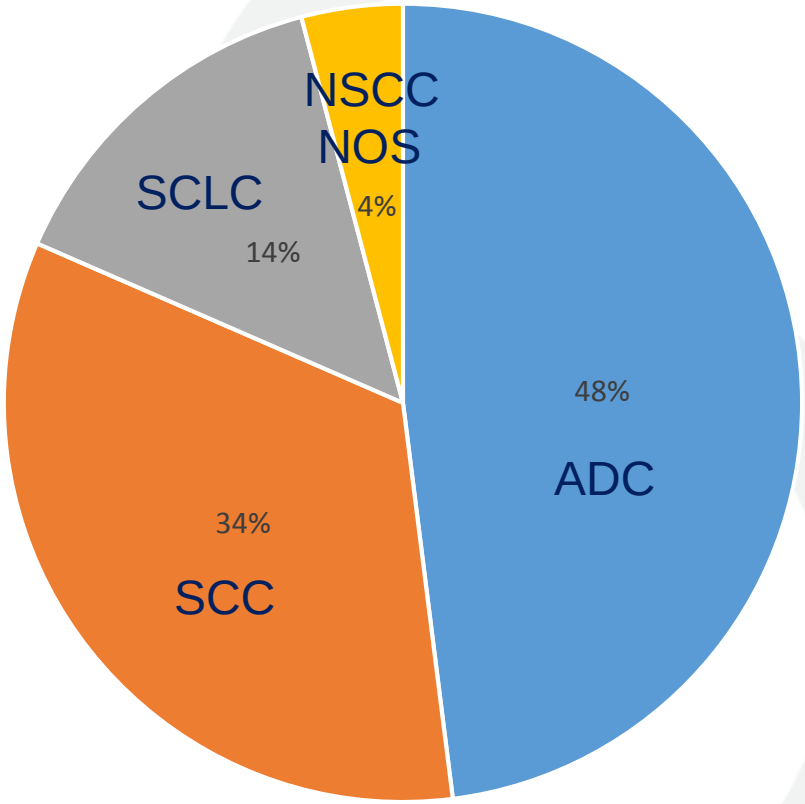
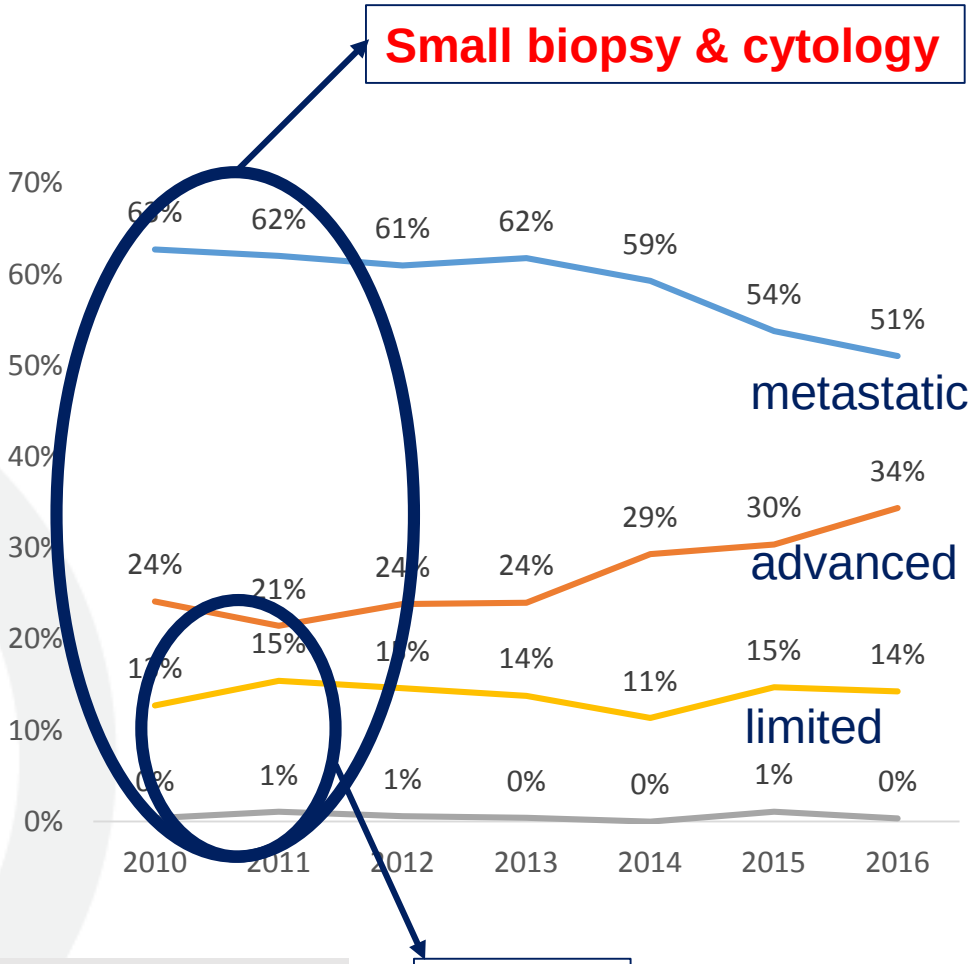
LUNG CANCER
pathology & molecular biology

Izidor Kern

University Clinic Golnik, Slovenia

Pathology and epidemiology





Clinical Registry UCG 2010-2016

Specimens

What's the problem?
I gave you at least 10 cells!

TUMOR

TISSUE

Small biopsy, resection

CYTOLOGY

FNAB, TBNA, effusion

BLOOD

ctDNA, CTC, exosome

Personalized medicine needs optimal tumor sample

Tissue management starts with interaction sample collector-pathologist

Sample collector:

Sampling more (≥4) biopsies/ tumor tissue

Clinical request for diagnosis + prediction?

Clinical suspicion of metastases y/n?

Pathology:

Distribute samples over >1 block

Careful initial cut

Spare section for reflex analysis

Focused diagnostic analysis

Classification of lung cancer

NSCC group

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic, spindle cell, giant cell ca
- L-E like carcinoma
- Carcinosarcoma, pulmonary blastoma

Neuroendocrine tumors

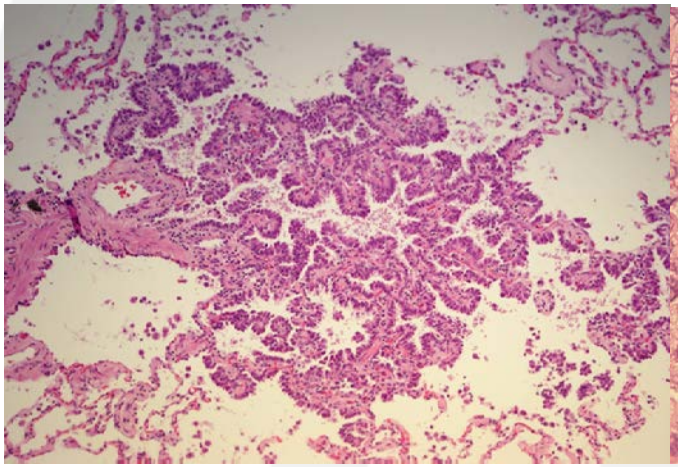
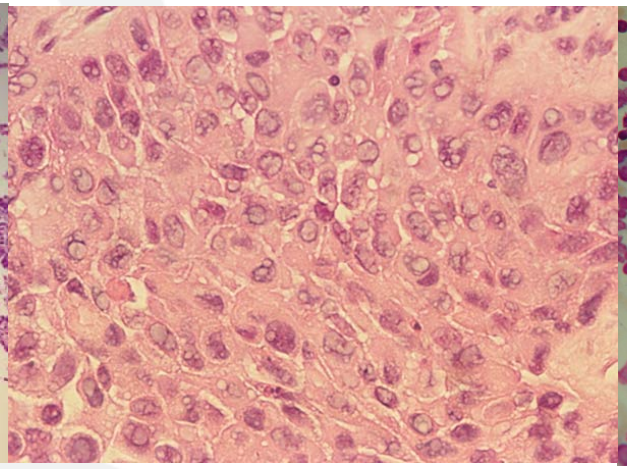
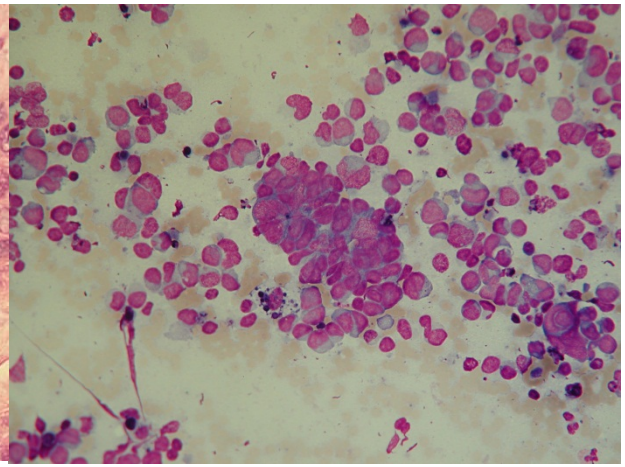
- Carcinoid (typical, atipical)
- Large cell neuroendocrine carcinoma
- Small cell lung carcinoma
- Combined small cell lung carcinoma

Other /rare tumors

- Salivary gland-type tumors
- Lymphomas
- Soft tissue tumors

WHO lung tumors, 2015

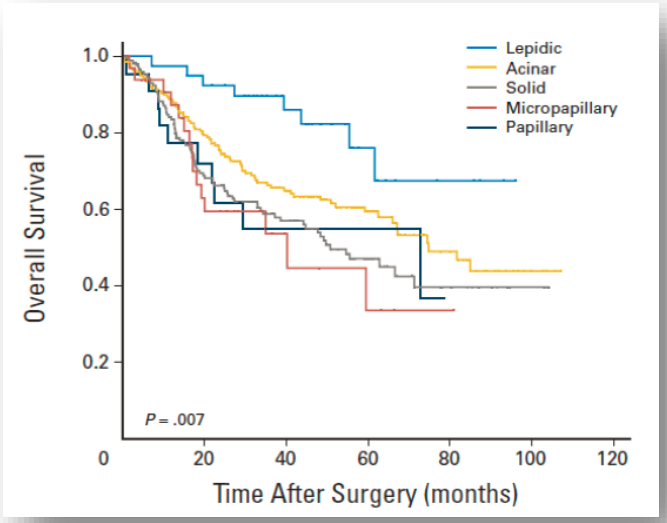
95% of all lung tumors are carcinomas

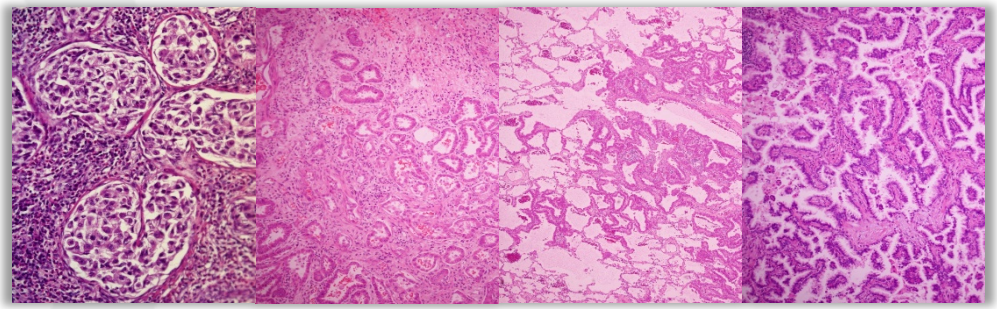




	ADC	SCC	SCLC
p40	-	+	-
TTF1	+	-	+
napsin A	+	-	-
CK5/6	-	+	-
CD56	-	-	+

Adenocarcinoma

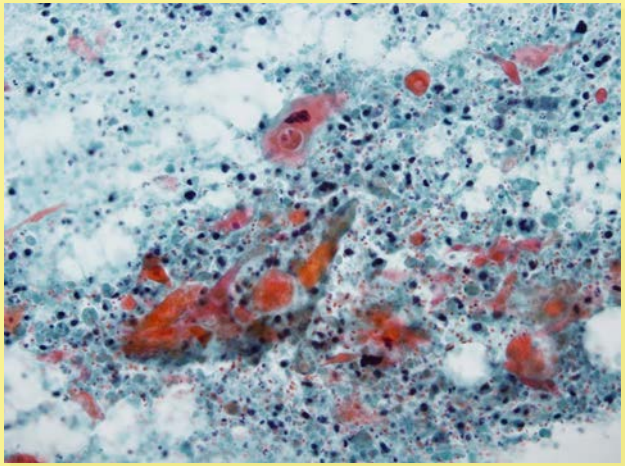
- Growth pattern → grading
  1. G1 – lepidic
  2. G2 – acinar, papillary
  3. G3 – solid, micropapillary
- Terminal respiratory unit
- TTF1 positivity
- Preinvasive lesion & early types
  - AAH, AIS, MIA
- Heterogeneity is a rule
- Rare types
  - Mucinous, colloid
  - Fetal
  - Enteric

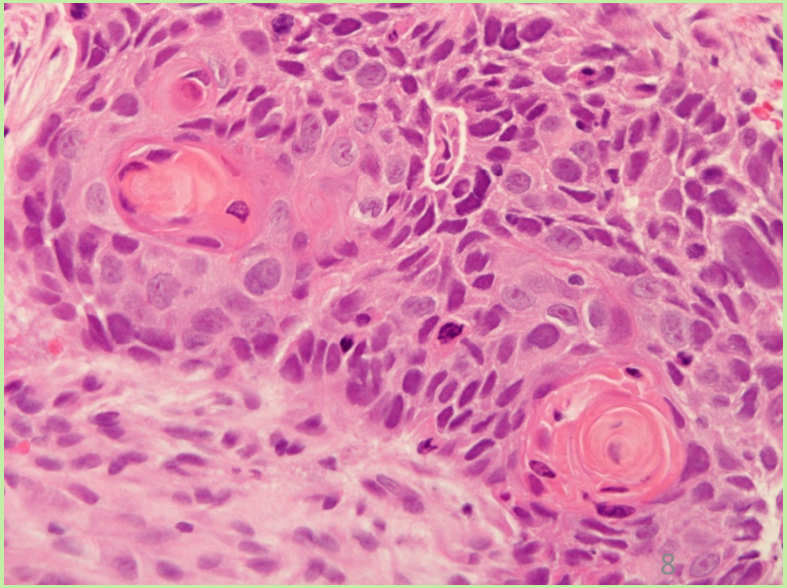




Squamous cell carcinoma

- No established grading system
- Keratinizing and nonkeratinizing
- Rare type
  - Basaloid
- No organ specific marker
  - but (HPV)
- Arise in large airways
- Smoking related tumor
- Drugable driver mutations?
  - FGFR family
  - PI3K/AKT

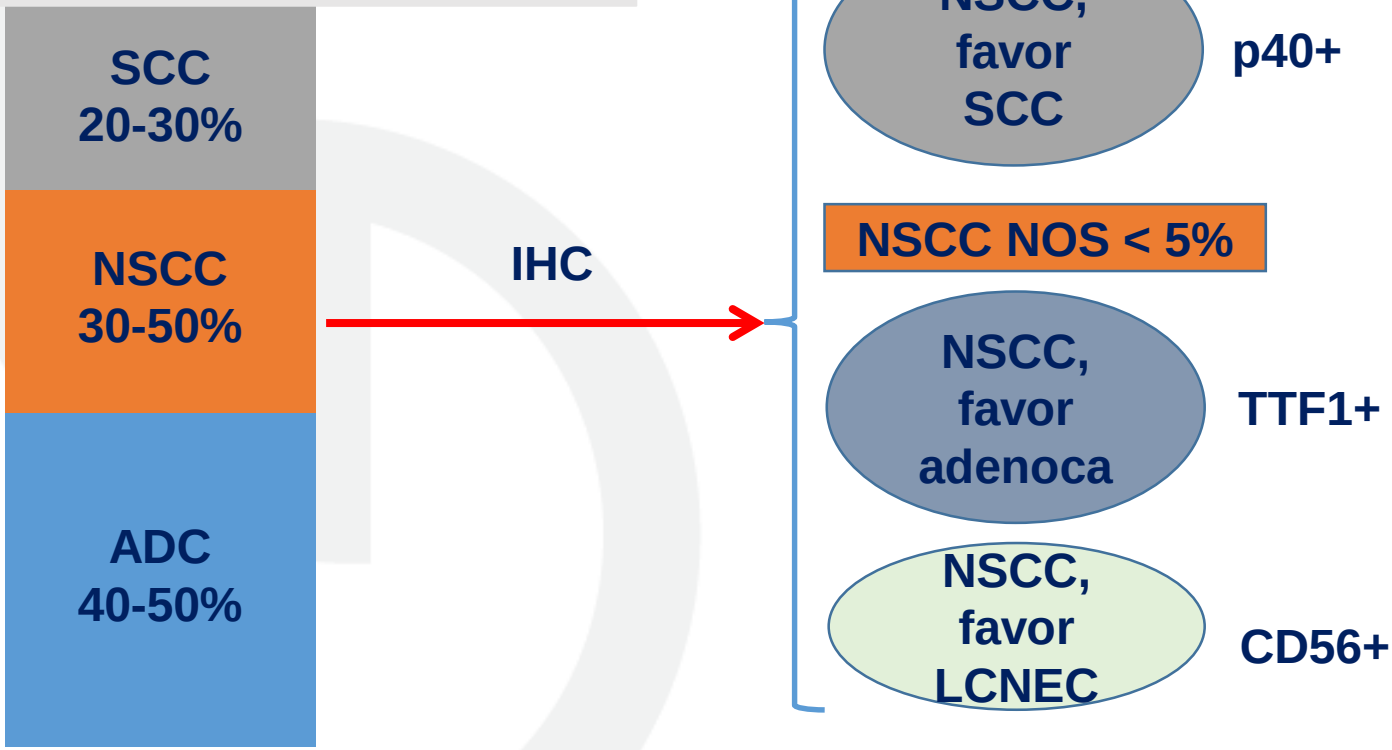




NSCC NOS

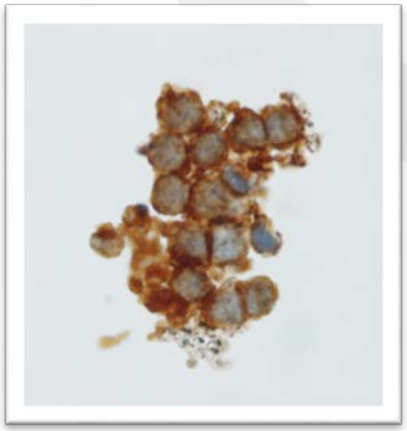
Diagnosis (entity?) reserved for small biopsies and cytology!

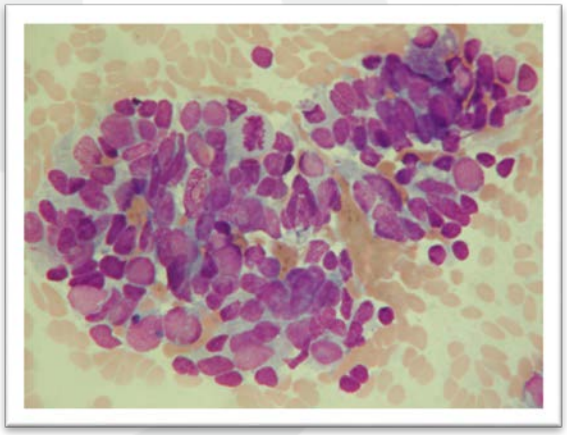
Routine morphology
HE, MGG/Pap, mucin

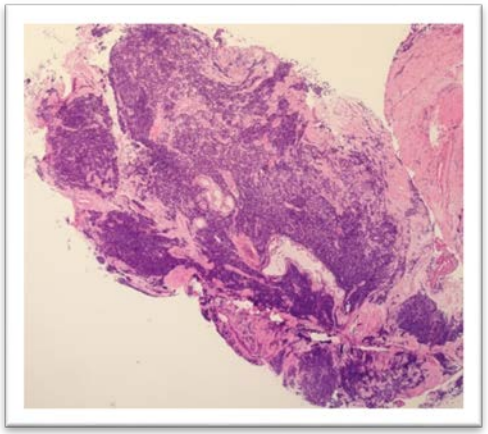


Small cell lung carcinoma

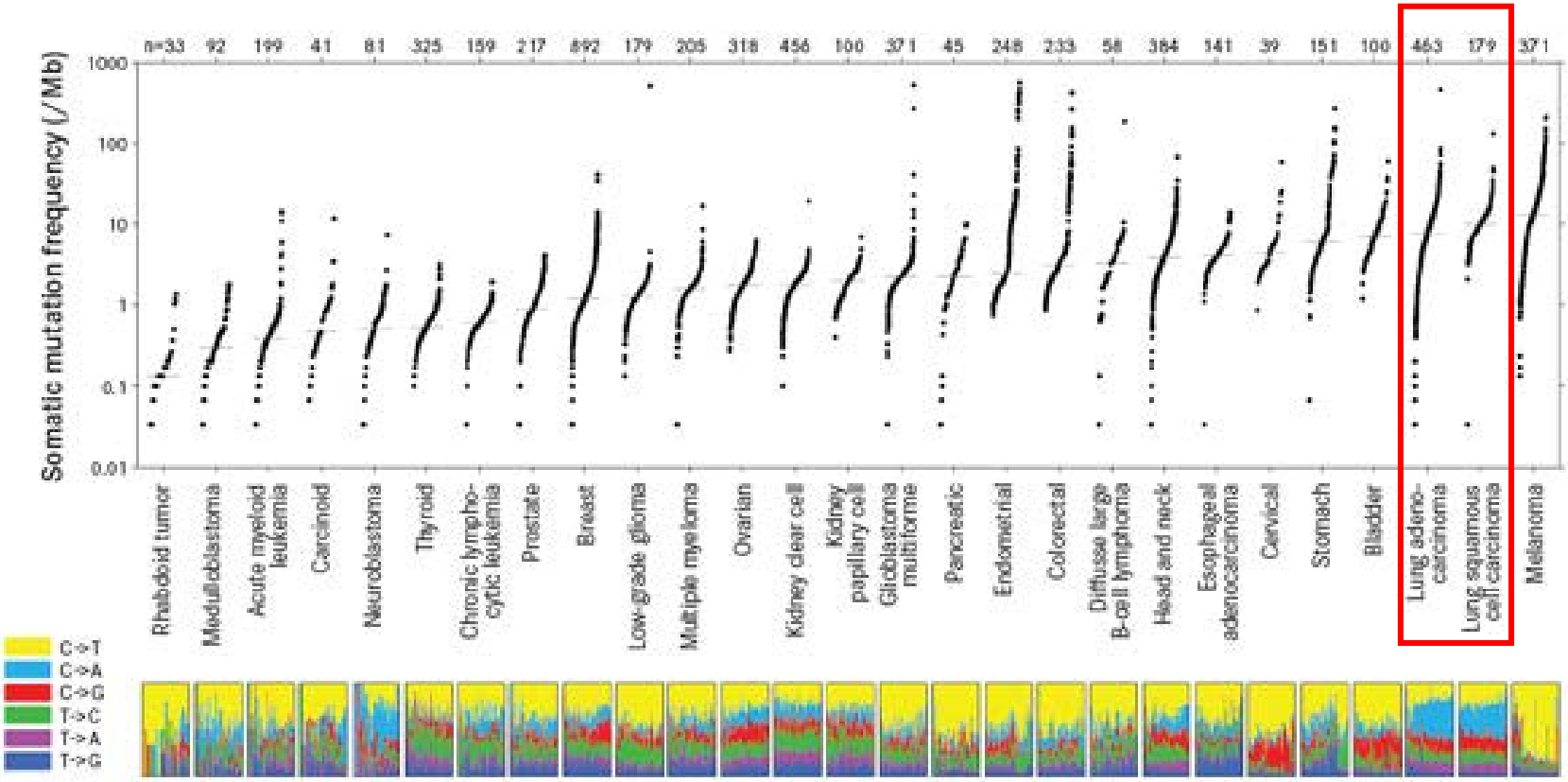
- Poorly differentiated neuroendocrine tumor
- NE markers (phenotype)
  - NCAM (CD56)
  - Chromogranin, synaptophysin
- Smoking related tumor
- Central airways
- Increased proliferation index→quick doubling time







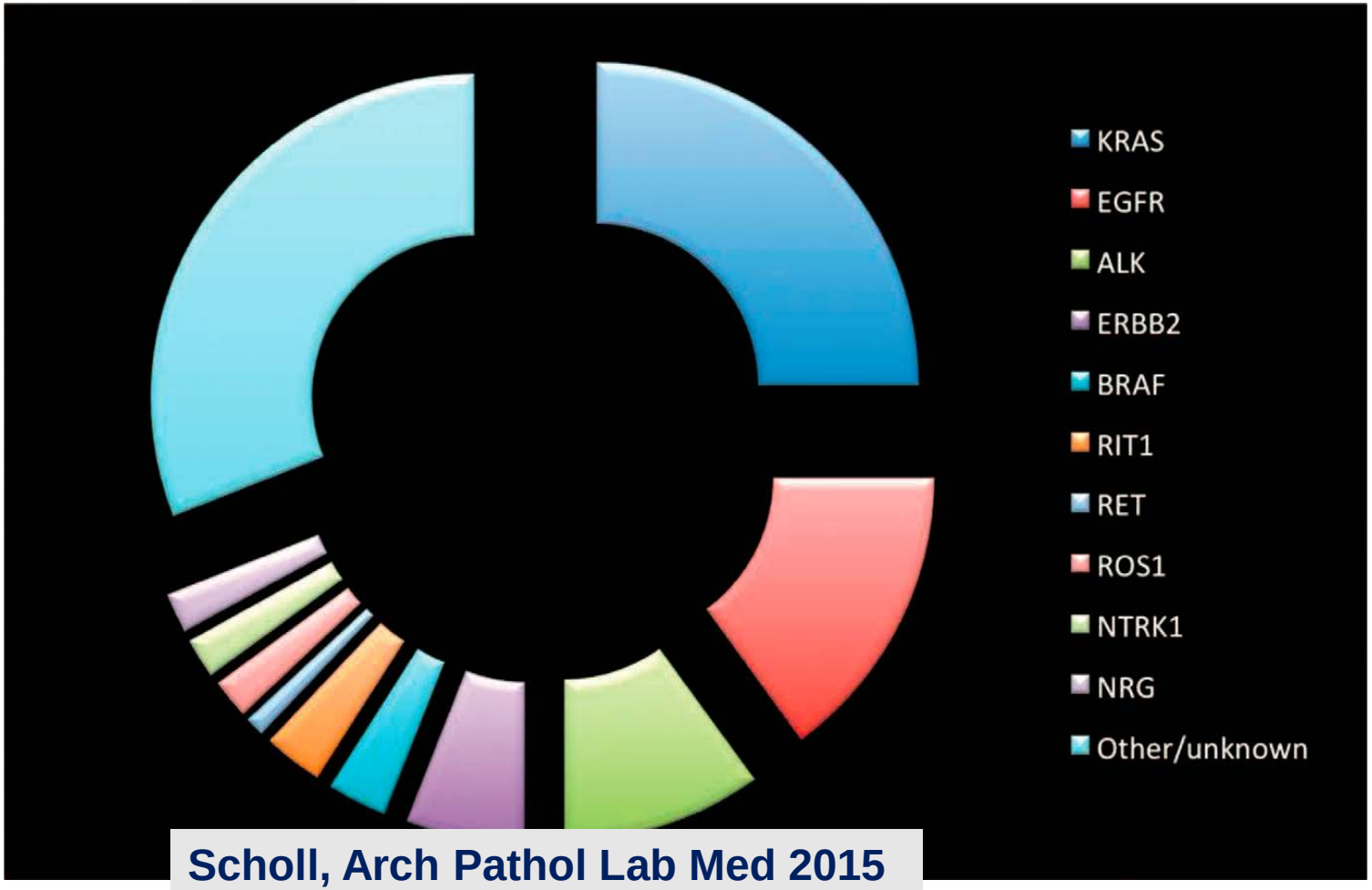
Lung cancer is highly mutated



Aleksandrov, Nature 2013

60% lung adenocarcinomas have a driver oncogene - trunk mutation

Mutually exclusive genetic changes:
KRAS, EGFR, ALK, ROS1, BRAF, RET, HER2



Scholl, Arch Pathol Lab Med 2015

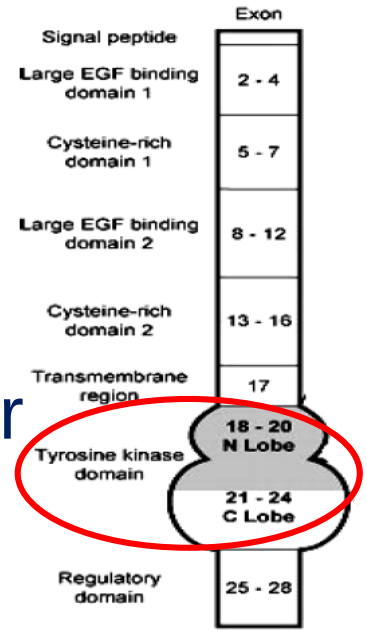
Predictive biomarkers: EGFR, ALK, ROS1

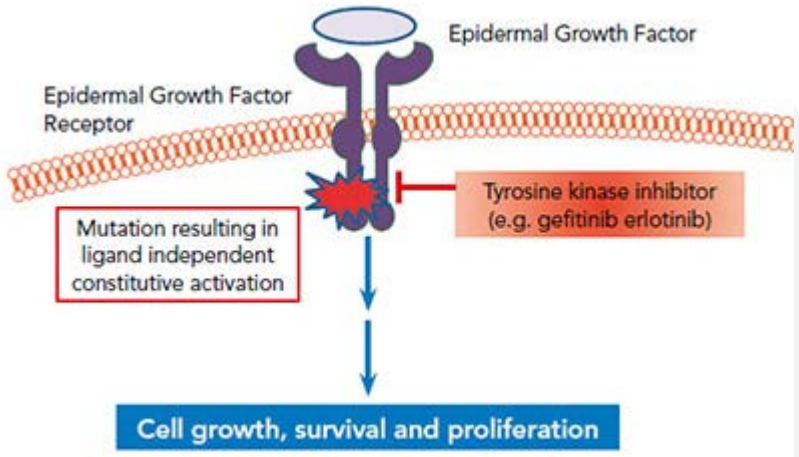
1. Which patients must be tested?
   - All AdC, NSCLC NOS, carcinomas with adeno
   - Stage IV, optional for early stages & other histologies
   - Primary tumor or metastasis
   - Adequate tumor sample (cytology or tissue)
2. When to test?
   - At the time of diagnosis – reflex approach
   - Tumor sample prioritized for testing
3. How rapid should be testing?
   - <10 working days
   - Sample should be sent <3working days for testing
   - Testing result incorporated in pathology report
4. EQA is a must

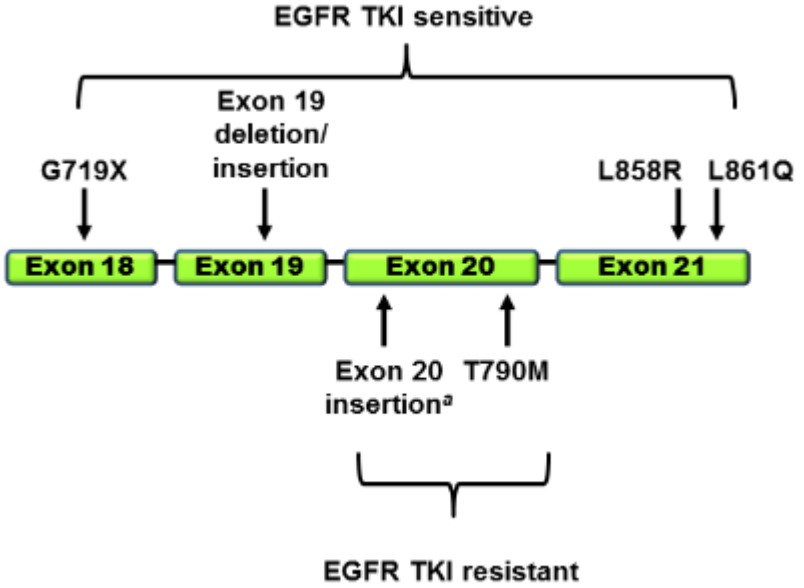
CAP guidelines 2018

EGFR

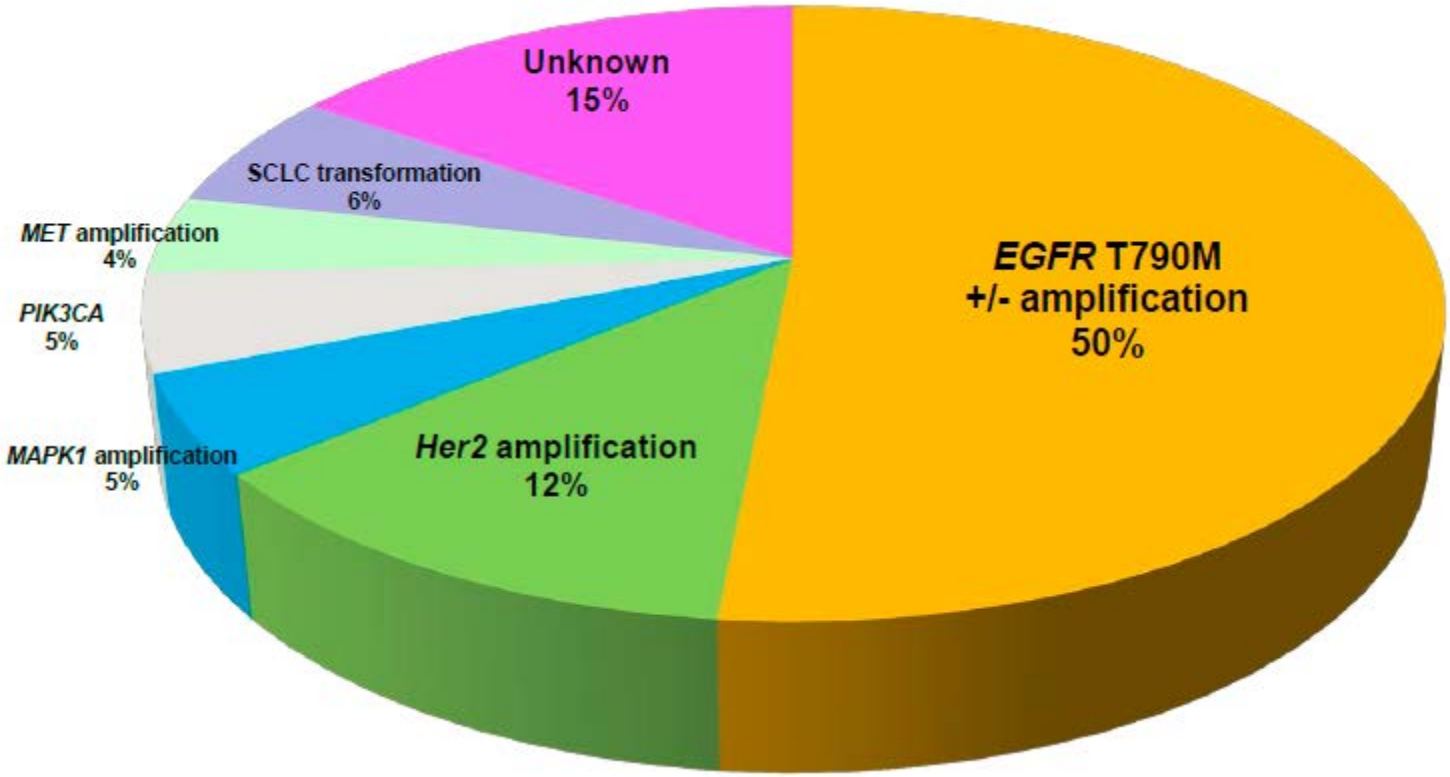
- ErbB transmembrane growth factor receptor
- Sensitizing and resistance mutations
- Best predictor of TKI treatment







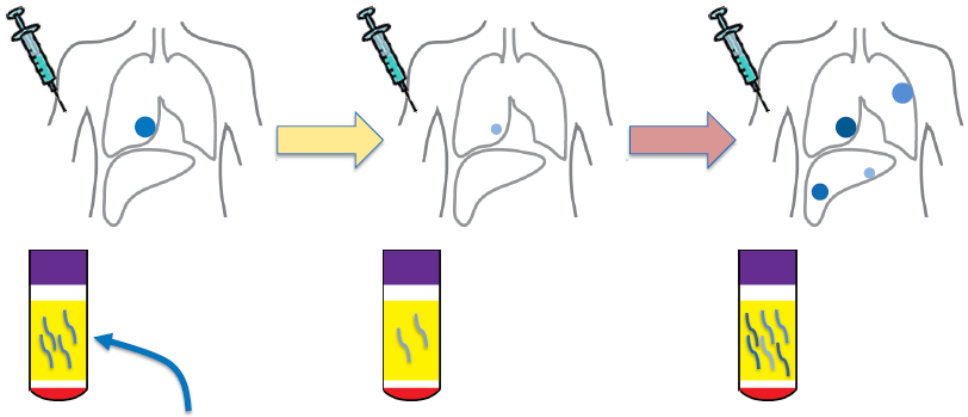
EGFR resistance

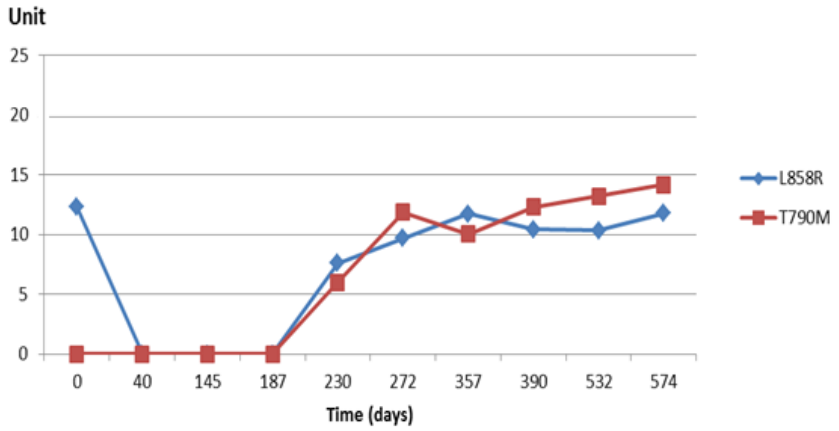


- T790M must testing at time of disease progression
- To select patients for targeted therapy
- Liquid biopsy is the first step

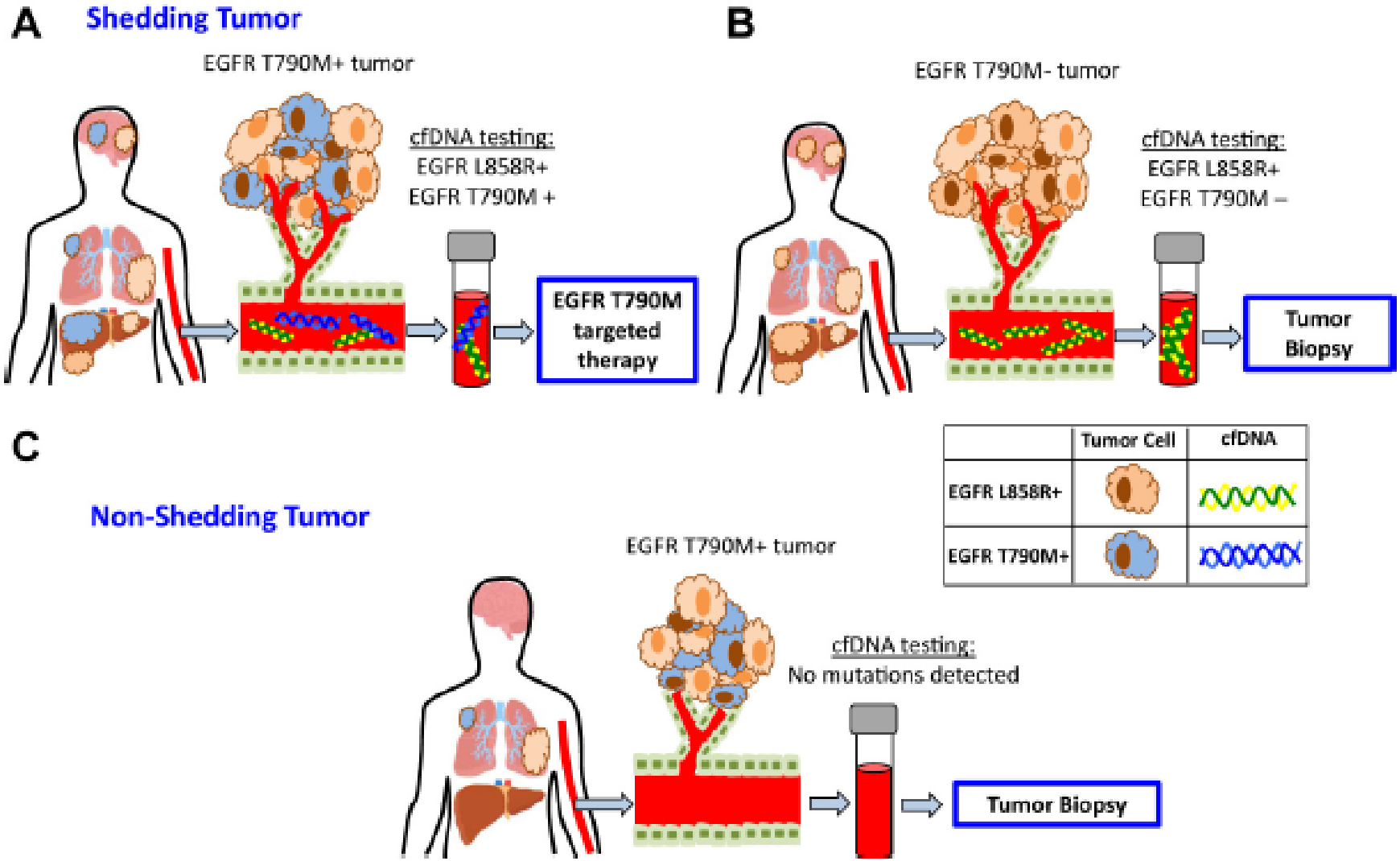
Liquid biopsy

1. Minimally invasive procedure
   - Enables serial EGFR testing
2. Baseline EGFR testing
   - No tumor tissue available for molecular analysis
   - May capture tumor heterogeneity
3. Monitoring and prediction of TKI treatment
4. Detection of resistance EGFR mutation before clinical progression





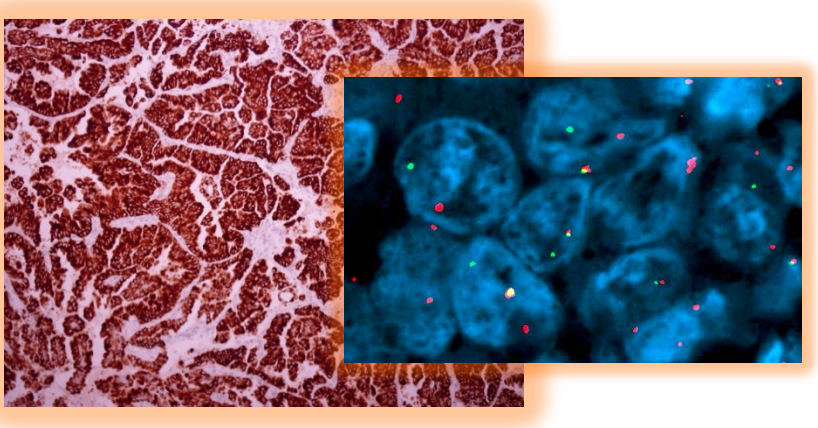
Liquid biopsy ≠ tumor biopsy

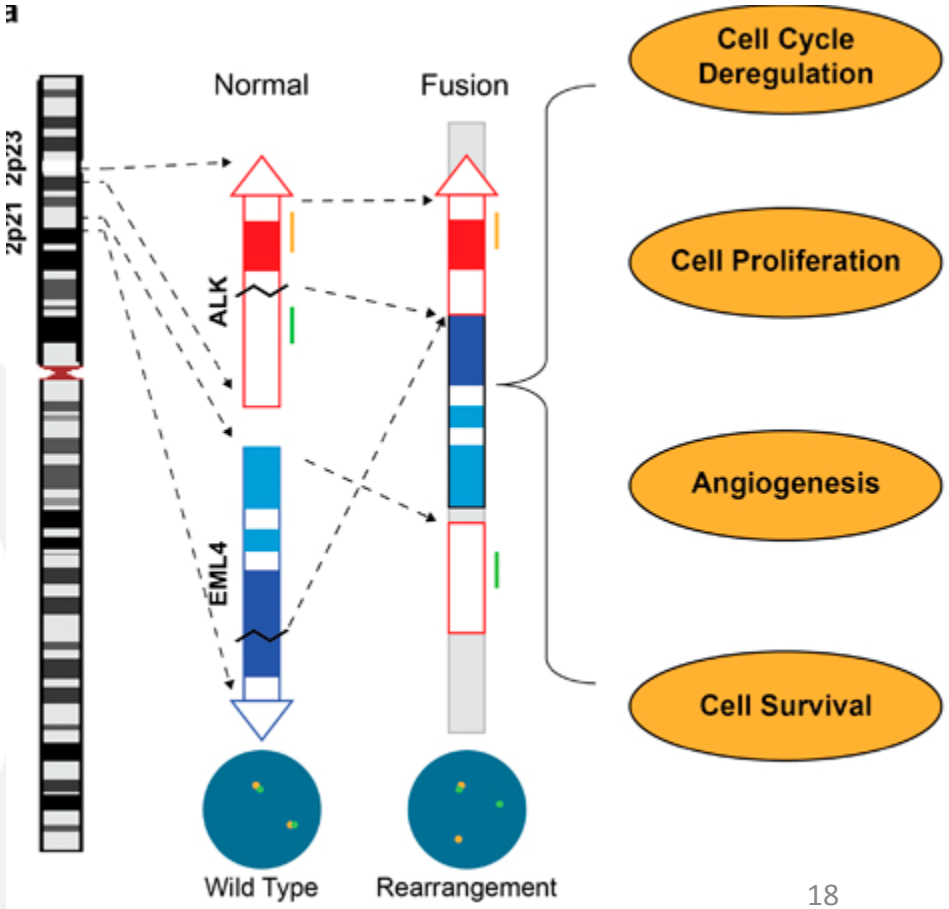


Sacher, JTO 2017

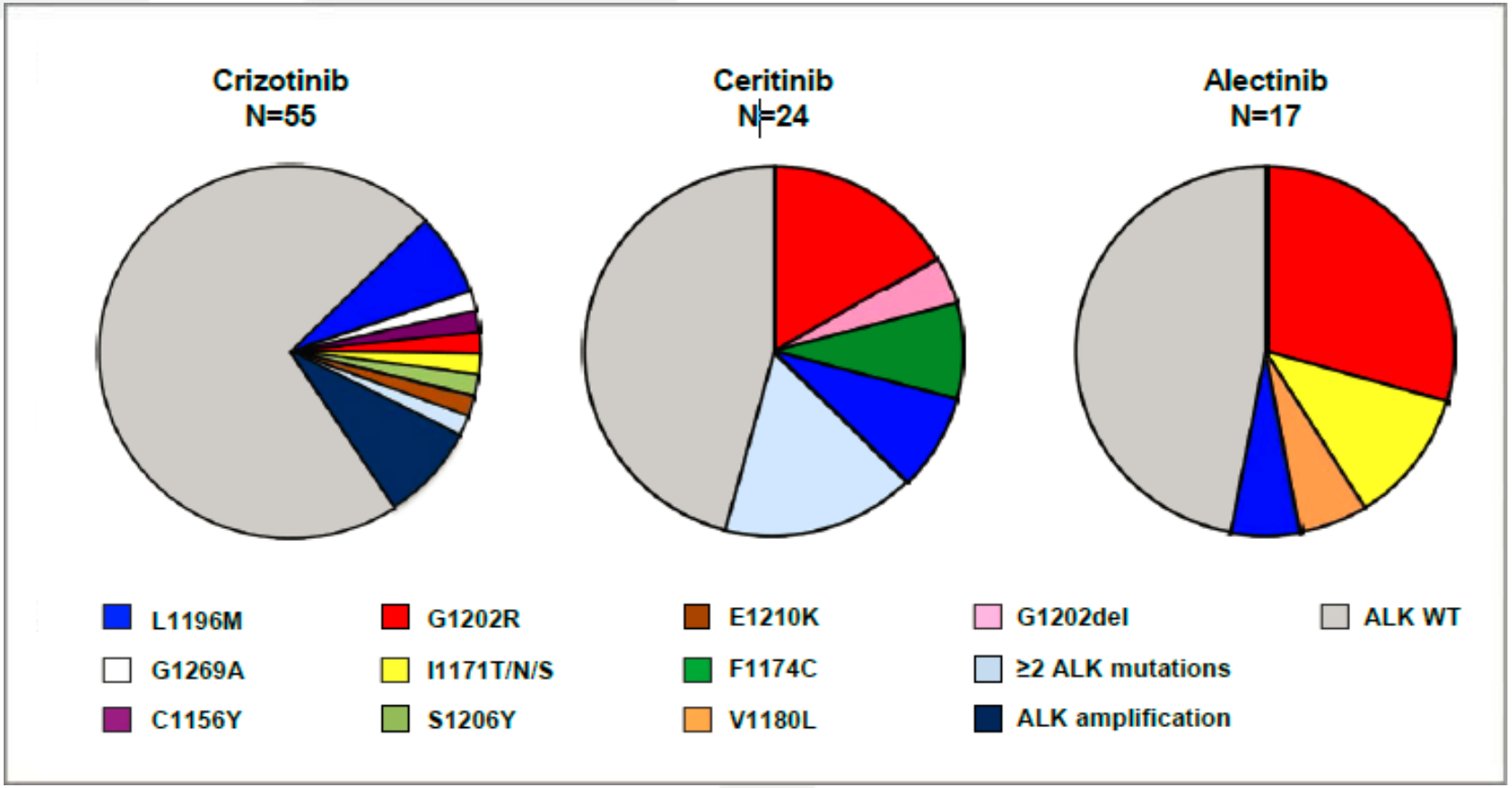
ALK

- Transmembrane insulin receptor
- Tyrosine kinase
- Normally expressed in nervous tissue, testis
- Several fusion partners
- Younger patients, nonsmokers
- IHC or FISH
- IHC+/FISH- respond to crizotinib
- Testing for resistance not recommended





ALK resistance

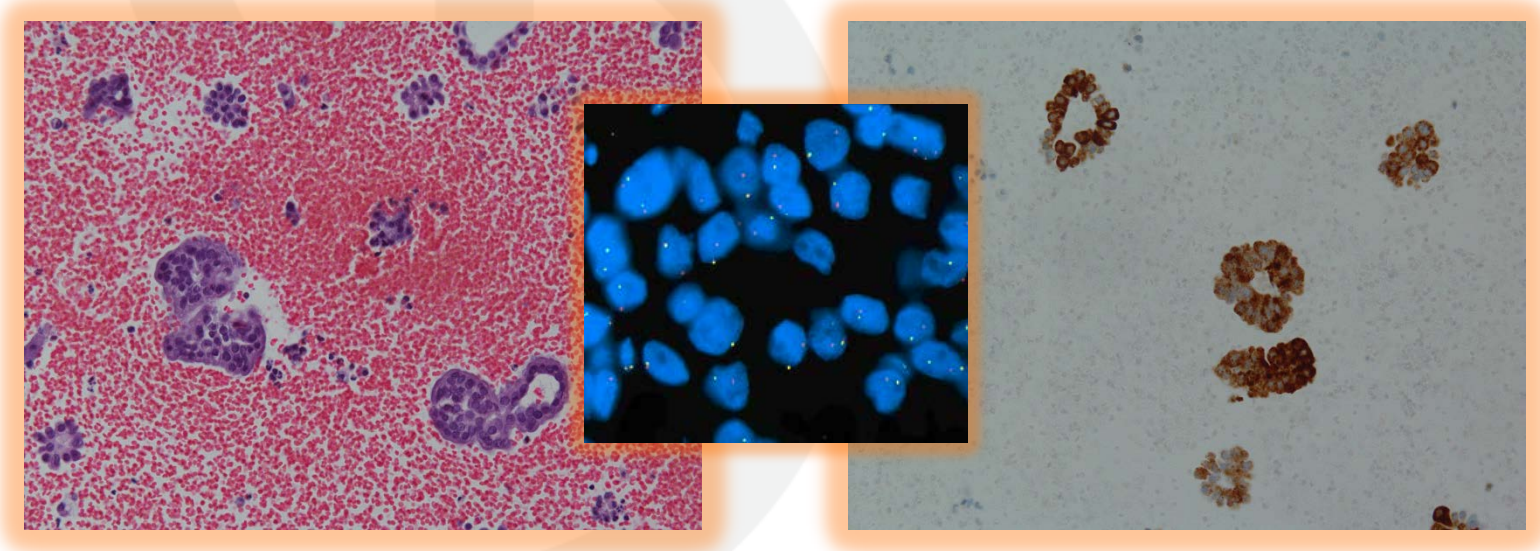


Doebele, CCR 2012
Gainor, Cancer Discov 2016

ROS1

- Insulin receptor family
- Tyrosine kinase
- 6q22 translocation
- FISH>>IHC
- IHC screening method
- Younger patients, nonsmokers

CLONE D4D6
SENSITIVITY ~100%
SPECIFICITY 92-97%

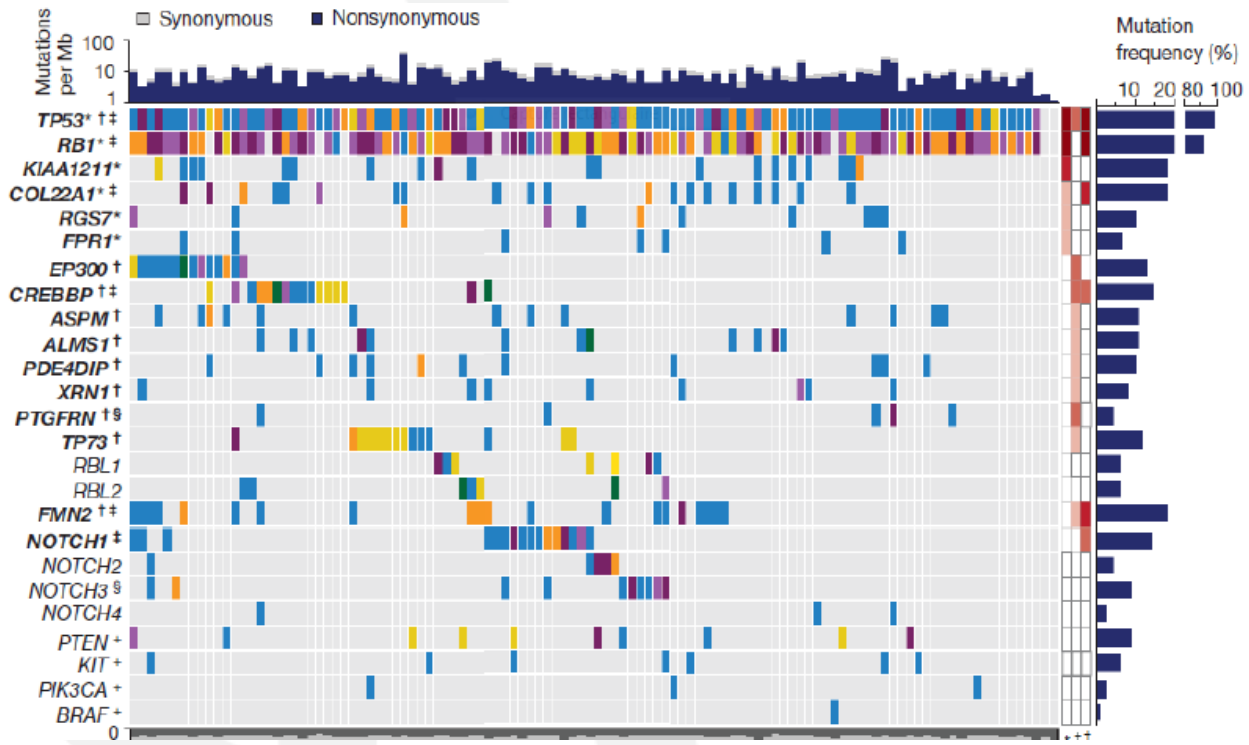


Other predicitve biomarkers

- KRAS
  - No targeted therapy yet
  - The most common driver mutation in lung adenocarcinoma
  - Mucinous adenocarcinomas
- RET
  - Gene rearrangement 10q11.2
  - Younger nonsmokers, poorly differentiated adenoca
- MET
  - Tyrosine kinase receptor, crizotinib
  - Overexpression, gene amplification, exon 14 skipping mutation
  - EGFR-TKI resistance mechanism
  - Sarcomatoid carcinoma
- BRAF
  - V600E mutation in 50%
  - Micropapillary morphology
- HER2
  - Exon 20 mutations
  - Younger non-smokers
  - EGFR-TKI resistance mechanism (mutations and or amplification)

Multigene panel testing - NGS

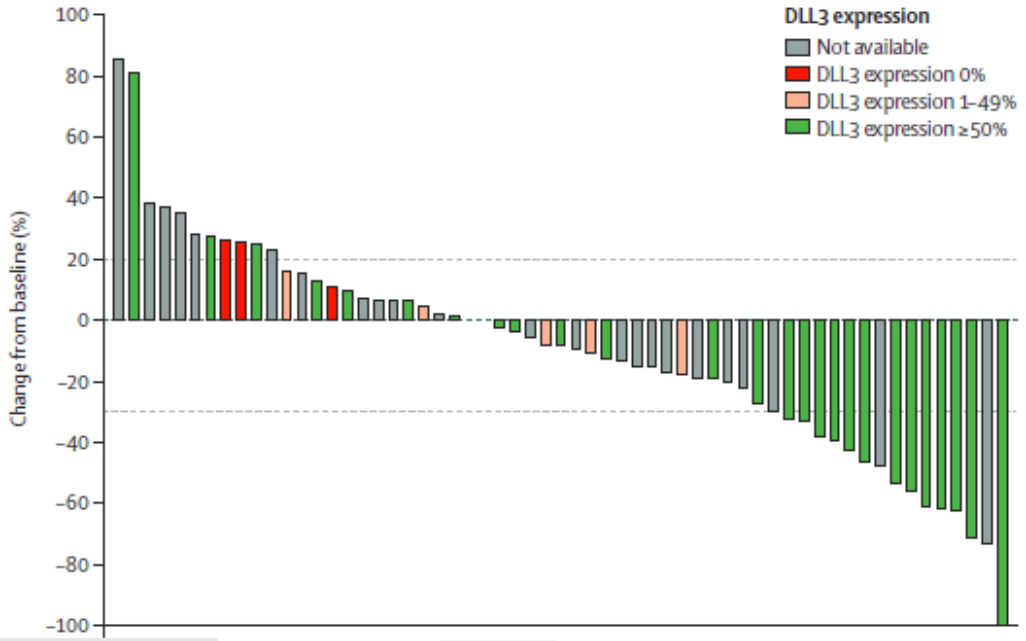
SCLC – genomic aberrations



- Chromosome instability is high
- Increased telomerase activity
- TP53 and RB1 mutations are common and typical
- DLL3 abnormal expression – predictive biomarker?
- DLL3 inhibits NOTCH1 in GA

SCLC

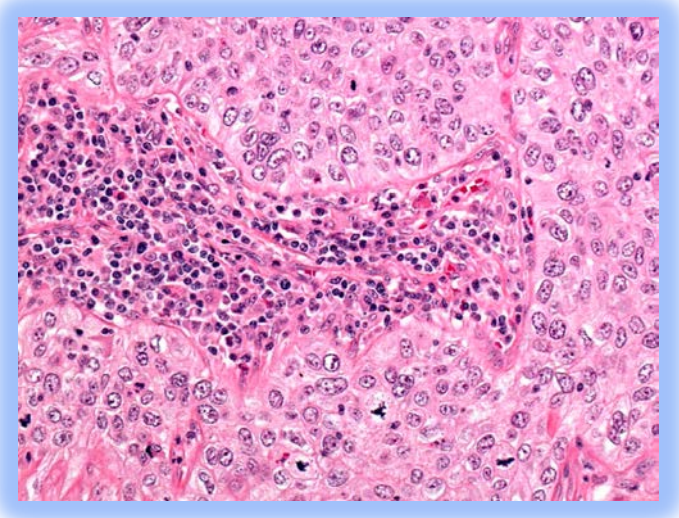
- DLL3 – Notch receptor ligand family
- Overexpression in 80% of SCLC - cell membrane protein (IHC)
- Inovative targeted therapy (conjugate of anti-DLL3 mAb and toxic drug)

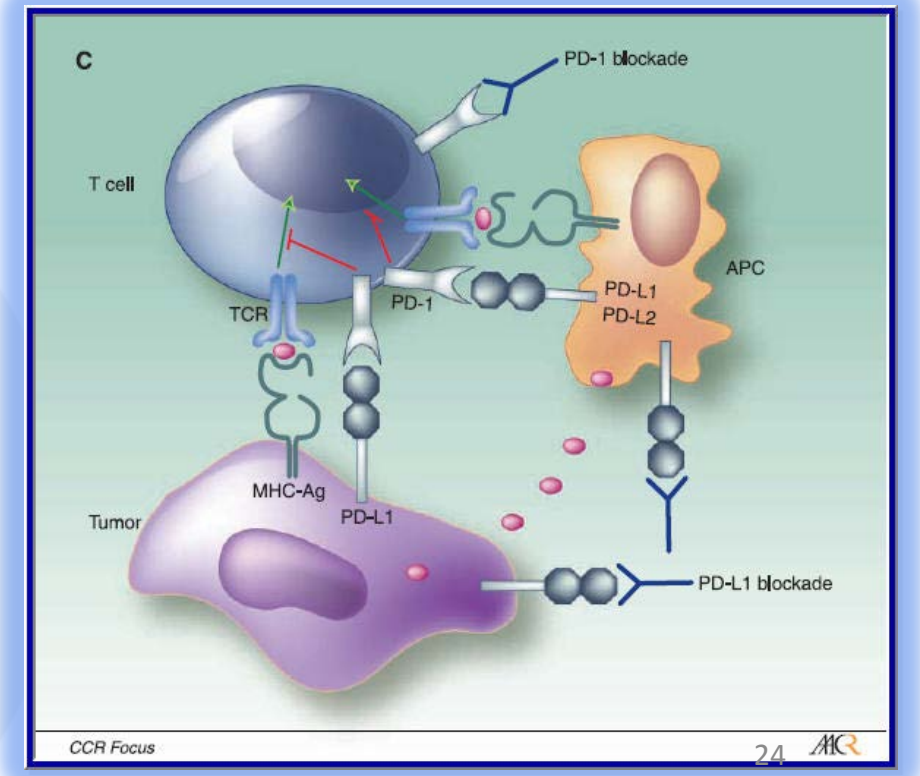


Rudin, Lancet Oncol 2017

PD-L1

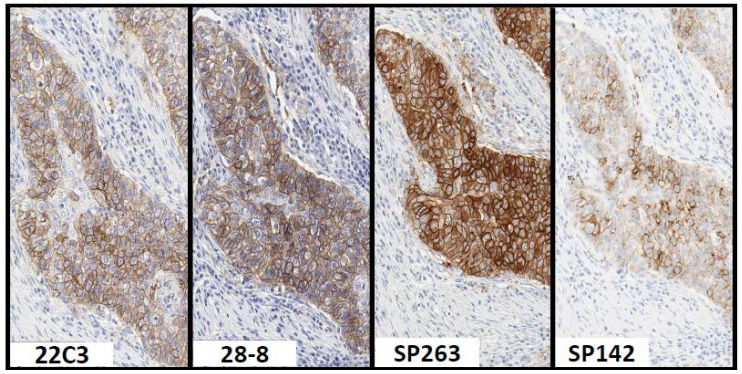
- PD-1 (programmed cell death) co-inhibitory receptor expressed on lymphoid and other cells
- Negatively regulates T-cell response
- PDL-1 major PD-1 ligand expressed on tumour cells
- Immunotherapy – to unmask tumor





PD-L1

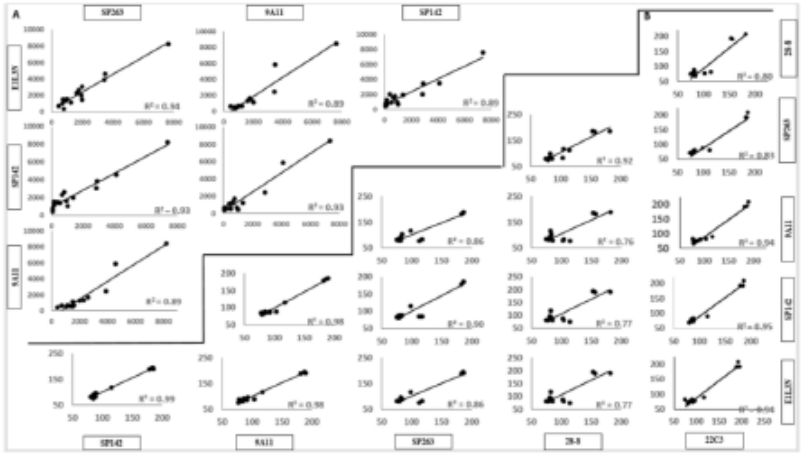
- Reliable biomarker? **Enrichment biomarker**
- Dynamic and inducible expression
- Biopsy size, cytology
- Clones, platforms, cut-offs
- Interobserver concordance
- Harmonization studies



ICC for pathologists by each antibody in Tumor Cells					
	22c3	28-8	SP142	E1L3N	Summary
All, N=90	0.882	0.832	0.869	0.859	0.86(0.02)

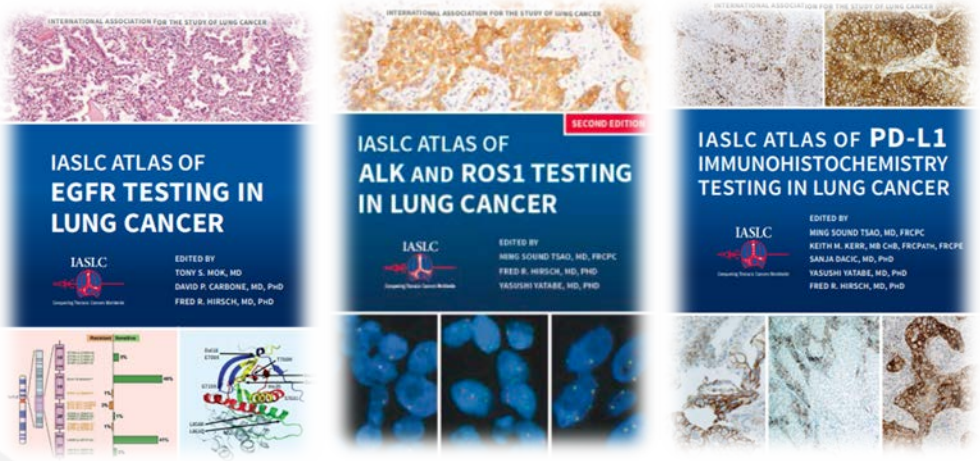
ICC for pathologists by each antibody in Immune Cells					
	22c3	28-8	SP142	E1L3N	Summary
All, N=90	0.207	0.172	0.185	0.229	0.19(0.03)

Rimm, JAMA 2017



Gaule, JAMA Oncology 2017

Recommended readings



Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology