COLLEGE of AMERICAN PATHOLOGISTS

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

AMP ASSOCIATION FOR MOLECULAR PATHOLOGY

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Statements and Strength of Recommendations

Summary of Recommendations

Guideline Statement		Strength of Recommendation
Key Question 1: Which new genes should be tested for lung cancer patients?		
1.	*ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics.	Strong Recommendation
2.	ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.	Expert Consensus Opinion
3.	*BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK,* and *ROS1* testing are negative.	Expert Consensus Opinion
4.	*RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are negative.	Expert Consensus Opinion
5.	*ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are negative.	Expert Consensus Opinion
6.	*KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are negative.	Expert Consensus Opinion
7.	*MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK,* and *ROS1* testing are negative.	Expert Consensus Opinion
Key Question 2: What methods should be used to perform molecular testing?		
8.	IHC is an equivalent alternative to FISH for ALK testing.	Recommendation
9.	Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK*, and *ROS1*.	Expert Consensus Opinion
10.	Laboratories should ensure test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved using an alternative method or sample.	Expert Consensus Opinion

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Summary of Recommendations continued

Guideline Statement		Strength of Recommendation
Key Question 3: Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?		
11.	Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.	Expert Consensus Opinion
Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?		
12.	In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use *EGFR* T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.	Strong Recommendation
13.	Laboratories testing for *EGFR* T790M mutation in patients with secondary clinical resistance to EGFR-targeted kinase inhibitors should deploy assays capable of detecting *EGFR* T790M mutations in as little as 5% of viable cells.	Recommendation
14.	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 TKI.	No Recommendation
Key Question 5: What is the role of testing for circulating cell-free DNA for lung cancer patients?		
15.	There is currently insufficient evidence to support the use of circulating cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma.	No Recommendation
16.	In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify *EGFR* mutations.	Recommendation
17.	Physicians may use cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKI; testing of the tumor sample is recommended if the plasma result is negative.	Expert Consensus Opinion
18.	There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI resistance.	No Recommendation

Abbreviations: ROS1, ROS Proto-Oncogene 1, Receptor Tyrosine Kinase; IHC, Immunohistochemistry; BRAF, B-Raf Proto-Oncogene, Serine/Threonine Kinase; EGFR, Epidermal Growth Factor Receptor; ALK, RET, Ret Proto-Oncogene; ERBB2, Erb-B2 Receptor Tyrosine Kinase 2; HER2, human epidermal growth factorreceptor 2; KRAS, MET, MET Proto-Oncogene, Receptor Tyrosine Kinase; FISH, fluorescence *in situ* hybridization; TKI, tyrosine kinase inhibitors; cfDNA, cell-free plasma DNA

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Summary of Recommendations continued

Summary of the Updated Statements with Strength of Recommendations	
2013 Statements	**2017 Statements**
Expert Consensus Opinion: Cytologic samples are also suitable for *EGFR* and *ALK* testing, with cell blocks being preferred over smear preparations.	Recommendation: Pathologists may use either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.
Expert Consensus Opinion: Laboratories should use *EGFR* test methods that are able to detect mutations in specimens with at least 50% cancer cell content, although laboratories are strongly encouraged to use (or have available at an external reference laboratory) more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells.	Expert Consensus Opinion: Laboratories should use, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells.
Recommendation: IHC for total EGFR is not recommended for selection of EGFR TKI therapy.	Strong Recommendation: Laboratories should not use total EGFR expression by IHC testing to select patients for EGFR-targeted TKI therapy.

Abbreviations: EGFR, Epidermal Growth Factor Receptor; ALK, IHC, Immunohistochemistry; TKI, tyrosine kinase inhibitors

Note: A listing of the reaffirmed and updated 2013 guideline statements can be found in Table 4b of the supplemental digital content.

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. *Arch Pathol Lab Med*. 2018;142(3):321-346. doi: 10.5858/arpa.2017-0388-CP

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