

ACS Cancer Conference 2025

March 12-14 | Phoenix, AZ

Integration of Genetics and Genomics: Lung Cancer

Timothy Wm. Mullett, MD, MBA, FACS
Professor, Thoracic Surgery
University of Kentucky College of Medicine
Markey Cancer Center

ACS Cancer Programs
American College of Surgeons

- No disclosures

© American College of Surgeons. Content cannot be reproduced or repurposed without written permission of the American College of Surgeons.

ACS Cancer Conference 2025 | March 12-14 | Phoenix, AZ

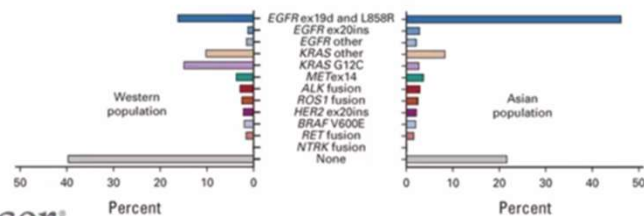
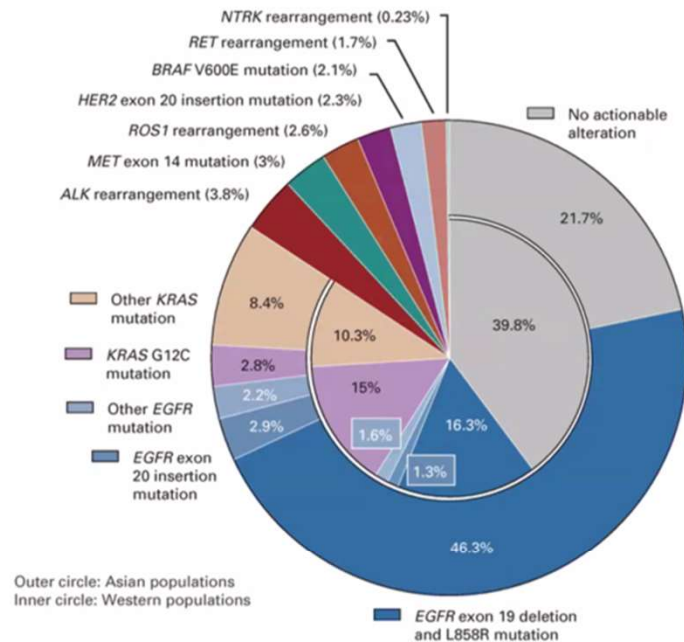
Genetic Emphasis is on Diagnosed Patients

- There are 'signals' from genetic testing and some familial patterns
 - Several Multicancer Detection (MCD) strategies emerging
 - Need to be more sensitive and specific
- We don't have effective driver mutations as seen in other tumors
- Prevention and Early Detection is largely overshadowed by the dramatic influence of tobacco exposure
 - Responsible for over 85% of lung cancer cases
- Early detection is prioritized for age and tobacco exposure

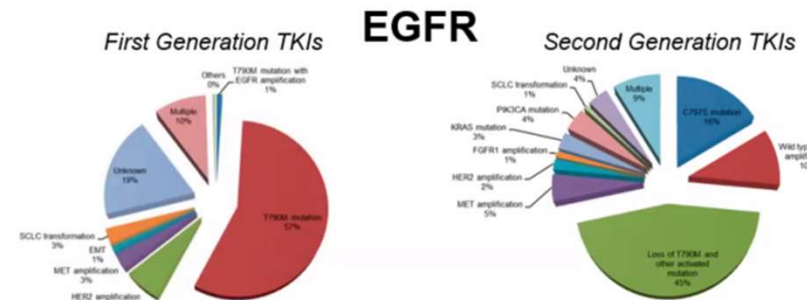
© American College of Surgeons. Content cannot be reproduced or repurposed without written permission of the American College of Surgeons.

Genomic Abnormalities in Lung Adenocarcinoma

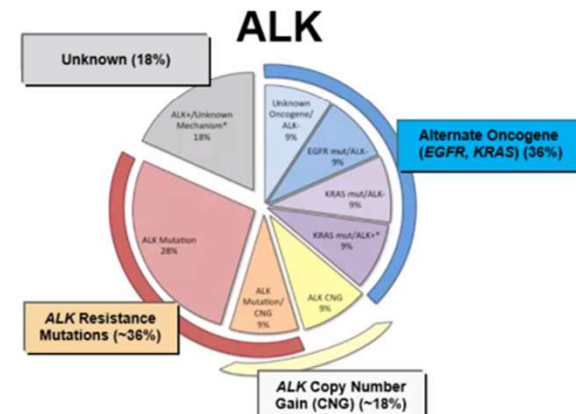
Mechanisms of Resistance



A. Tan, J Clin Oncol, 2022



Nagano T, et al. Cells. 2018;7:212.



Doebele RC, et al. Clin Cancer Res. 2012;18:1472

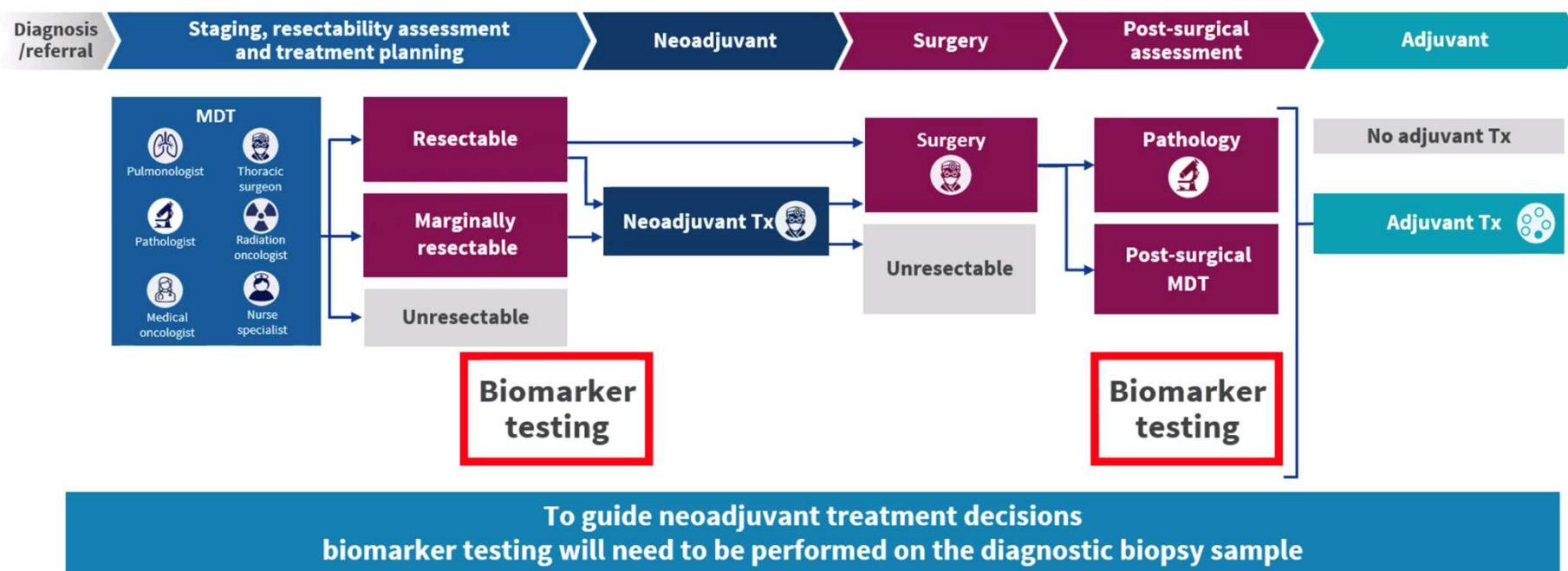
Evolution and Expanding List of Guideline Recommendations for Genomic Testing in Advanced Stage NSCLC

“The NCCN NSCLC Guidelines Panel strongly endorses **broader molecular profiling** with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials.

Broad molecular profiling is a key component of the improvement of care of patients with NSCLC).”

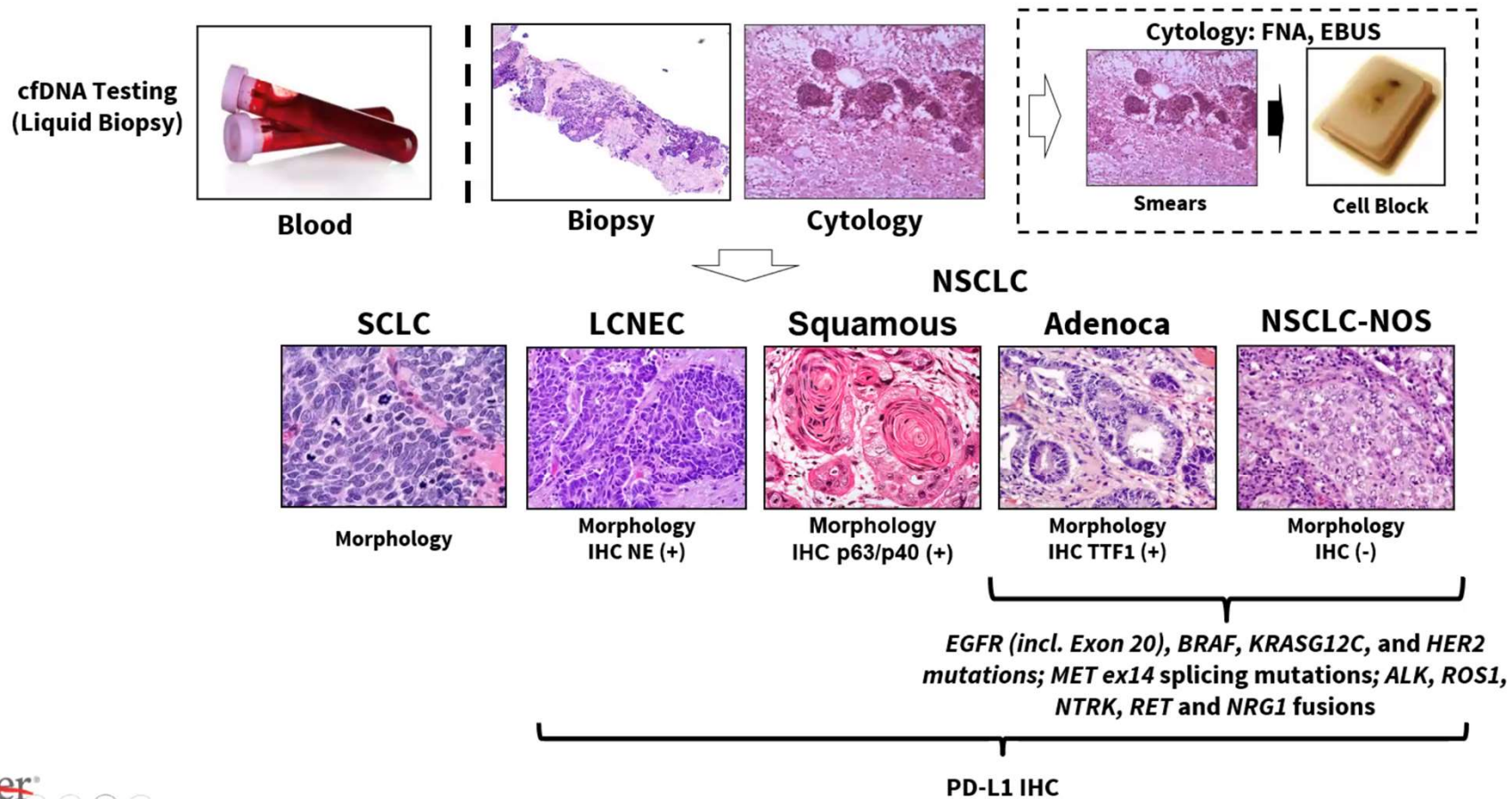
Genomic alteration (i.e., driver event)	Available targeted agents with activity against driver event in lung cancer
<i>EGFR</i> mutations	Osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
<i>ALK</i> rearrangements	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
<i>ROS1</i> rearrangements	Crizotinib, ceritinib, entrectinib
<i>BRAF</i> V600E mutations	Dabrafenib + trametinib, vemurafenib
<i>HER2</i> mutations	Ado-trastuzumab emtansine, afatinib, trastuzumab deruxtecan
<i>MET</i> amplification/mutation	Crizotinib, capmatinib
<i>RET</i> rearrangements	Cabozantinib, vandetanib, selpercatinib, pralsetinib
<i>NTRK</i> rearrangements	Entrectinib, larotrectinib,
<i>EGFR</i> Ex20ins	<i>Amivantamab</i>
<i>KRAS</i> G12C	<i>Sotorasib</i>

Biomarker Testing for Resectable NSCLC Helps to Inform Treatment Decisions



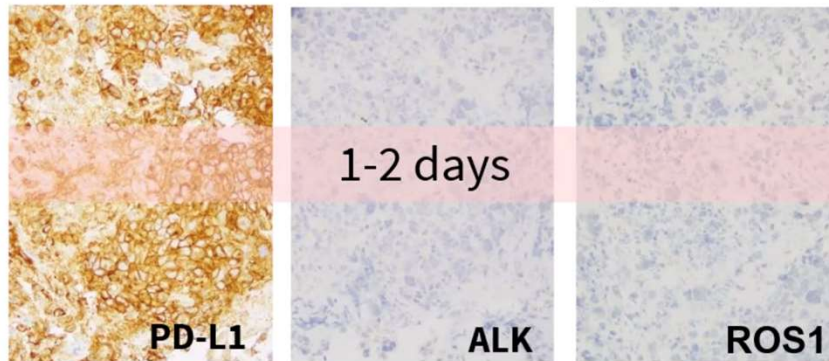
MDT, multidisciplinary team; NSCLC, non-small cell lung cancer; Tx, treatment
Remon J, et al. Ann Oncol 2021;32:1637-42

Diagnostic Algorithm for Lung Cancer Diagnosis 2024

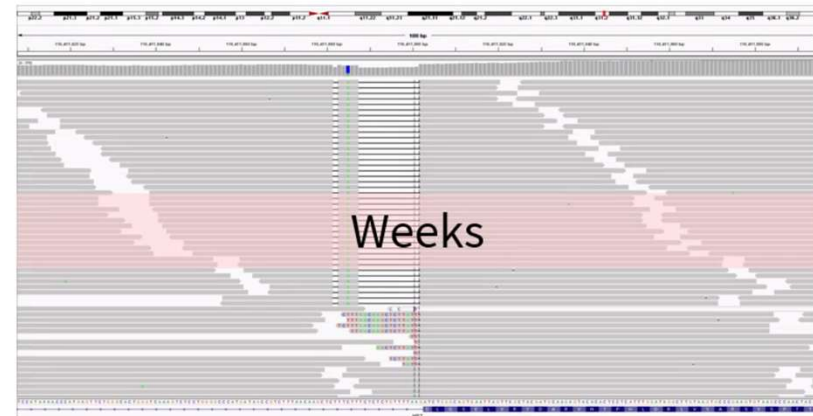


NSCLC Biomarker Testing → Tricky Timing

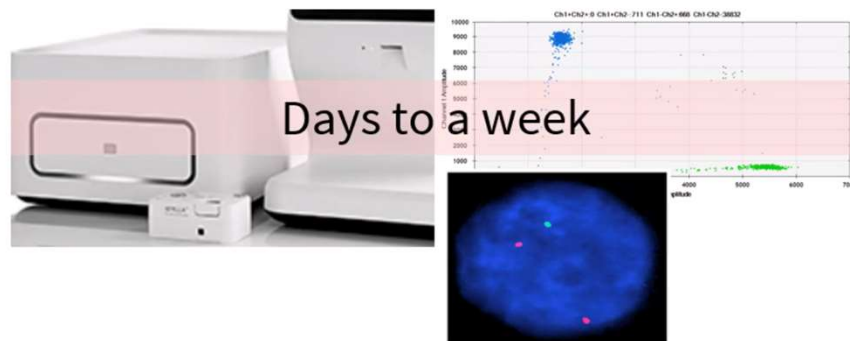
Immunohistochemistry



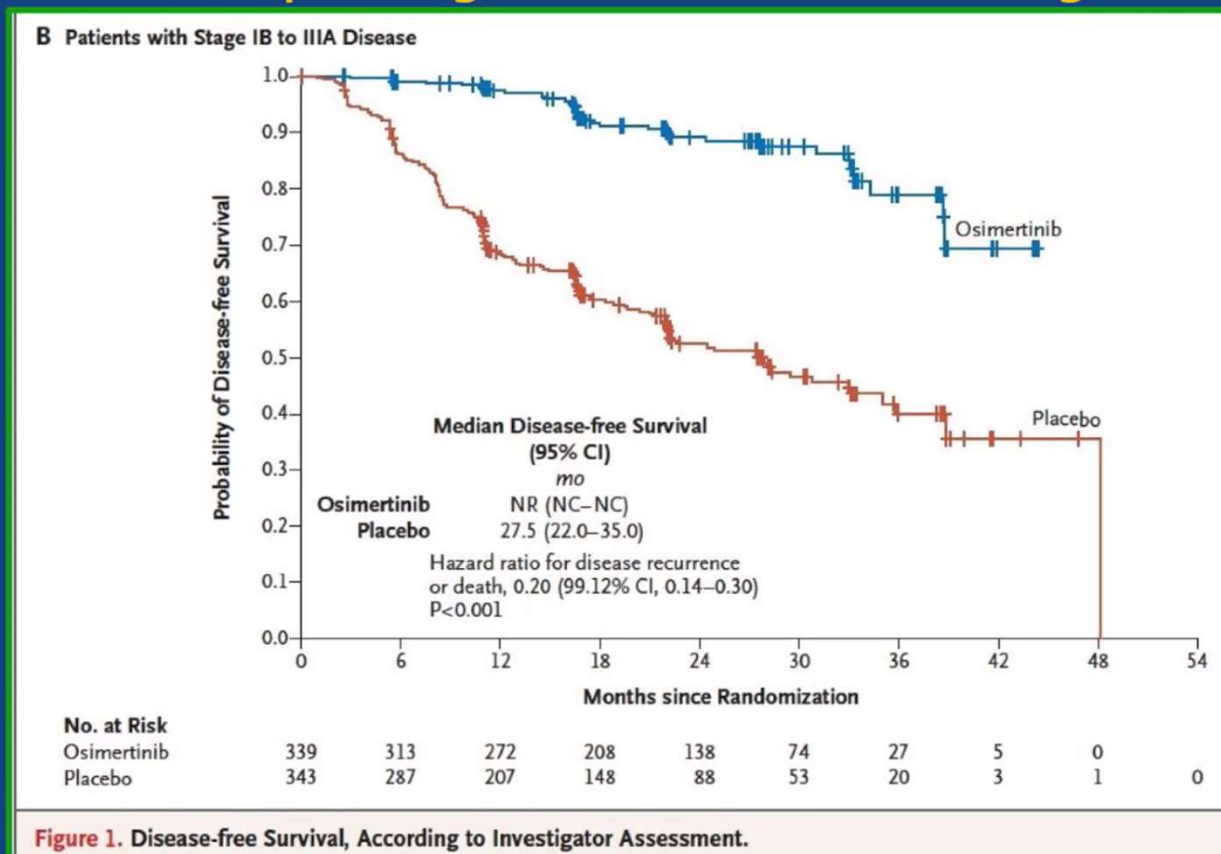
Next Generation of Sequencing (NGS)



PCR-based Assay and FISH



The expanding role of biomarker testing



Wu et al. NEJM 2020, 383: 1711-1723

Biomarkers for Lung Cancer Treatment September 2020

Target	Prevalence	Initial FDA Approval	Drugs
EGFR	10-15%	2003	Gefitinib, Erlotinib, Afatinib, Osimertinib
ALK	2-7%	2011	Crizotinib, Ceritinib, Alectinib, Lorlatinib, Brigantiniib
R0S-1	1-2%	2016	Crizotinib, Entrectinib, Ceritinib, Lorlatinib
PD-L1 TPS 50%	30%	2016	Pembrolizumab, Atezolizumab
B-RAF^{V600E}	2%	2017	Dabrafenib+Trametinib, Vemurafenib
NTRK	0.2-3%	2018	Larotrectinib, Entrectinib
HER-2 (ERBB2)	2-5%	May 2020	Trastuzumab deruxtecan (Enhertu)
MET exon 14 skipping	3-4%	May 2020	Capmatinib; ?Tepotinib?, Crizotinib
RET	1-2%	September 4, 2020	Salpercatinib, Pralsetinib, Carbozantinib, Vandetanib
K-RAS G12C	12%	?	AMG510

Summary

- Genetic Testing and Genomic Analysis have a limited role in risk prediction or early detection in lung cancer
- Genomic anomalies are becoming increasingly recognized
 - Therapeutic targets are increasing
 - Essentially all stages of lung cancer should have genomic analysis
- Workflows to incorporate testing early in the evaluation are critical to avoid delays or miss opportunities to provide improved outcomes

© American College of Surgeons. Content cannot be reproduced or repurposed without written permission of the American College of Surgeons.