

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, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Q: How is the strength of recommendation determined in the new molecular testing guideline?

A: The strength of recommendation is determined by the strength of the available data (evidence).

Strong Recommendation: Supported by convincing or adequate quality of data and clear benefit that outweighs any harms.

Recommendation: Some limitations in quality of evidence (adequate or inadequate), balance of benefits and harms, values or costs, but panel concludes that there is sufficient data to recommend.

Expert Consensus Opinion: Serious limitations in quality of evidence (inadequate or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary.

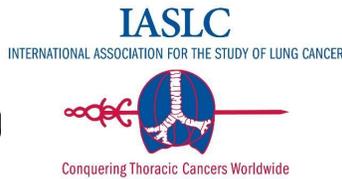
No Recommendation: Insufficient evidence, confidence, or agreement to provide a consensus recommendation at this time.

Q: Does the guideline recommend therapy based on the molecular testing results?

A: The purpose of the guideline is to set the standards for the molecular analysis of lung cancers in order to guide targeted therapy treatment decisions based on the molecular results. Targeted tyrosine kinase inhibitor (TKI) therapy provides significant improvement in survival and quality of life for those patients whose tumors harbor certain specific molecular alterations. Guidelines and consensus statements are supported by the best available evidence and expert consensus and they are intended to assist physicians and patients in clinical decision-making. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient.

Q: The guideline mentions testing only for advanced stage patients. How is advanced stage defined?

A: Advanced stage is defined as those patients with stage IIIB (lymph node involvement i) on the opposite side of the chest from the affected lung, ii) above the collarbone, iii) or at the top of the lung; or stage IV (distant metastasis) lung cancer.



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Q: Does the guideline recommend molecular testing on early stage lung cancer patients?

A: Molecular testing of tumors at diagnosis from patients presenting with early stage disease is encouraged, as per expert consensus opinion, but the decision to do so should be made locally by each laboratory, in collaboration with its multidisciplinary oncology team.

Q: Have any new genes been added to the new molecular testing guideline?

A: *ROS1* testing is strongly recommended and must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics.

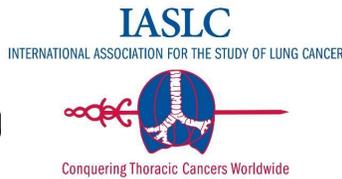
BRAF, *RET ERBB2 (HER2)*, *MET* and *KRAS* molecular testing are not currently indicated as routine stand-alone tests outside the context of a clinical trial; however, the expert consensus opinion is that it is appropriate to include these as either part of larger testing panels performed initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.

Q: Why is *BRAF* not included in the “must-test” list of genes?

A: The published evidence available at the time of publication lacked controlled prospective trials and, therefore, lacked the strength to warrant an international recommendation for single-gene *BRAF* testing for all lung adenocarcinoma patients. It is anticipated that the next revision of this guideline will include a recommendation to include single-gene testing for *BRAF* alongside *EGFR*, *ALK*, and *ROS1*, as the publication of stronger evidence supporting the utility of *BRAF* inhibition in *BRAF*-mutant lung cancer is expected.

Q: *EGFR* and *ALK* testing was recommended in the 2013 guideline - does this change in the new 2018 guideline?

A: There is currently sufficient evidence to support a strong recommendation that physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients, irrespective of clinical characteristics, at the time of diagnosis for patients presenting with advanced stage disease, or at progression in patients who originally presented with lower stage disease but were not previously tested.



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Q: Does the guideline recommend next generation sequencing (NGS) for molecular testing?

A: The expert consensus opinion is that multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*. NGS enables the simultaneous assessment of all three of the "must test" genes in lung cancer - *EGFR*, *ALK*, *ROS1* - as well as each of the genes suggested for inclusion in larger panels - *BRAF*, *RET*, *ERBB2(HER2)*, *KRAS*, *MET* - and hundreds of other genes that may have potential roles in cancer development. In addition to small mutations, NGS assays have the capability to detect fusions/rearrangements and copy number changes in the examined genes. NGS also enables the use of small specimens (e.g., fine needle aspirates) that are standard of care and help avoid the risks to the patient associated with obtaining surgical biopsies.

Q: Is it acceptable to use plasma for initial diagnosis of molecular abnormalities?

A: In some clinical settings, tissue-based *EGFR* analysis cannot be performed because either tissue biopsy material is unavailable or insufficient or tissue re-biopsy is not feasible. In these situations, a cell-free DNA assay to identify activating *EGFR* mutations is recommended as an alternative molecular diagnostic procedure.

Q: According to the guideline, are cytology specimens suitable for molecular testing?

A: Pathologists may utilize either cell blocks or other cytologic preparations, like a smear, with adequate cellularity and preservation for lung cancer biomarker molecular testing.

Q: Does the guideline recommend immunohistochemistry for *ALK* fusion testing?

A: Immunohistochemistry is recommended as an equivalent alternative to fluorescent *in situ* hybridization (FISH) for *ALK* testing.

Q: Does the guideline recommended immunohistochemistry for *ROS1* fusion testing?

A: As an expert consensus opinion, *ROS1* immunohistochemistry may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive *ROS1* immunohistochemistry results should be confirmed by a molecular or cytogenetic method.



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Q: Is using immunohistochemistry to determine *EGFR* gene amplification or total protein expression appropriate according to the guideline?

A: It is strongly recommended that total *EGFR* expression analysis by immunohistochemistry should not be used to select patients for *EGFR*-targeted tyrosine kinase inhibitor therapy. In addition, it is recommended that *EGFR* copy number [AN1] analysis should not be used to select patients for *EGFR*-targeted tyrosine kinase inhibitor therapy.

Q: Can mutation specific immunohistochemistry antibodies be used to test for mutations within the *EGFR* gene?

A: Overall, the performance *EGFR* mutation-specific antibodies are suboptimal for reliable detection of *EGFR* mutations. Given that advances in molecular diagnostic technology now enable analysis of very limited samples as well as circulating tumor DNA, at this time there is no role for routine use of mutant-specific immunohistochemistry in selecting anti-*EGFR* treatment for lung cancer patients.

Q: According to the guideline, should patients that progress or relapse on targeted therapy have a new molecular test done on their tumor? Which genes should be analyzed?

A: It is strongly recommended that in lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an *EGFR*-targeted tyrosine kinase inhibitor, *EGFR* T790M mutation testing should be used to guide selection of treatment with third generation *EGFR* inhibitors. Laboratories testing for *EGFR* T790M mutation in patients with secondary clinical resistance to *EGFR*-targeted kinase inhibitors are recommended to use assays capable of detecting these mutations in as little as 5% of viable cells.

There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for lung adenocarcinoma patients with sensitizing *ALK* mutations who have progressed after treatment with an *ALK*-targeted tyrosine kinase inhibitor. As more patients experience resistance and receive second-generation inhibitors, future data may show an association between secondary mutation and sensitivity/resistance to different inhibitors.



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Q: For patients that progress or relapse, is a re-biopsy required or is plasma circulating cell-free DNA suitable for molecular testing?

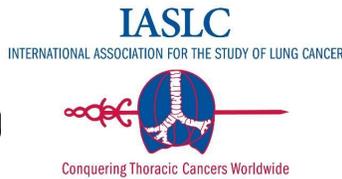
A: The expert consensus opinion is that physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to *EGFR*-targeted tyrosine kinase inhibitors; however, testing of a re-biopsy of the tumor sample is recommended if the plasma result is negative.

Q: Should patients with squamous cell carcinoma of the lung or small cell lung cancer have molecular testing performed on their tumor?

A: Stringent reliance upon adenocarcinoma histology may occasionally exclude some patients (those without a definitive diagnosis of adenocarcinoma) from the potential benefits of a targeted therapy, particularly for small biopsies that only partially sample a larger tumor. The expert consensus opinion is that physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features, like young age and absence of tobacco exposure, indicate a higher likelihood of a targetable mutation.

Q: What is the role of testing to select patients for treatment with immunomodulatory therapies like the checkpoint inhibitors for PD-1 or PD-L1?

A: This topic was not subject to the systematic review of evidence because the prominence of immunotherapies became apparent after developing the key questions and beginning the systematic review process. However, the expert panel decided to issue an opinion statement addressing this important question, aware that separate efforts are currently underway to develop evidence-based recommendations regarding the use of biomarkers to select patients for immunomodulatory therapies. The opinion expressed is that samples should be preserved for assessment of biomarkers that predict response to immunomodulatory therapies, in accordance with the labeling requirements of the drugs under consideration.



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Q: How will the guideline be enforced? What happens if a laboratory doesn't follow the guideline?

A: As with any evidence-based clinical practice guideline, following this guideline is not mandatory. These recommendations may be added to future versions of your laboratory's accreditation requirements; however, they are not currently required by any regulatory accrediting agency unless as previously defined in CLIA. It is encouraged however, that laboratories adopt these high-level evidence-based recommendations.

Q: Are there plans to update the guideline again in the future?

A: Collectively, all three organizations look forward to the continuing evolution in diagnostics and care for lung cancer patients as technology, scientific understanding, and clinical practice evolve. Since these recommendations represent current best practice in a rapidly developing field, we anticipate a need for additional updates in the future.

References:

Lindeman NI, Cagle PT, Aisner DL et al. 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 [published online January 22, 2018]. *Arch Pathol Lab Med*. doi: [10.5858/arpa.2017-0388-CP](https://doi.org/10.5858/arpa.2017-0388-CP)

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