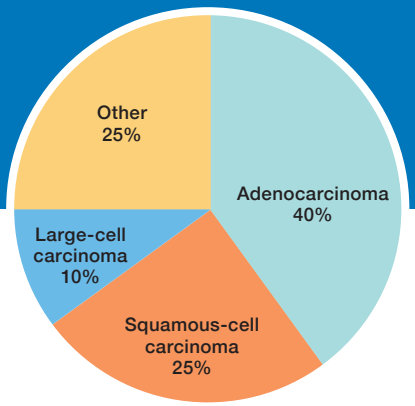
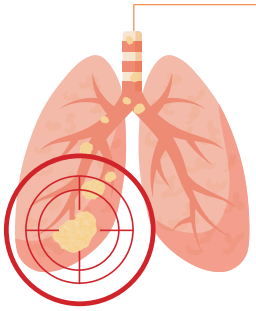
Quick Reference Guide to Biomarker Testing in Metastatic Non-Small Cell Lung Cancer



Subtypes of NSCLC[1]

Why test for biomarkers in metastatic non-small cell lung cancer (mNSCLC)?

- mNSCLC is not a single disease[1]
- Driver mutations have been identified in up to 50% of mNSCLC and 64% of adenocarcinomas[2,3]
- These mutations occur in genes that control cellular proliferation, survival, maintenance, and death

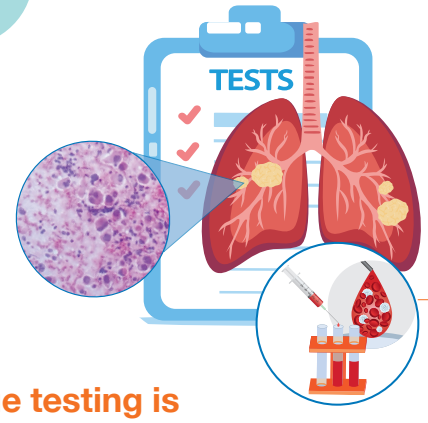


Biomarker testing facilitates precision medicine

- Biomarker testing is important for identifying potentially efficacious targeted therapies and avoiding therapies that are unlikely to provide clinical benefit[4]
- Targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic variants[5]
- Emerging biomarkers and corresponding targeted therapies are expanding the options for patients with mNSCLC

Clinical guidelines recommend broad panel biomarker testing for appropriate patients with mNSCLC

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (v3.2022)[5]
  - Perform PD-L1 testing in all patients
  - Perform molecular testing in patients with adenocarcinoma, large-cell carcinoma, and not otherwise specified (*EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET*)
  - Consider molecular testing in squamous-cell carcinoma (*EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET*)
  - Testing should be conducted as part of broad, panel-based molecular profiling when feasible
  - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements; however, these features should not be used in selecting patients for testing
  - The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories
- College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology (2018)[6]
  - Offer a comprehensive panel that includes "must test" genes (*EGFR, ALK, ROS1*) and "recommended" genes (*BRAF, MET, RET, ERBB2 [HER2], KRAS*) **or**
  - Offer targeted testing for "must test" genes *and* offer an expanded panel containing "recommended" genes for patients who are candidates for clinical trials, with possible *KRAS* testing to exclude testing for "recommended" genes



Tissue testing is recommended but liquid biopsies can be considered when there is insufficient tissue

- Formalin-fixed paraffin-embedded specimens are most commonly used but other specimen types may be accepted by testing laboratories[5]
- Plasma circulating tumor DNA testing (liquid biopsies) can be considered if[5]:
  - Patient is medically unfit for invasive tissue sampling
  - Insufficient material is available at initial diagnosis but follow-up tissue-based analysis is planned if an oncogenic driver is not identified
- Due to lower sensitivity, liquid biopsies can result in false-negative results[5]

Established and Emerging Biomarkers in Non-Small Cell Lung Cancer

Biomarker	Prevalence[a]	Clinicopathologic Correlates	Approved and Investigational Therapies
Established Biomarkers			
ALK fusions[7]	4% of adenocarcinomas	Adenocarcinomas in never-smokers, younger patients	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib
BRAF V600E mutation[7]	1%-3%	Smokers, former smokers	Dabrafenib + trametinib
EGFR mutations[1,7,8]	15% of adenocarcinomas (US) Up to 62% (Asian populations)	Adenocarcinomas in never-smokers	Afatinib Dacomitinib Erlotinib ± ramucirumab Gefitinib Osimertinib
EGFR exon 20 insertion mutations[1,7,9]	2% 12% of NSCLC with *EGFR* mutations	Adenocarcinomas	Amivantamab-vmjw Mobocertinib **Poziotinib**
MET exon 14 skipping mutations[7]	3% of adenocarcinomas 20% of sarcomatoid histology NSCLC	N/A	Capmatinib Tepotinib
NTRK fusions[1,7]	<1%	Adenocarcinomas in never-smokers	Entrectinib Larotrectinib
PD-L1[1,10-12]	24%-60%	Identifies disease most likely to respond to immune checkpoint inhibitors	Atezolizumab Cemiplimab-rwlc[b] Nivolumab ± ipilimumab Pembrolizumab
RET fusions[7]	1%-2% of adenocarcinomas	Adenocarcinomas in never-smokers, younger patients	**Cabozantinib** Pralsetinib Selpercatinib
ROS1 fusions[7]	1%-2%	Adenocarcinomas in never-smokers, younger patients	**Ceritinib** Crizotinib Entrectinib **Lorlatinib**
Emerging/Prognostic Biomarkers			
ERBB2 (HER2) mutations[7]	1%-3%	Adenocarcinomas in never-smokers, women	**Ado-trastuzumab emtansine** **Fam-trastuzumab deruxtecan-nxki**
KRAS G12C mutations[1,13-15]	~11% (*KRAS* mutations: ~33%)	Smokers, former smokers	**Adagrasib** **JDQ443**[14] Sotorasib
MET high-level amplifications[7]	2%-4% 5%-20% of *EGFR*-mutated tumors that are *EGFR*-inhibitor resistant	Associated with secondary resistance to *EGFR* TKI therapy	**Capmatinib** **Crizotinib** **Tipotinib**
NRG1 fusions[16]	1%	Adenocarcinomas in never-smokers	**Afatinib**
STK11 (LKB1) mutations[17]	5%-30%	Prognostic of worse survival with immune checkpoint inhibitors	N/A

[a]Prevalence may vary according to racial background, stage of disease, and treatments received. Unless otherwise noted, percentages represent prevalence in NSCLC.

[b]In patients with high (≥50%) PD-L1 expression.

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5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. Version 3.2022 – March 16, 2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed June 16, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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