

NSCLC Biomarker Testing Resource Guide

**for Pathologists and
Laboratory Professionals**



STRONGERTOGETHER

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Background and Purpose of This Guide

As the landscape of biomarker testing in non-small cell lung cancer (NSCLC) continues to expand and evolve, pathologists and laboratory professionals need resources to stay current and to ensure that appropriate testing is being performed for the right patients. Several recent FDA approvals have expanded the list of actionable biomarkers in NSCLC or have added new therapy options for patients with targetable genomic alterations:

- On August 8, 2025, the FDA granted accelerated approval to **zongertinib** for adults with unresectable or metastatic non-squamous NSCLC whose tumors have **HER2 (ERBB2) tyrosine kinase domain (TKD) activating mutations**, as detected by an FDA-approved test, and who have received prior systemic therapy.⁷
- On July 2, 2025, the FDA granted accelerated approval to **sunvozertinib** for adult patients with locally advanced or metastatic **EGFR exon 20 insertion mutations**, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.⁸
- On June 23, 2025, the FDA granted accelerated approval to **datopotamab deruxtecan-dlnk** for adults with locally advanced or metastatic **EGFR-mutated NSCLC** who have received prior EGFR-directed therapy and platinum-based chemotherapy.⁹
- On June 11, 2025, the FDA granted accelerated approval to **taletrectinib** for adults with locally advanced or metastatic **ROS1-positive** NSCLC.¹⁰
- On May 14, 2025, the FDA granted accelerated approval to **telisotuzumab vedotin-tllv**, a c-Met-directed antibody and microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous NSCLC with **high c-Met protein overexpression** [≥50% of tumor cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy. FDA also approved the VENTANA MET (SP44) RxDx Assay (Roche Diagnostics) as a companion diagnostic test to aid in detecting c-Met protein overexpression in patients with non-squamous NSCLC who may be eligible for treatment.¹¹
- On December 4, 2025, the FDA granted accelerated approval to zenocutuzumab-zbco for adults with advanced, unresectable, or metastatic NSCLC harboring a neuregulin 1 (**NRG1**) **gene fusion** with disease progression on or after prior systemic therapy.¹²

The use of next-generation sequencing (NGS) is recommended to identify targetable genomic alterations such as *EGFR*, *HER2 (ERBB2)*, or *ROS1* gene mutations.¹³ Immunohistochemistry (IHC)-based tests detect PD-L1 and HER2 protein expression. c-Met protein (also called MET protein) overexpression by IHC is a new addition to the NSCLC test menu.

Recognizing that the pathology community needs to keep up with the expanding landscape of biomarker testing in NSCLC, ASCP organized a series of Learning Collaborative meetings with pathologists and laboratory professionals in 2025. These meetings allowed pathologists and laboratory professionals to discuss how they perform biomarker testing and outline some of the challenges they face at their institutions. This resource guide summarizes key findings from those discussions and is designed to help pathologists, laboratory professionals, and other members of the cancer care team to develop or update NSCLC biomarker testing processes.

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Navigating Clinical Practice Guidelines

The historic lung cancer molecular testing guidelines published in 2013 by College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) were last updated in 2018.¹ Given that these are now outdated, most cancer centers seem to follow the NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines.

These guidelines can be found here:

[nccn.org/professionals/physician_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)

As of September 2025, the latest version of the NCCN guidelines for NSCLC is Version 8.2025 (August 15, 2025) and contain 287 pages in the PDF file.⁷ Several pages provide guidance on biomarker testing in NSCLC:



Section NSCL-H (starts on page 96 in the PDF) is titled, “Principles of Molecular and Biomarker Analysis” and outlines specific recommendations for actionable biomarkers



Section NSCL-H 8 of 8 (page 103 in the PDF) outlines the role of circulating tumor DNA (ctDNA) testing



Section NSCLC-20 (page 45 in the PDF) lists Testing Results and links to treatment-specific pages



Section NSCLC-J 1 of 6 (page 105 in the PDF) lists “Molecular and Biomarker-Directed Therapy for Advanced or Metastatic Disease”



Section NSCLC-I (page 104 in the PDF) outlines “Emerging Biomarkers to Identify Novel Therapy for Patients with Metastatic NSCLC”

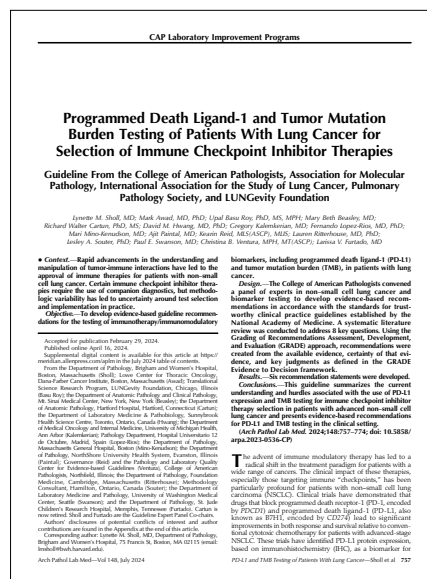


Section NSCLC-E 1 of 6 (page 86 in the PDF) is titled, “Perioperative Systemic Therapy” and outlines the role of biomarker testing in early-stage NSCLC

PD-L1 and TMB

In 2024, College of American Pathologists, Association for Molecular Pathology, International Association for the Study of Lung Cancer, Pulmonary Pathology Society, and LUNGevity Foundation published guidelines covering PD-L1 and tumor mutation burden (TMB) testing in patients with lung cancer for selection of immune checkpoint inhibitor therapies.² These guidelines were developed to specifically address the following questions:

- In patients with advanced-stage NSCLC who are being considered for ICI therapy, does PD-L1 and TMB testing improve treatment response rates and survival rates?
- When selecting patients for anti-PD-1 and anti-PD-L1 therapy, does testing of different specimen types provide concordant clinical outcomes?
- Does the use of ICI therapy in patients with advanced NSCLC with targetable *ALK*, *EGFR*, *ROS1*, or *BRAF* molecular alterations affect their long-term clinical outcomes?
- When selecting patients for anti-PD-1 and anti-PD-L1 therapy, does TMB testing have the analytic validity to identify a complementary population who will benefit from therapy?
- In patients with NSCLC with more than 1 available sample, do multiple samples provide concordant PD-L1 and TMB testing results and downstream clinical outcomes?
- Does clinical validity of PD-L1 testing differ by levels of PD-L1 expression in tumor or immune cells?
- How reproducible are PD-L1 tumor cell scores and immune cell scores across specimen types?
- Do the available PD-L1 assays provide concordant expression profiles when evaluating the same sample, and which IHC expression cutoff provides the most reproducible expression categorization across the assays?



OTHER HELPFUL RESOURCES PUBLISHED BY NATIONAL SOCIETIES WITHIN THE PAST FEW YEARS:

- IASLC's Atlas of Molecular Testing for Targeted Therapy in Lung Cancer (latest version is 2023)
[iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer](https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer)
- AMP Molecular in My Pocket Oncology: Molecular Biomarkers of Lung Cancer (latest version is 2024)
amp.org/AMP/assets/File/education/MIMP/LungCancer.pdf

Avoiding Confusing Terminology: HER2 (ERBB2), MET, and c-Met Protein

For NSCLC, there are several biomarkers that may cause confusion:

- HER2 (*ERBB2*) may refer to HER2 protein overexpression, *HER2 (ERBB2)* gene amplification, or *HER2 (ERBB2)* activating mutation. When reporting HER2 (*ERBB2*), use clear language to reduce confusion.
- *MET* and c-Met protein (also called MET protein) also need to be clearly distinguished (gene vs. protein). Patients may have a *MET* exon 14 skipping mutation (detected by NGS) or they may have c-Met protein overexpression (detected by IHC) and different therapies are indicated for each situation.

See **Table 1** for a summary overview of *HER2 (ERBB2)* gene, HER2 protein, *MET* gene, and c-Met protein.

TABLE 1: GENE ALTERATIONS AND PROTEIN EXPRESSION

GENE ALTERATION (NGS TESTING)	PROTEIN EXPRESSION (IHC TESTING)	CLINICAL RELEVANCE (ADVANCED NSCLC) ⁶
<i>HER2 (ERBB2)</i>	HER2 protein	• <i>HER2 (ERBB2)</i> gene mutations are targetable with FDA-approved therapies: trastuzumab deruxtecan or zongertinib • HER2 protein overexpression is targetable with an FDA-approved therapy: trastuzumab deruxtecan
<i>MET</i>	c-Met protein (also called MET protein)	• <i>MET</i> exon 14 skipping mutations are targetable with FDA-approved therapies: capmatinib, tepotinib • High-level <i>MET</i> amplification may be an emerging biomarker in NSCLC⁶ • c-Met protein overexpression is targetable with an FDA-approved therapy: telisotuzumab vedotin-tliv

Most Common Gene Alterations in NSCLC

There are many specific types of alterations that may affect a gene, so look closely at the test report to see if the alteration is actionable (targetable) or if the alteration is of unknown significance. Some of the most common gene alterations found in NSCLC include *EGFR* and *KRAS* mutations. Oncologists will want to ensure the test reports indicate which alterations are actionable.

EGFR

Several types of *EGFR* mutations are targetable in advanced NSCLC including exon 19 deletion, p.L858R point mutation in exon 21, p.T790M point mutation in exon 20, exon 20 insertions, and others. Refer to the NCCN guidelines in NSCLC (page: NSCL-J) to see the list of *EGFR* mutations and biomarker-directed therapies. Examples of common targetable *EGFR* mutations:

- Exon 19 deletion or Exon 21 L858R
- S768I, L861Q, and/or G719X
- Exon 20 insertion

KRAS

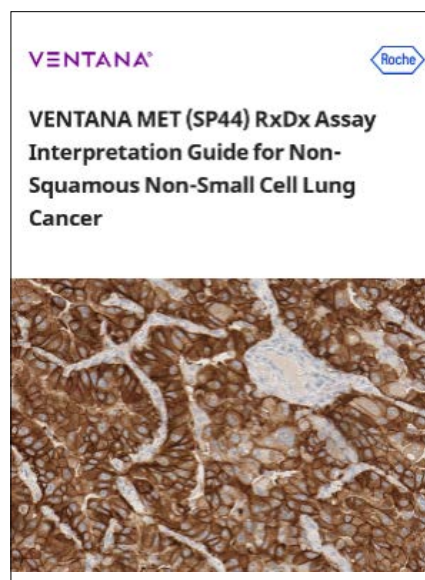
KRAS mutations are found in up to 30% of lung adenocarcinomas.³ G12C is the most common type of *KRAS* mutation found in NSCLC. Other common types include G12V and G12D. Currently, *KRAS* G12C is the only mutation that has FDA-approved targeted therapies for advanced NSCLC: adagrasib, sotorasib.

New: VENTANA MET (SP44) RxDx Assay for c-Met Protein

The VENTANA MET (SP44) RxDx Assay is the first FDA-approved immunohistochemistry (IHC) assay to identify patients with non-squamous, non-small cell lung cancer (NSQ-NSCLC) who are eligible for MET-targeted treatment with telisotizumab vedotin.

Review the package insert for more information about this test.⁴

- c-Met protein (also called MET protein) overexpression is found in approximately 25% of advanced EGFR wild-type NSQ-NSCLC⁵
- NSQ-NSCLC tissue cases are considered positive for MET protein overexpression status if $\geq 50\%$ of viable tumor cells demonstrate strong membranous and/or cytoplasmic staining⁹



Updated CAP Biomarker Reporting Templates

The College of Pathologists (CAP) Cancer Protocols provide guidance on collecting essential data elements for complete reporting. Synoptic reporting helps laboratories and hospitals comply with requirements for organizations like the American College of Surgeons Commission on Cancer, the CAP Laboratory Accreditation Program, and others.

These protocol templates can be found here: cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates

CAP also has a set of **Biomarker Reporting Protocols** that are intended to provide reporting guidance for commonly ordered biomarkers and are not required for accreditation purposes.

- The **Lung, Biomarker** reporting template was updated in September 2025: Updates/Additions to PD-L1, *BRAF*, *NTRK*, *NRG1*, and Tumor Mutational Burden sections. Note: The lung biomarker reporting template does not include c-Met protein overexpression.
- The **General IHC Quantitative Biomarkers** was updated in September 2025: Addition of optional Cold Ischemic Time, Fixative, and Fixation Time, Membranous Staining Intensity questions, and added responses for reporting internal controls

Biomarker Testing in Early-Stage NSCLC

Biomarker testing is also recommended in patients with early-stage resectable NSCLC. Oncologists use biomarker results when planning neoadjuvant and/or adjuvant systemic therapy.

In the NCCN guidelines for NSCLC, refer to the section titled, “Perioperative Systemic Therapy” to find the latest recommendation for biomarker testing in early-stage NSCLC. The current recommendation is to test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB-IIIa, IIIB).⁷

Healthcare Quality Domains

As the pathology community works to equip the laboratory to optimally perform biomarker testing in NSCLC, their work can be viewed across each domain of healthcare quality:⁶



SAFE

By providing accurate biomarker test results, laboratories will ensure that patients are being treated with the appropriate therapies that balance efficiency with adverse events

EFFECTIVE

Accurate test results will ensure that patients who are eligible for targeted therapies are identified and offered treatment

PATIENT-CENTERED

Providing personalized cancer care is respectful of and responsive to individual patient preferences, needs, and values and ensures that patient values guide clinical decisions

TIMELY

Establishing standardized biomarker testing protocols for early vs. advanced-stage NSCLC may reduce delays

EFFICIENT

Avoiding waste, such as excessive or redundant testing in patients who may have already received testing elsewhere or who may not be candidates for treatment

EQUITABLE

Ensuring that the decision to test is not impacted by characteristics such as gender, ethnicity, geographic location, socioeconomic status, or any other patient factor that may contribute to healthcare disparities

CME/CMLE Activities from ASCP

ASCP has developed the following free CME/CMLE activities on NSCLC biomarker testing for pathologists and laboratory professionals:



Current
NSCLC
Biomarker
Testing
Guidelines

Equity of
Biomarker
Testing in
NSCLC

Optimizing
Sample Sizes
for NSCLC
Biomarker
Testing

Optimizing
Testing in the
Laboratory with
a Special Focus
on Antibody
Validation

Summary

This resource guide provides a quick overview of the rapidly evolving landscape of biomarker testing in NSCLC and highlights several recent changes including new FDA and new biomarkers. The guide outlines a few ways to reduce the use of confusing terminology and summarizes updates from clinical practice guidelines and CAP reporting templates. ASCP has also launched several CME/CMLE resources to support pathologists and laboratory professionals for developing safe, effective, patient-centered, timely, efficient, and equitable biomarker processes to patients with early-stage and advanced NSCLC.

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