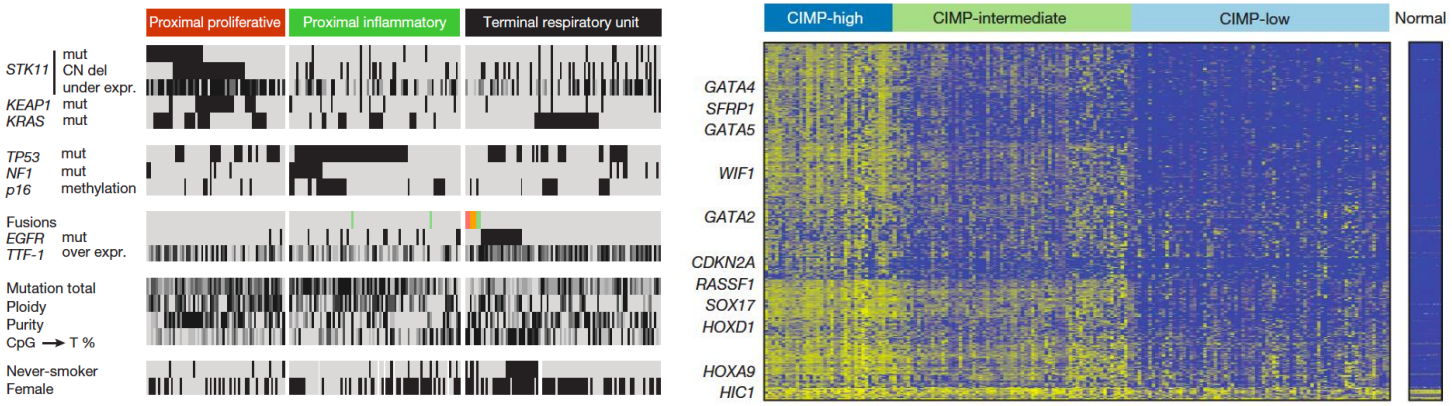
LUAD subtypes: Examining TCGA data



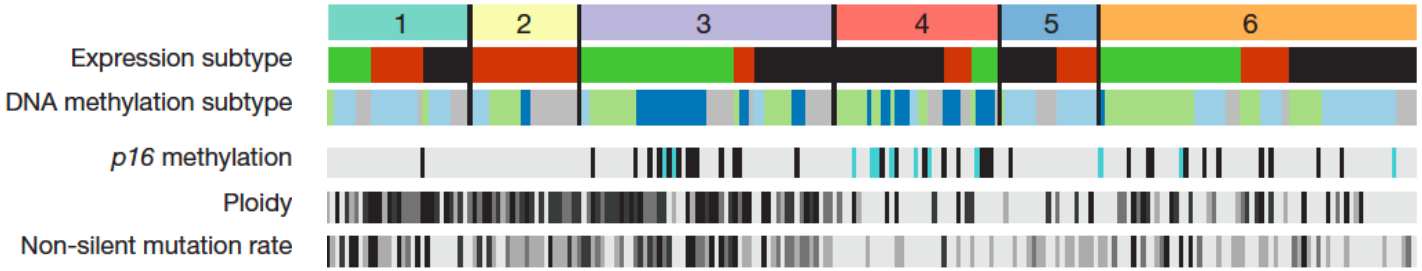
TCGA, *Nature 2014;* **511**, 543–550.

LUAD subtypes: Examining TCGA data

TCGA, *Nature 2014;* **511**, 543–550.



Integrative clusters



TCGA, *Nature 2014;* **511**, 543–550.

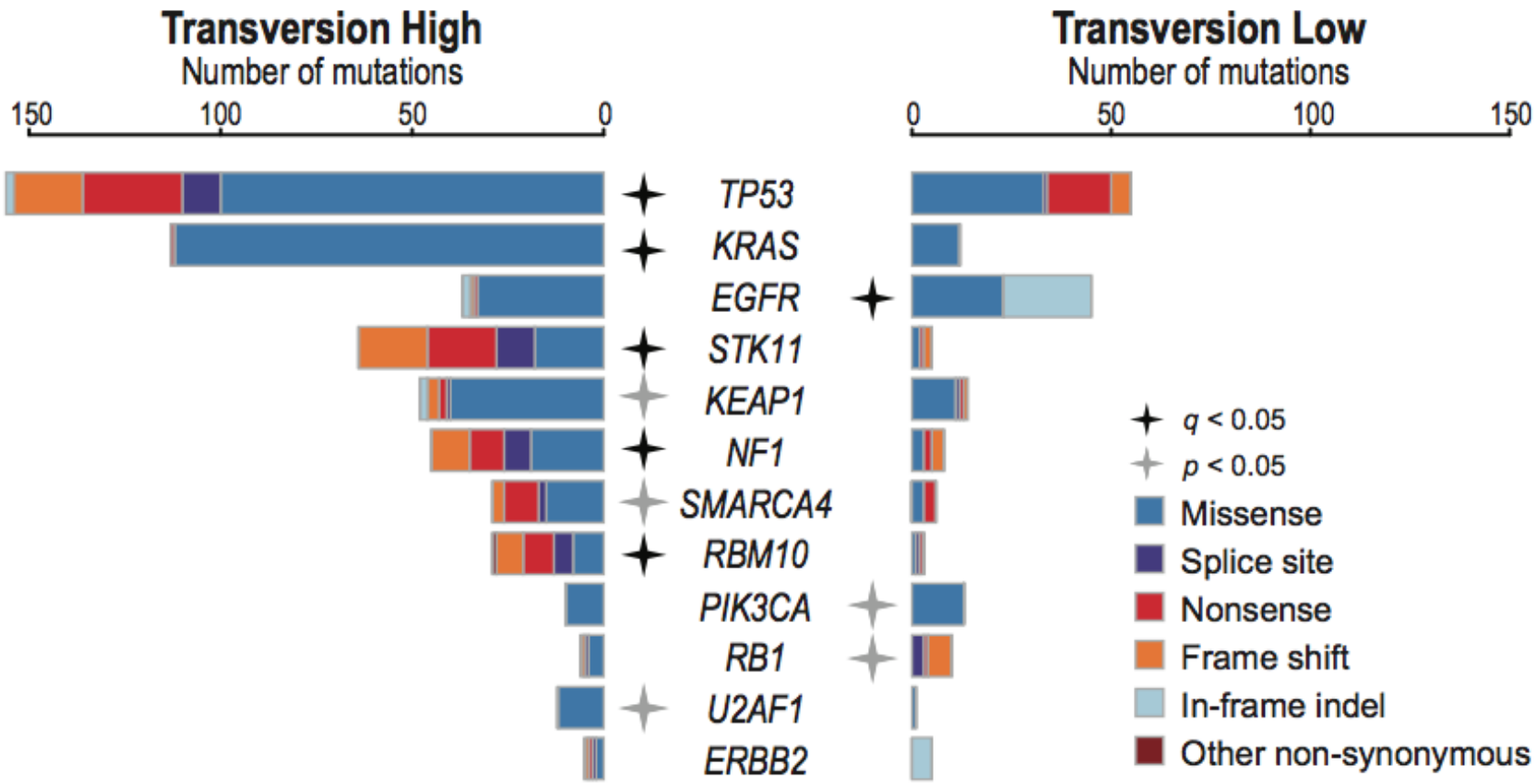
Integrative clustering of LUAD: Characteristic features

Cluster	1	2	3	4	5	6
SCNA associated expression changes	3q	8q	7 and 15q	6q	4 and 19p	
Frequently associated expression subtype	PP and PI			TRU		
Ploidy and mutation rate	High			Low		
DNA methylation subtype			CIMP-(H) tumors			

Adapted from TCGA, *Nature 2014;* **511**, 543–550.

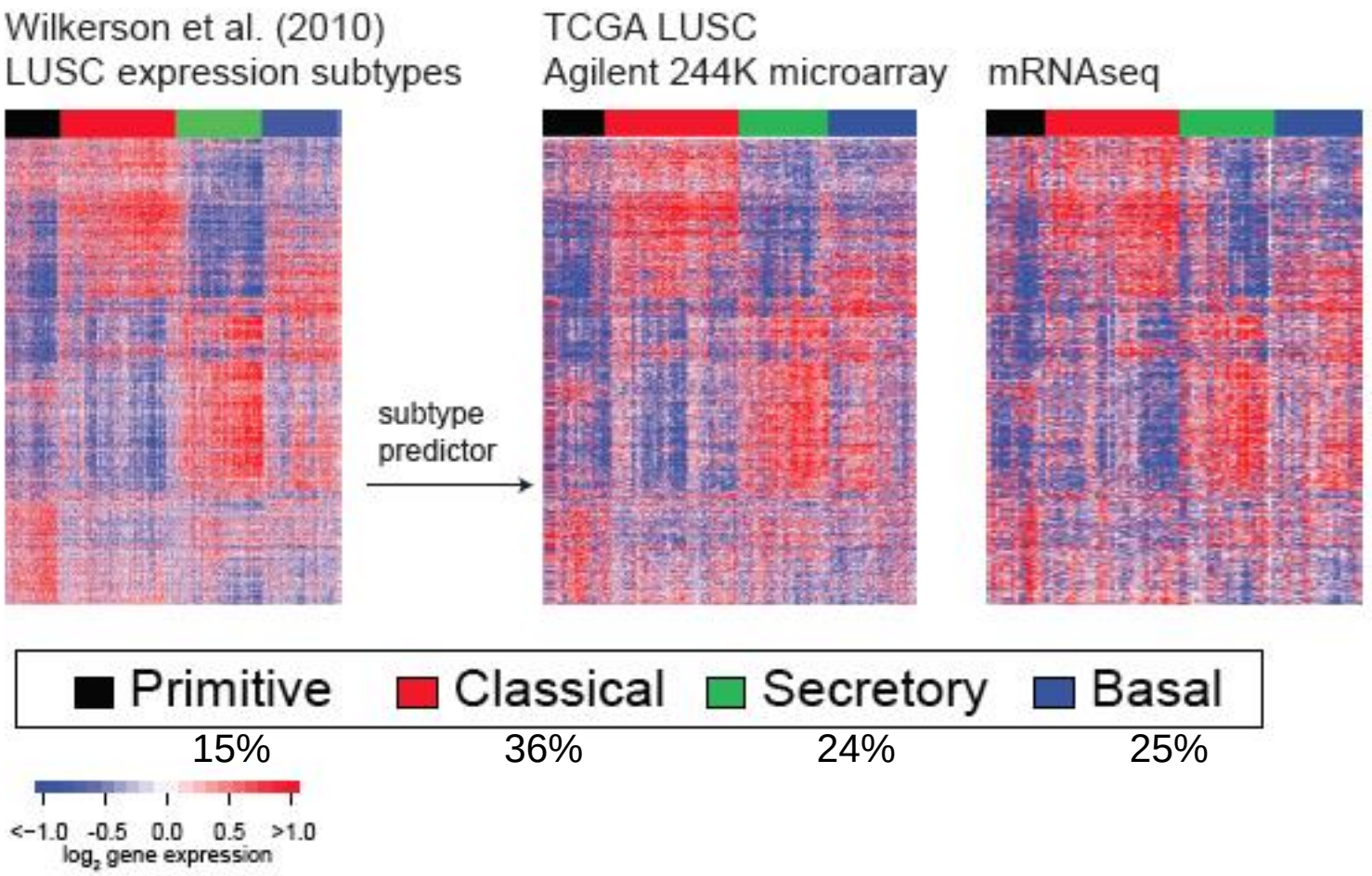
Exome-Wide Patterns of Mutation

Patterns of Mutation In Specific Genes

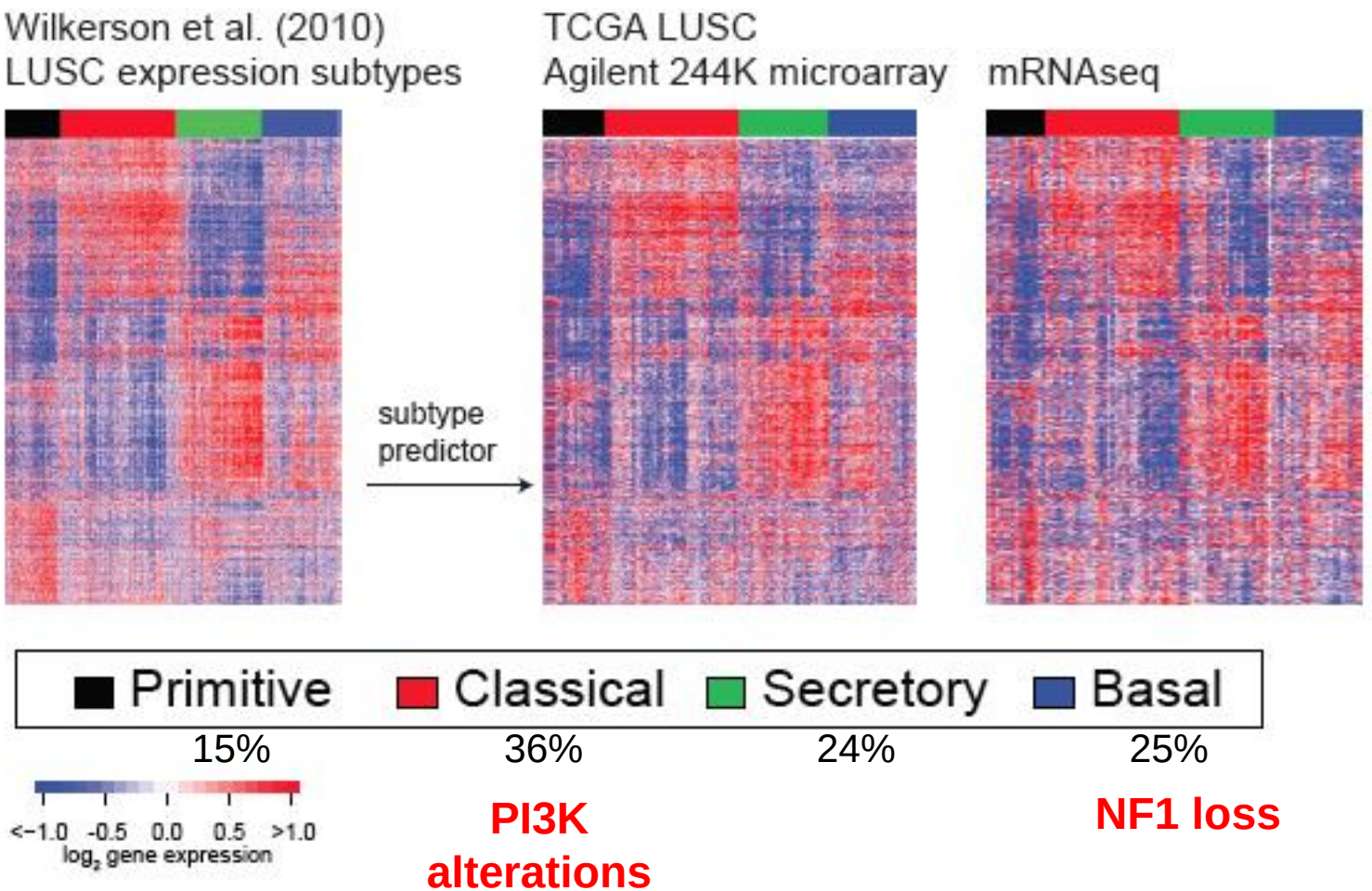


William Lee, Marc Ladanyi

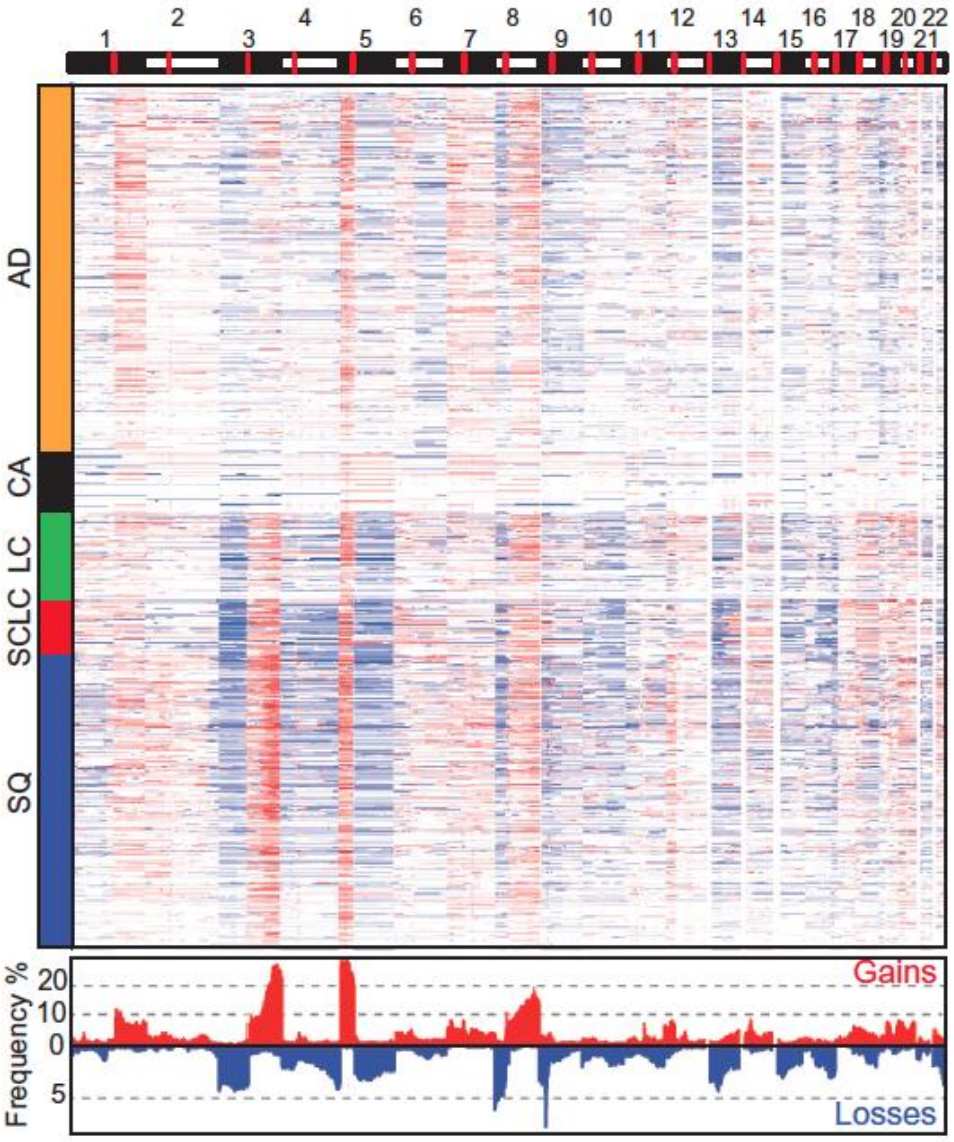
Squamous Cell Carcinoma of the lung mRNA Expression Analysis

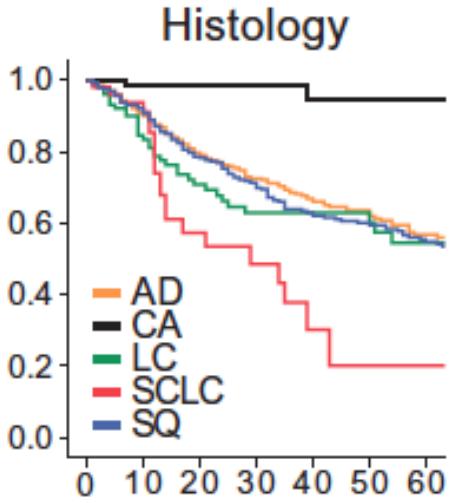


Squamous Cell Carcinoma of the lung
mRNA Expression Analysis

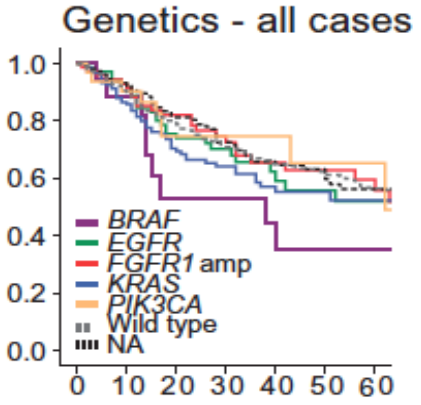


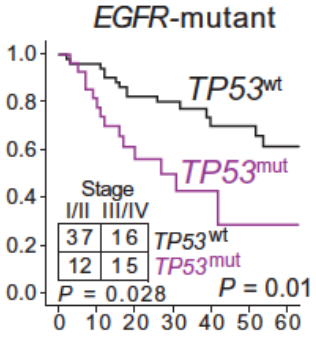
The Cancer Genome Atlas



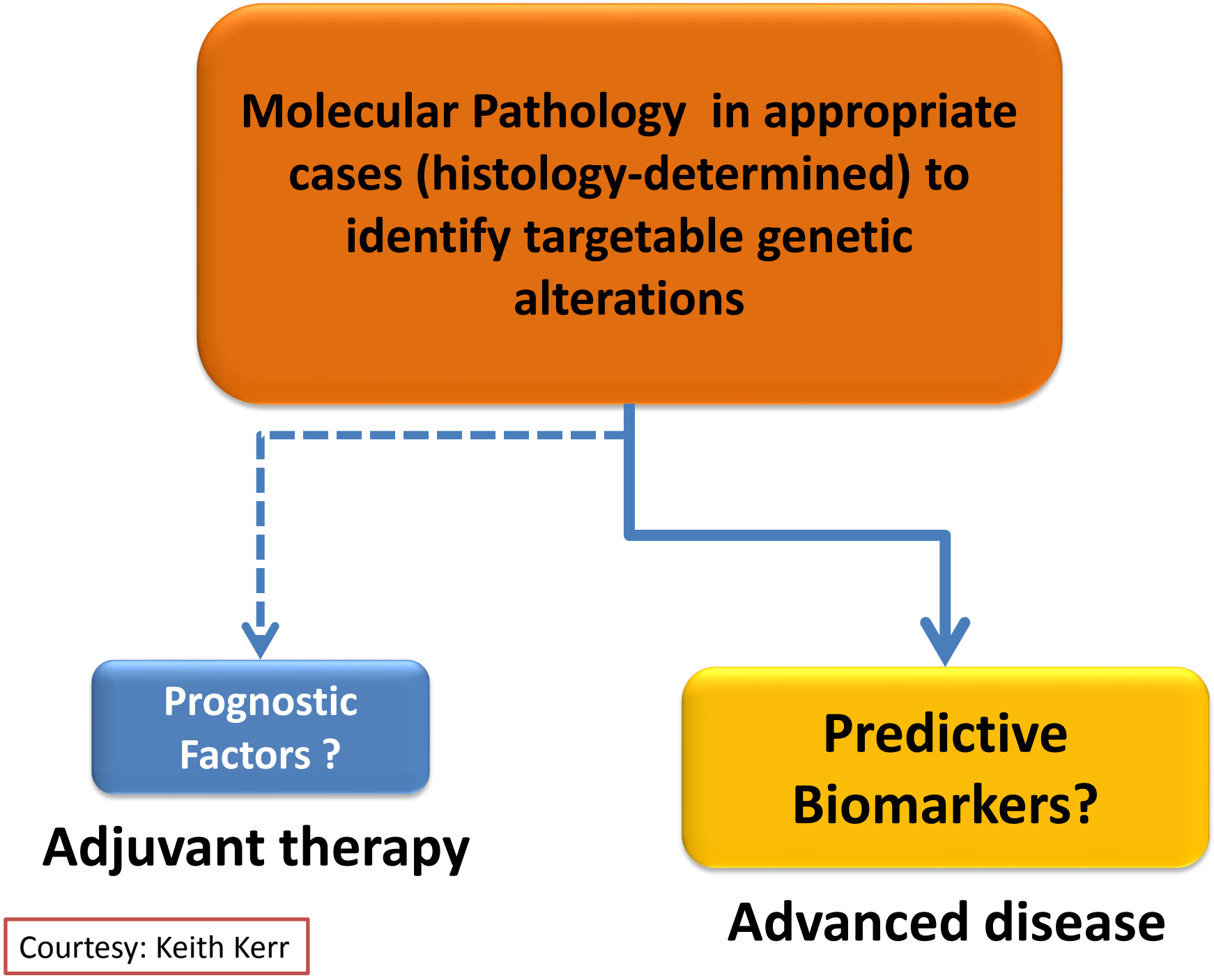


Overall Survival





Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM), *Sci Transl Med* 2013;5:209ra153.


Molecular Pathology in appropriate cases (histology-determined) to identify targetable genetic alterations
Prognostic Factors ?
Adjuvant therapy
Predictive Biomarkers?
Advanced disease
Courtesy: Keith Kerr

Gene Expression–Based Prognostic Signatures in Lung Cancer: Ready for Clinical Use?

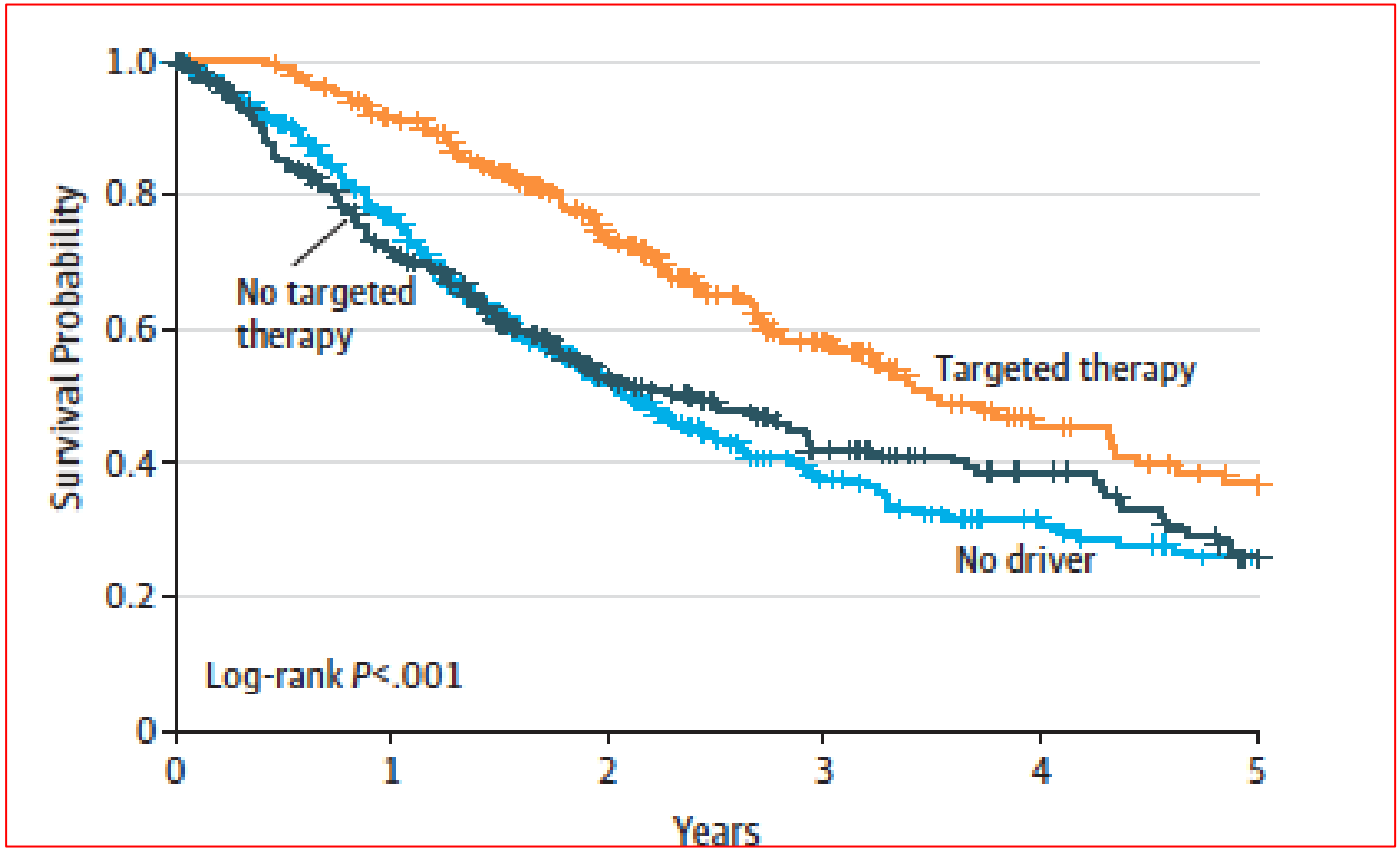
Jyothi Subramanian, Richard Simon

Based on this review, we found little evidence that any of the reported gene expression signatures are ready for clinical application

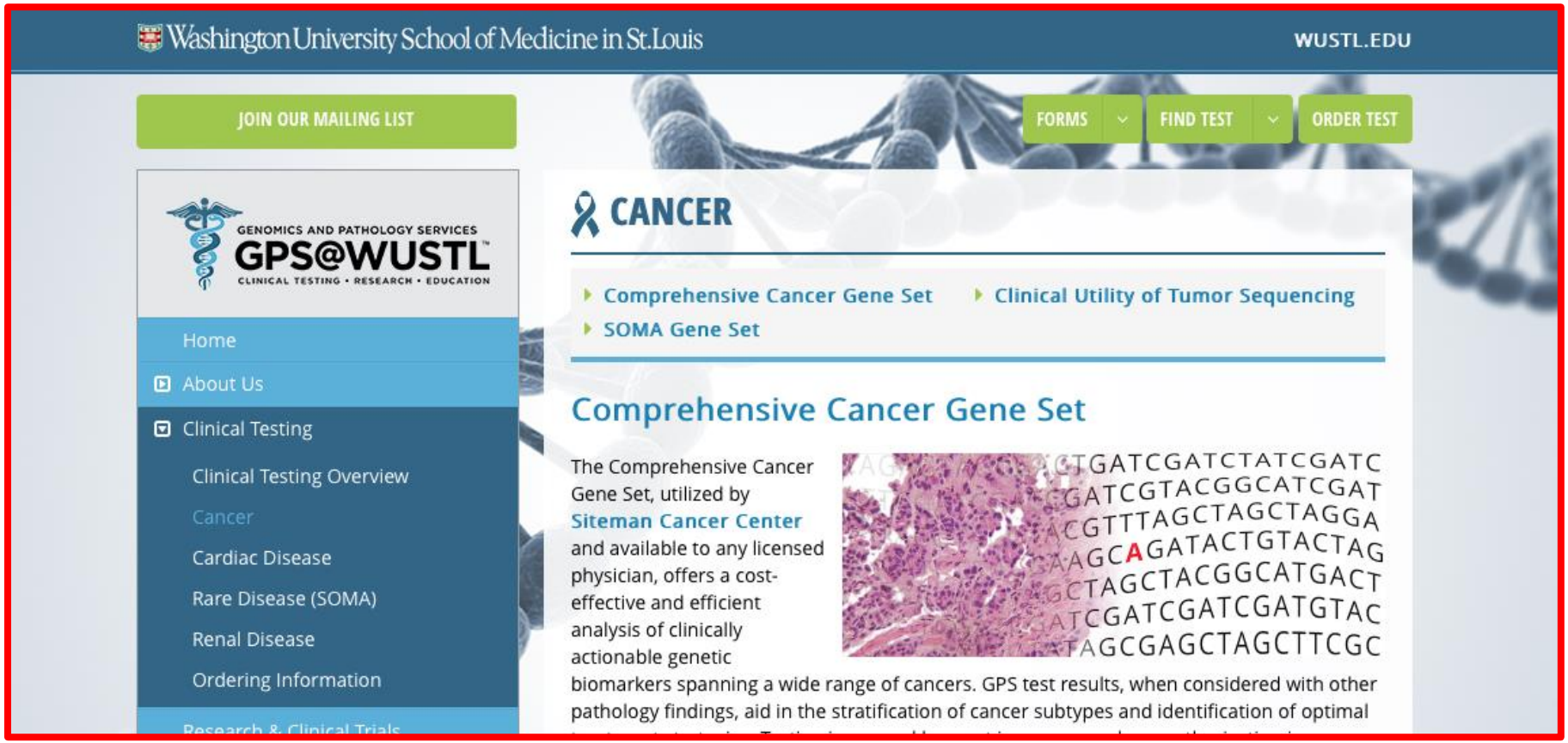
We also found serious problems in the design and analysis of many of the studies.

J Natl Cancer Inst 2010;102:464–474

Impact of Molecularly Targeted Therapy in Patients with Oncogenic Driver Mutation



JAMA. 2014;311(19):1998-2006



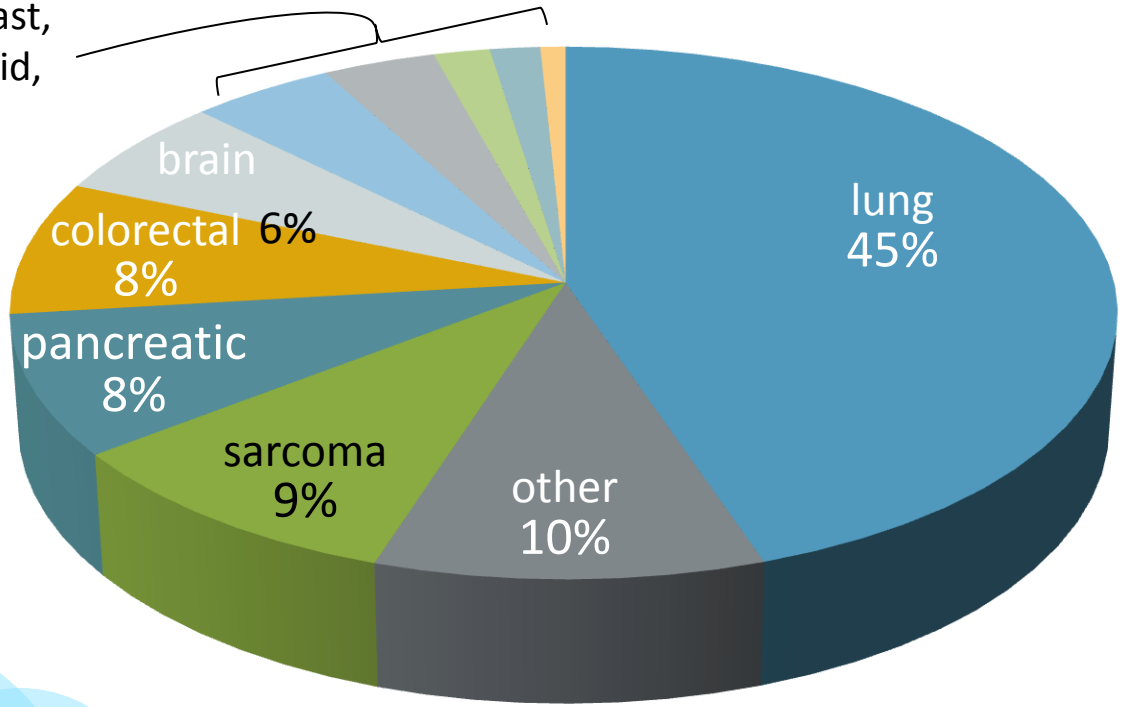
Challenges

Cost
Adequacy of tissue material
Turn around time
Actionable mutation but no FDA approved drug

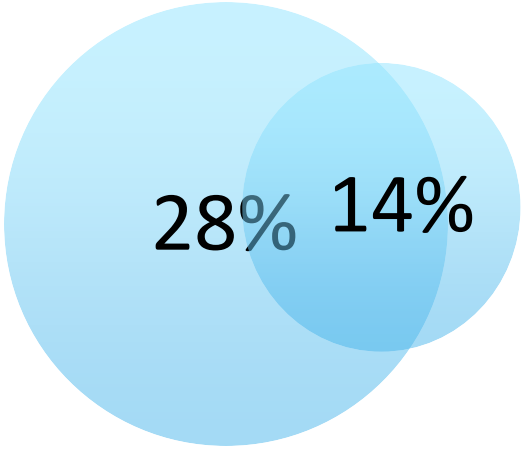
GENOMICS AND PATHOLOGY SERVICES
GPS@WUSTL
CLINICAL TESTING • RESEARCH • EDUCATION

GPS Oncology Testing Experience

1200 samples over 16 months

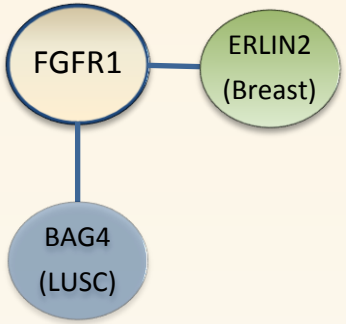


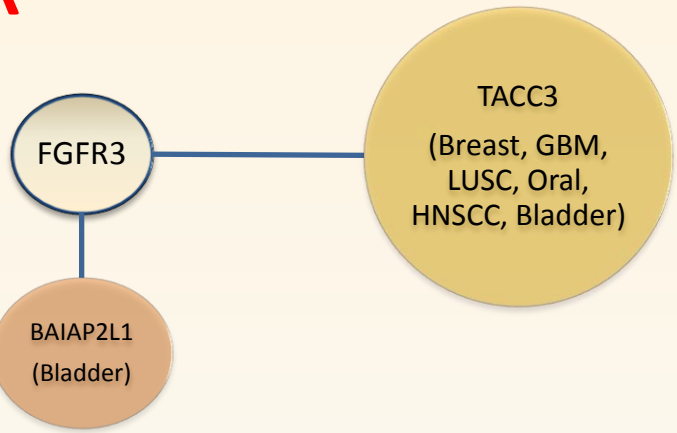
Actionable in patient's cancer type

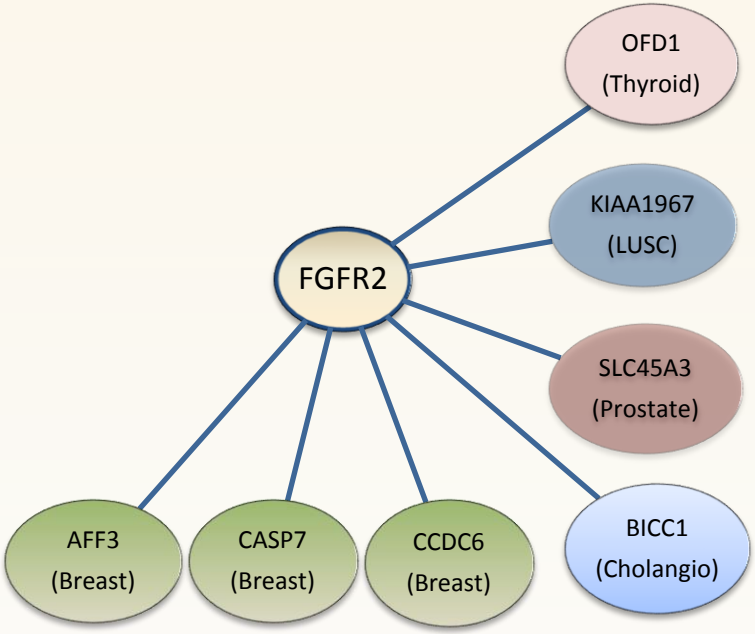


Actionable in another cancer type

Translocation partners of FGFR



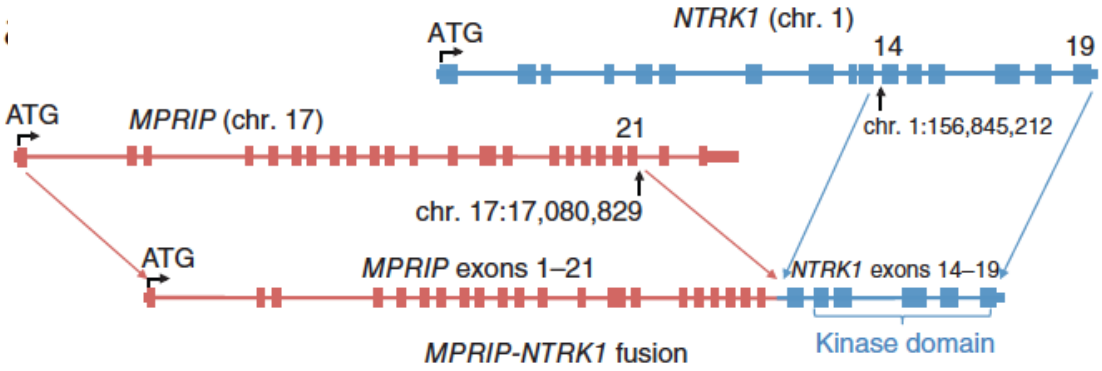


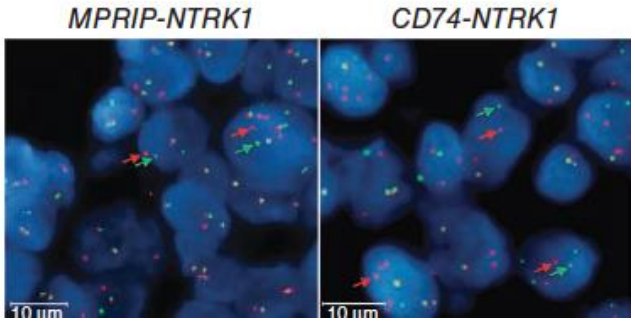


FGFR fusions in SQCC Lung (TCGA data)

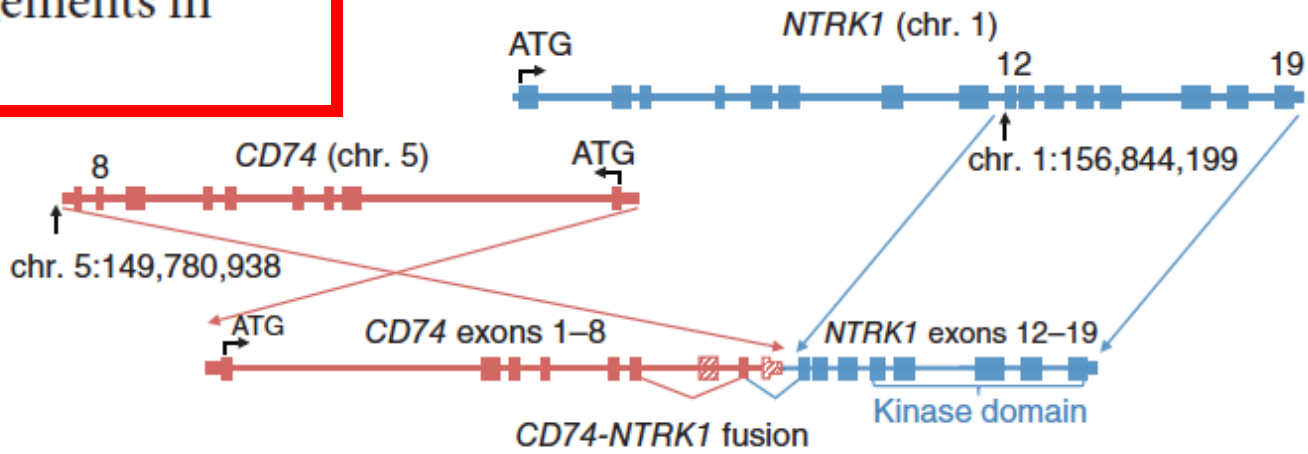
Fusion (Identified by transcriptome seq.)	**Number of samples (n=222)**	**Predominant FGFR isoform**
BAG4-FGFR1	1	IIIc
FGFR2-KIAA1967	1	IIIc
FGFR3-TACC3	4	IIIb

Adapted from:
Wu et al. Cancer Discov 2013.



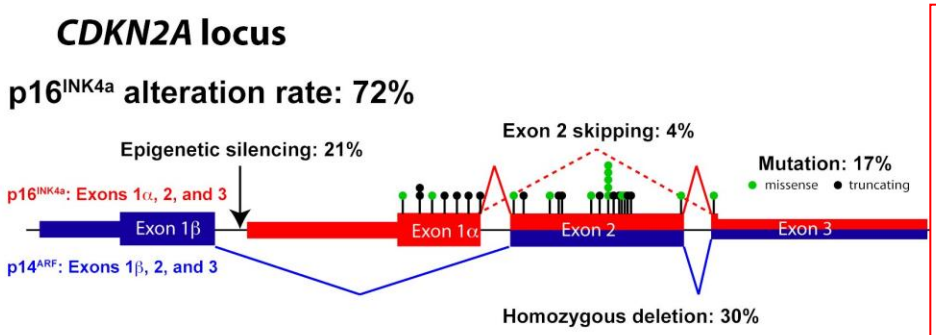


Oncogenic and drug-sensitive *NTRK1* rearrangements in lung cancer



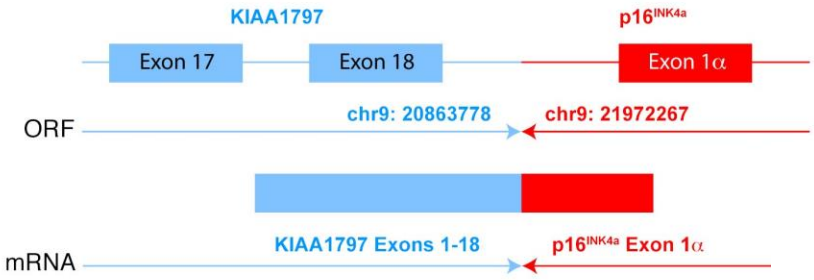
Nature Medicine, AOP 10/27/13

CDKN2A: Loss of Function Through Multiple Mechanisms

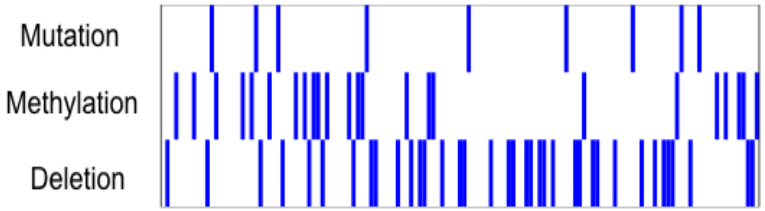


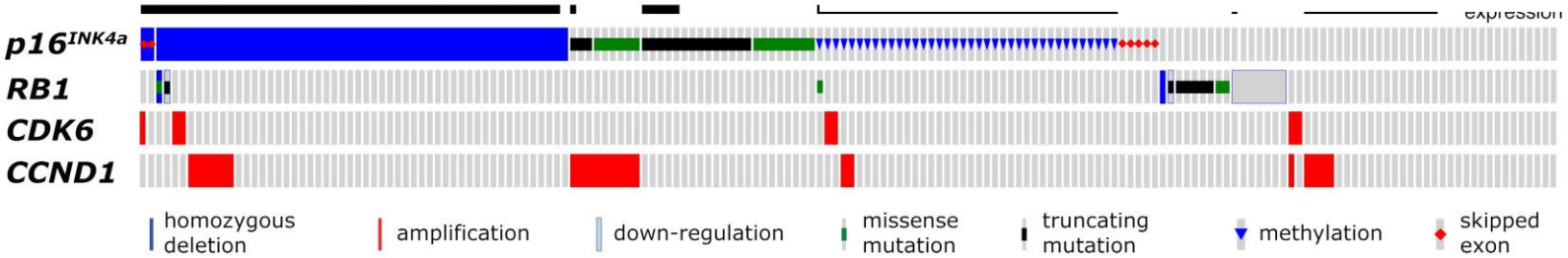
Three most common mechanisms

Homozygous deletion	30%
Methylation	21%
Mutation	17%



Tumor samples





In Treatment for Leukemia, Glimpses of the Future

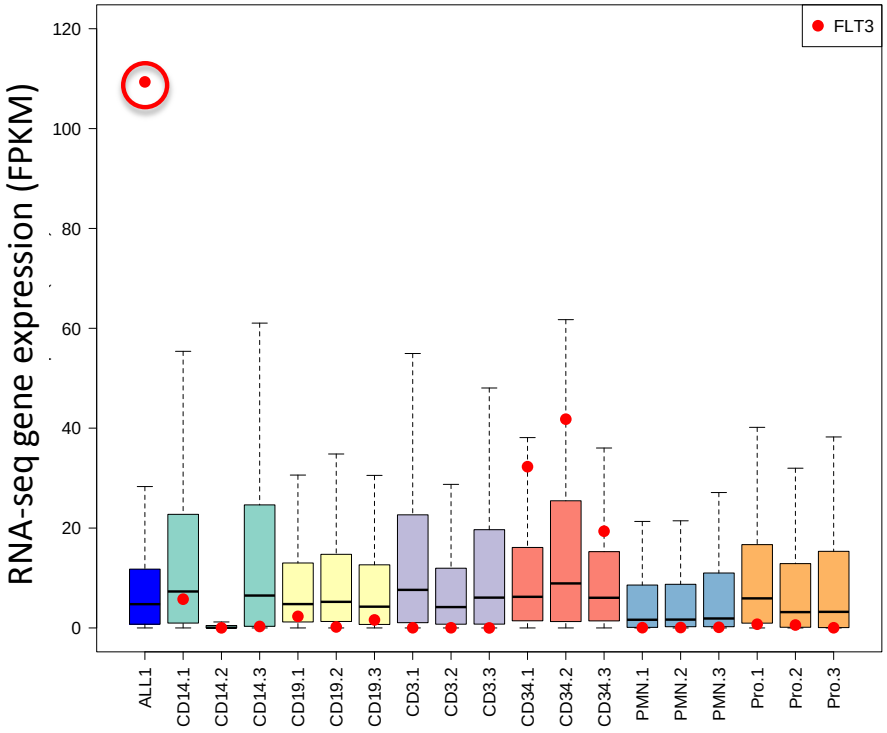
Second Chance: Lukas Wartman, a leukemia doctor and researcher, developed the disease himself. As he faced death, his colleagues sequenced his cancer genome. The result was a totally unexpected treatment.

By GINA KOLATA
Published: July 7, 2012 | 304 Comments

July 8, 2012

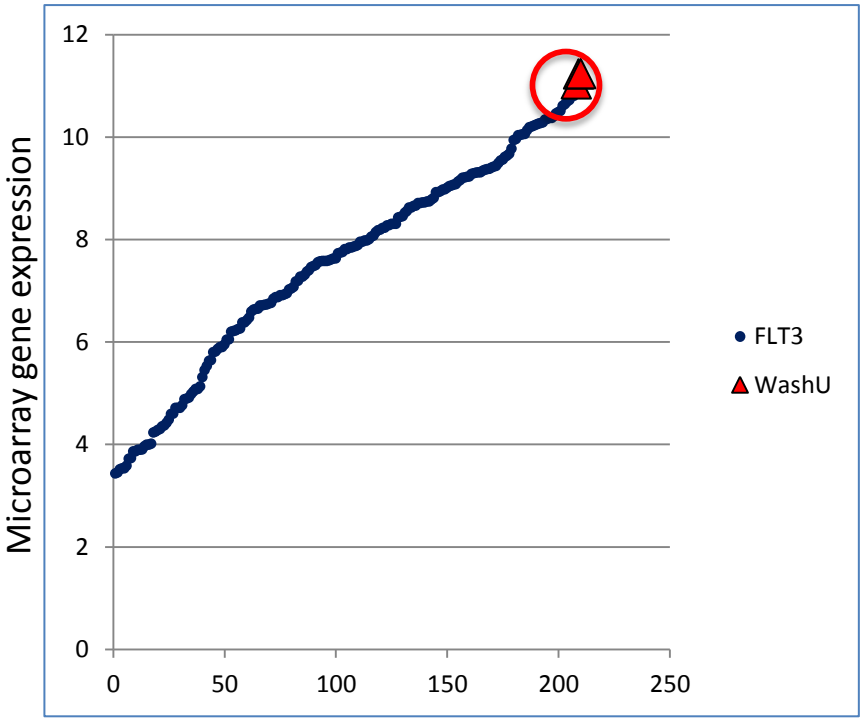
Case “ALL1”: Extreme *FLT3* over-expression

RNA-seq expression data



ALL1 and 18 healthy donor samples

Microarray expression data



ALL1 (triplicates) and >200 B-ALL’s

★ **Activated FLT3 gene was targeted with sunitinib (*not approved by insurance company*), complete clinical remission was achieved in 12 days**

Umbrella

Test impact of different drugs on different mutations in a single type of cancer

- **BATTLE**
- **I-SPY2**
- **SWOG Squamous Lung Master**

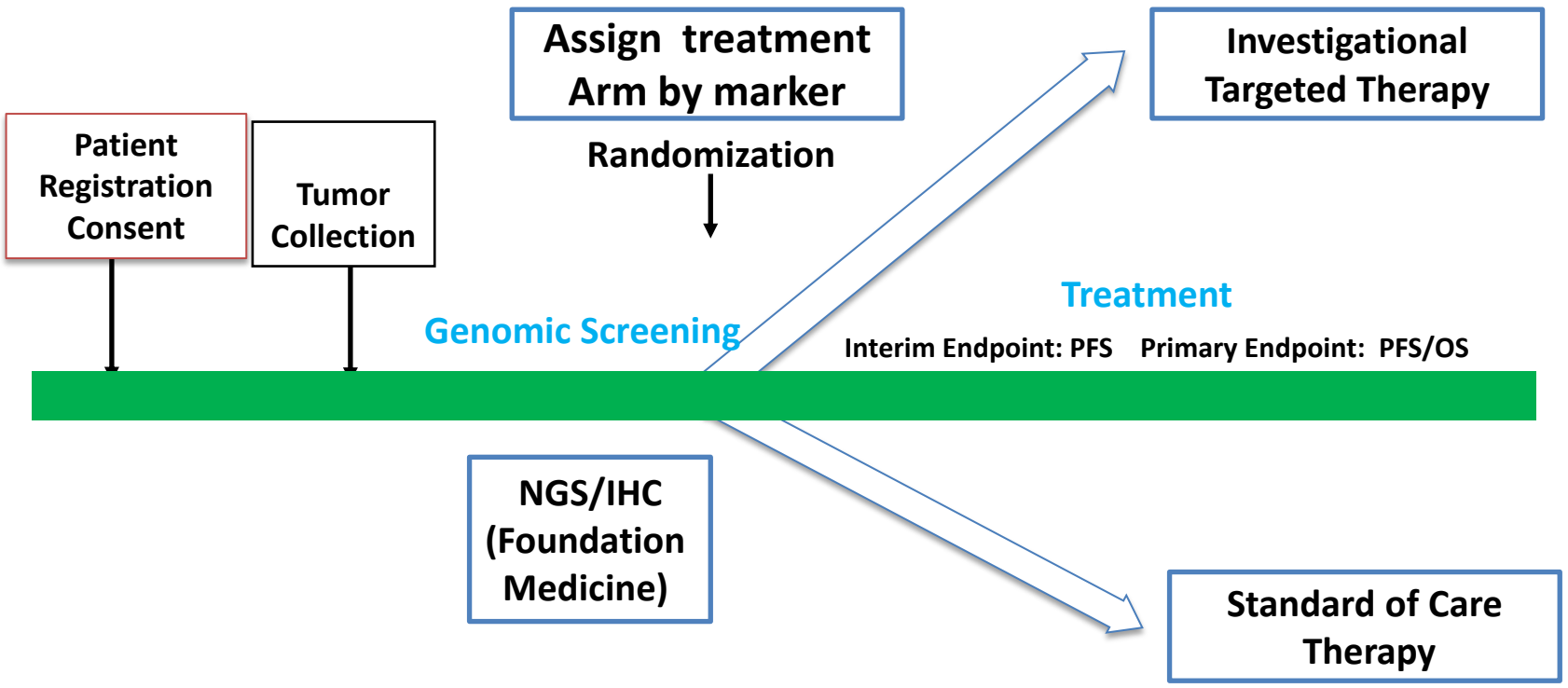
Basket

Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types

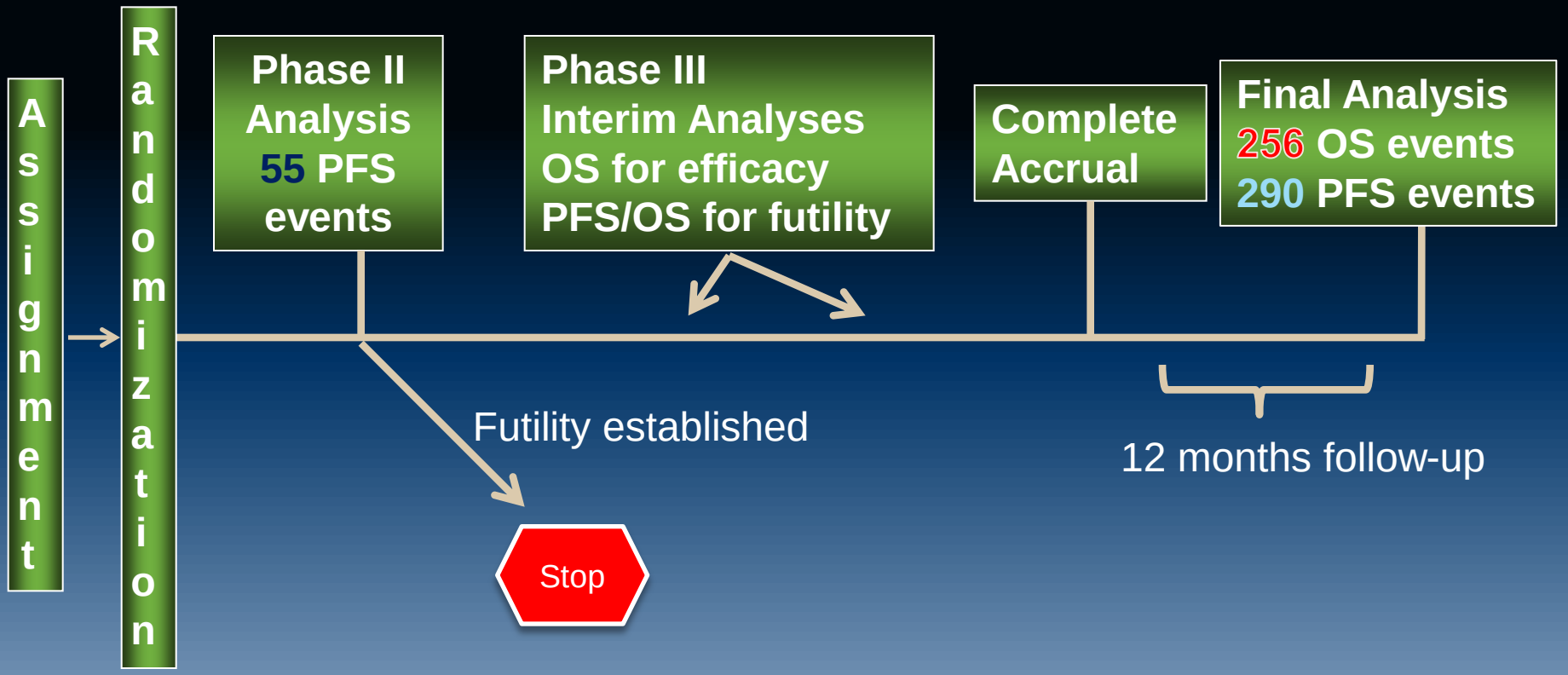
- **Imatinib Basket**
- **BRAF+**
- **NCI MATCH**

LUNG-MAP

LUNG-MAP


Assign treatment Arm by marker
Investigational Targeted Therapy
Patient Registration Consent
Tumor Collection
Randomization
Treatment
Genomic Screening
Interim Endpoint: PFS
Primary Endpoint: PFS/OS
NGS/IHC (Foundation Medicine)
Standard of Care Therapy

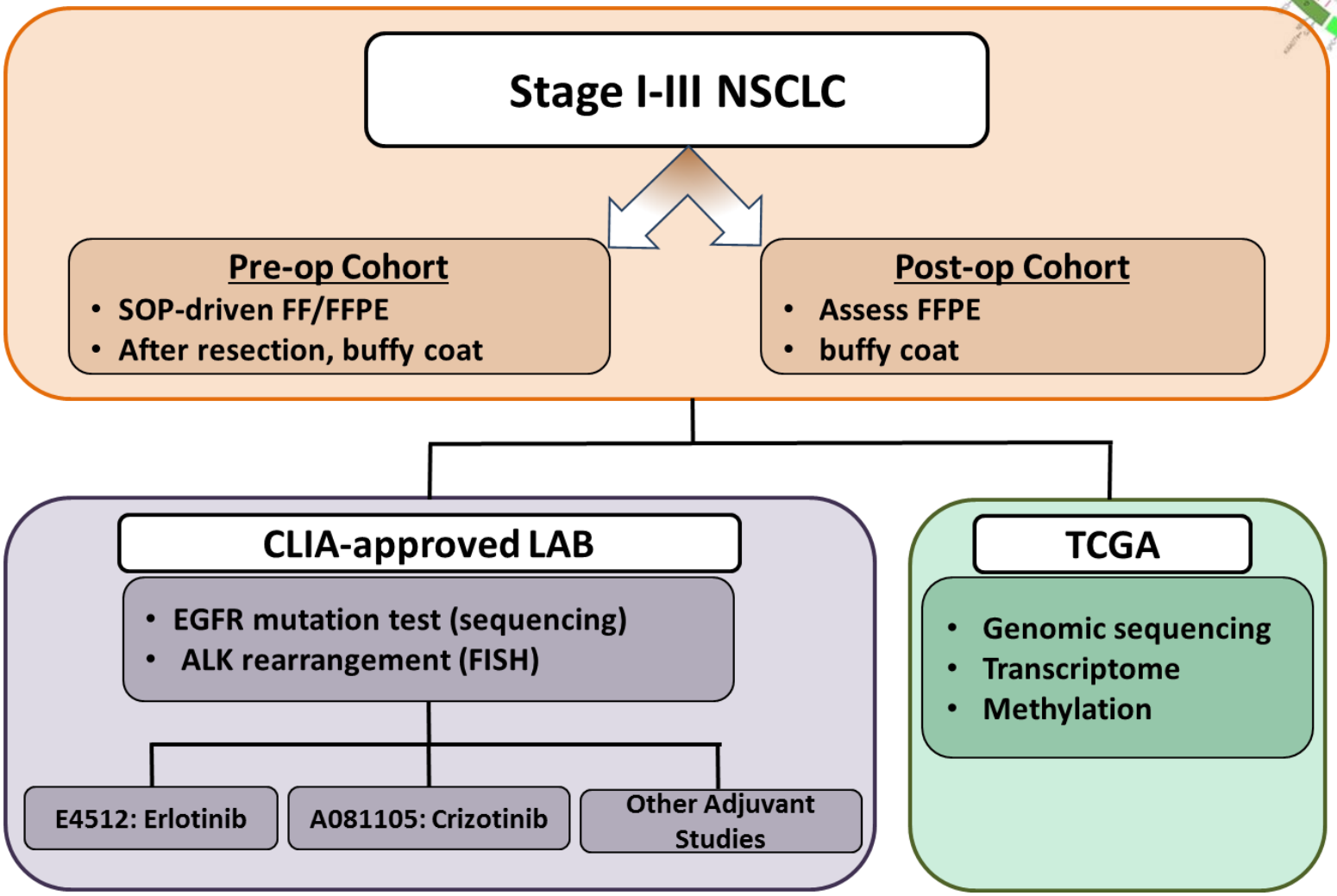
Study Design Within Each Biomarker-defined Subgroup

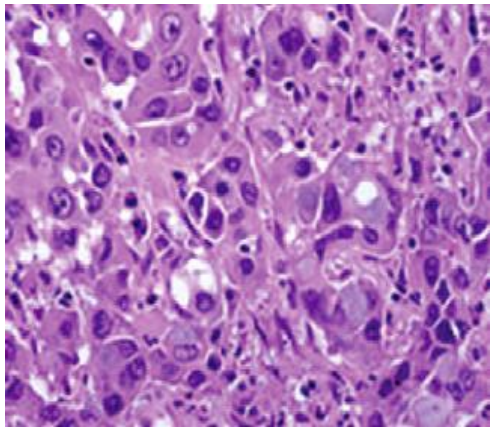


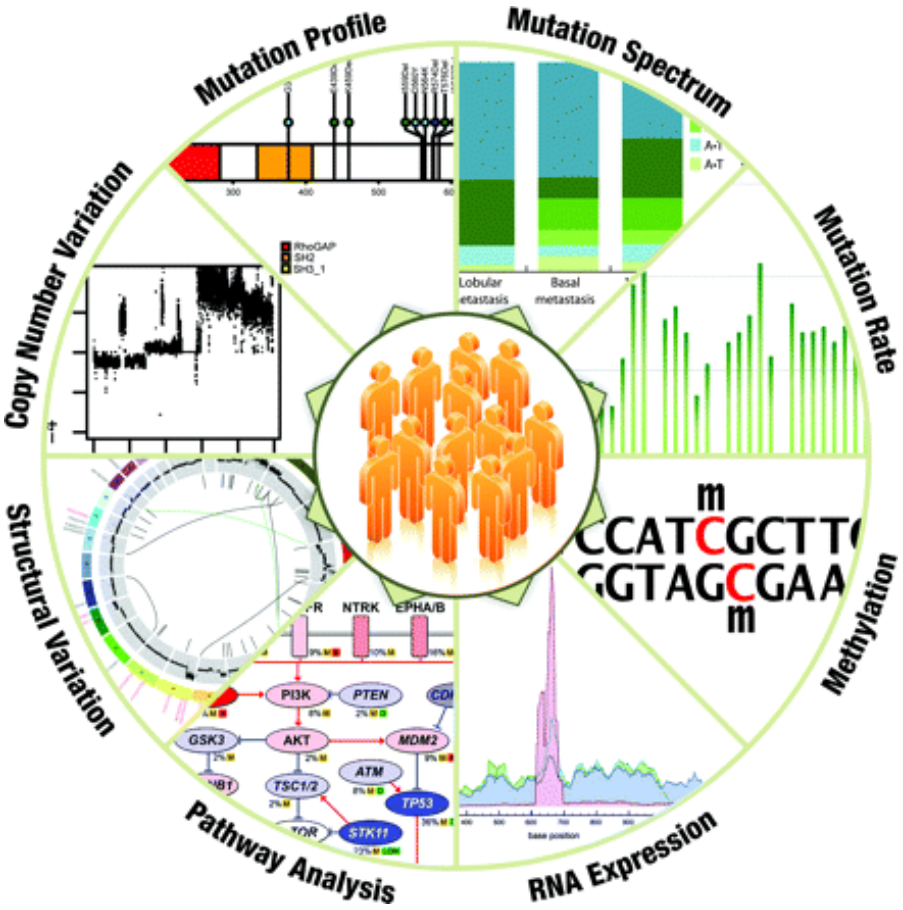
LUNG-MAP

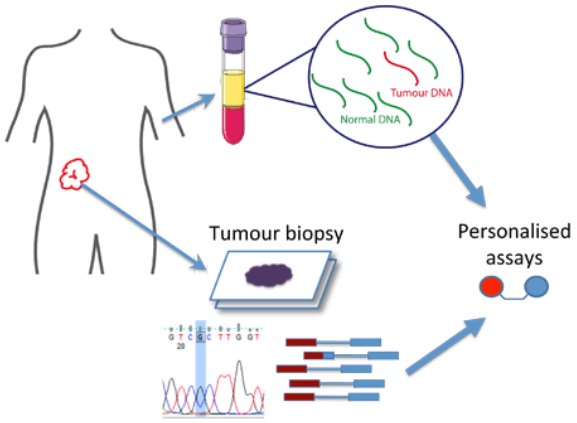
Courtesy of: Mary Redman

ALCHEMIST


Stage I-III NSCLC
Pre-op Cohort
• SOP-driven FF/FFPE
• After resection, buffy coat
Post-op Cohort
• Assess FFPE
• buffy coat
CLIA-approved LAB
• EGFR mutation test (sequencing)
• ALK rearrangement (FISH)
E4512: Erlotinib
A081105: Crizotinib
Other Adjuvant Studies
TCGA
• Genomic sequencing
• Transcriptome
• Methylation







Source:http://www.cruk.cam.ac.uk/research-groups/rosenfeld-group
http://hmg.oxfordjournals.org/content/19/R2.cover-expansion