An APP Guide to Optimal Integration of Biomarker Testing: Non-Small-Cell Lung Cancer

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Rationale for Molecular Testing in Lung Cancer

Molecular Testing for Early NSCLC

- Molecular testing should be performed early in resectable non-small-cell lung cancer (NSCLC) when perioperative systemic therapy is being considered, particularly for nonsquamous tumors and stage IB-IIIB disease, because *EGFR*, ALK, and PD-L1 results can inform treatment selection.[1-4]
- Core early-stage biomarkers include *EGFR* exon 19 deletion/exon 21 L858R, *ALK* fusions, and PD-L1 expression; broader profiling may be useful when tissue is adequate to support trial eligibility or future treatment planning.[1,2,5]
  - Healthcare professionals should avoid starting perioperative immunotherapy before receiving *EGFR* or *ALK* results in a clinically stable patient because perioperative immunotherapy and targeted-therapy pathways differ by driver status.[1-8]
  - For adjuvant atezolizumab use, a PD-L1 expression level of ≥1% may be useful in determining patient eligibility for this agent in the early/adjuvant setting.[1,2]
- If tissue is limited, testing should prioritize biomarkers that inform immediate perioperative decisions.[1,5]
  - Recent data presented at the American Society of Clinical Oncology (ASCO) 2026 Annual Meeting suggest that *RET* testing may soon be considered in the early-stage setting for the use of adjuvant selpercatinib in patients with *RET*-positive tumors.[9-11]

Molecular Testing for Advanced or Metastatic NSCLC

- Broad molecular testing should be ordered early for eligible patients with advanced or metastatic NSCLC, particularly nonsquamous disease, because actionable driver alterations can determine the preferred first-line systemic therapy.[1-6]
- Current routine biomarkers relevant to treatment selection include *EGFR* sensitizing mutations and *EGFR* exon 20 insertion mutations, *ALK, ROS1, BRAF* V600E, *MET* exon 14 skipping, *RET, NTRK, KRAS* G12C, *HER2* (ERBB2) activating mutations, and PD-L1 expression.[1-6]
  - PD-L1 expression remains key for immunotherapy selection when no targetable driver is present, but PD-L1 positivity alone should not override pending broad molecular results in a clinically stable patient.[1,6,7]
  - If tissue is limited or results are needed quickly, plasma testing can complement tissue testing; a negative plasma result does not exclude an actionable alteration and should prompt tissue testing when feasible.[1-6]
  - For second-line and beyond NSCLC therapy planning, immunohistochemistry-based markers may include PD-L1 tumor proportion score, HER2 3+, and high c-MET expression, defined as 3+ staining in ≥50% of tumor cells.

Approximate Incidence of Actionable Biomarkers in NSCLC (2026)

Early-Stage NSCLC (Stage IB-IIIA/IIIB): Biomarkers With FDA-Approved Therapies

EGFR classic mts	*ALK* fusions
~10% to 15%	~2% to 7%

For adjuvant TKI, avoid neoadjuvant ICI

Advanced-Stage NSCLC: Biomarkers With FDA-Approved Therapies

EGFR ex18-21 mts	*EGFR* exon 20 ins	*ALK* fusions	*ROS1* fusions	*BRAF* V600E	*RET* fusions
~10% to 20%	~1% to 2%	~3% to 7%	~1% to 2%	~1% to 2%	~1% to 2%

MET ex14 skip	*KRAS** G12C	*NRG1* fusions	*NTRK1/2/3* fusions	*ERBB2* mutations
~2%-4%	~8% to 15%	<1%	<1%	~1% to 4%

*Second-line and beyond therapies.

Genomic/molecular alterations

Other Considerations Affecting Molecular Testing

Report on Available Biomarkers

- A complete NSCLC report should be tailored to disease stage and treatment context: For resectable, early-stage disease (stage IB-IIIB), it should at a minimum include *EGFR* sensitizing mutations, *ALK* gene alterations, and PD-L1 status. For metastatic disease, a report should address *EGFR* sensitizing mutations, *EGFR* exon 20 insertion, *ALK, ROS1, BRAF* V600E, *MET* exon 14 skipping, *RET, NTRK, KRAS* G12C, *HER2* (ERBB2) activating mutations, and PD-L1. Some broad panels also report *MET* amplification and additional resistance or comutation findings.[1-8]
  - *PIK3CA* mutations may appear on broad panels as co-occurring or resistance associated events; they are biologically relevant but do not currently establish routine standard targeted therapy in NSCLC.[1,12]
  - If a report is unclear or incomplete, healthcare professionals should confirm whether testing is still pending, whether a plasma-negative result requires tissue follow-up, and whether any detected alteration should change treatment timing, sequencing, monitoring, or referral.[1-6]
  - Although RET-directed therapy is not yet approved as adjuvant treatment for early-stage NSCLC, the phase III LIBRETTO-432 data recently showed that selpercatinib significantly improved event-free survival (EFS) vs placebo in stage II-IIIA RET-positive NSCLC, with median EFS not reached vs 31.8 months and 2-year EFS of 91.5% vs 61.1%.[9,10]

A Suggested Biomarker Testing Workflow in Lung Cancer: When Should Biomarker Testing Occur in NSCLC?

Who?	Why?	When?	What?	How?
Patients with **early-stage NSCLC or advanced/ metastatic NSCLC**	**Personalize** treatments	At **diagnosis,** before systemic therapy, **upon confirmation of systemic disease**	**EGFR, ALK, PD-L1** at minimum for early-stage disease; **expanded multigene panel** for advanced disease	**Broad-panel NGS** and **IHC** are optimal

Early-Stage Testing in NSCLC

Biomarker result	Neoadjuvant planning	Surgery	Adjuvant planning
***EGFR* sensitizing mutation or *ALK* rearrangement**	**Perioperative IO generally not preferred when driver status is know**	Surg	**Adjuvant targeted therapy may be indicated; chemo as appropriate**
***EGFR/ALK* wild type**	**Neoadjuvant chemo-IO may be considered**	Surg	**PD-L1 helps inform select adjuvant IO options**
Other actionable or emerging drivers	**Consider clinical trials; IO benefit may be less certain for some drivers**	Surg	**Clinical trial or standard postoperative options by stage and risk**

Broad Testing for Advanced or Metastatic NSCLC

Order Early	Check Specimen	Wait if Stable	Reflex as Needed	Act on Results
Broad molecular testing + PD-L1 before first-line therapy when feasible	Tissue adequacy; DNA/RNA coverage; need for plasma ctDNA	Hold first-line selection when driver results could change treatment choice	Use tissue to confirm negative or incomplete plasma testing	Match alteration, histology, PD-L1, stage, therapy, and trials

If urgent symptoms require treatment
Use symptom-directed care or selected chemotherapy-based bridging while testing continues

Minimum metastatic report
EGFR including exon 20, *ALK, ROS1, BRAF* V600E, *MET* exon 14, *RET, NTRK, KRAS* G12C, HER2/ERBB2, and PD-L1

Clinical point: PD-L1 should inform immunotherapy only after actionable driver status is accounted for whenever clinically feasible

- Biomarker testing should be obtained for all patients with newly diagnosed early-stage NSCLC who are candidates for neoadjuvant/adjuvant therapy and initiated as soon as advanced or metastatic NSCLC is diagnosed or strongly suspected; testing should be completed promptly enough to guide first-line treatment before systemic therapy begins whenever clinically feasible.[1-6]
  - The ASCO, National Comprehensive Cancer Network, and European Society for Medical Oncology guidelines favor broad multigene profiling rather than sequential single-gene testing when possible, with PD-L1 immunohistochemistry ordered in parallel because both genomic and immune biomarkers may influence treatment selection.[1-3]
  - Patients should be assessed early enough in the disease course to avoid losing the opportunity for biomarker-matched first-line therapy or clinical trial referral.[1-4]

Identifying Adequate Tissue and RNA Coverage

- Plan biopsy with enough material for histology, PD-L1, and DNA/RNA testing for actionable mutations
- Limited or exhausted tissue may require repeat biopsy or plasma testing[1-7]

Turnaround time and reflex plasma testing

Plasma ctDNA can speed detection of actionable alterations when tissue is limited or results are urgent, but tissue should follow if plasma is negative or incomplete[1-7]

Treatment Timing in Stable vs Urgent Patients

- If the patient is clinically stable, first-line systemic therapy should usually wait for molecular results
- If urgent symptoms require intervention, symptom-directed management or short bridging strategies may be used while testing continues[1,6,7]

Report Interpretation

Confirm the exact alteration, specimen source, assay type, PD-L1 score, and whether each finding is actionable, resistance related, or a variant of uncertain significance before counseling on treatment implications[1-7]

Treatment Implications for Available Biomarkers in Lung Cancer

- In resected or locally advanced disease, the presence of select biomarkers influences perioperative and adjuvant therapy decisions; in advanced or metastatic NSCLC, biomarker testing results are central to first-line therapy selection and later-line sequencing.[1-3,7-26]
- For patients without an actionable biomarker, systemic therapy selection depends on histology, PD-L1 expression, disease burden, contraindications, and patient goals.[1-3]
- If treatment must begin before complete molecular results are available, chemotherapy-based bridging therapy may be considered in select symptomatic patients, but immunotherapy is generally deferred until key driver results are known when a targetable alteration is plausible.[1-3]

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