ASCO Guidelines

Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists /International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update	
Clinical Question	**CAP/IASLC/AMP Recommendation with ASCO Qualifying Statements in *Bold Italics***
2013 Recommendations that were Reaffirmed or Updated for 2018	Expert consensus opinion: Pathologists may utilize either cell blocks or ***smear*** preparations as suitable specimens for lung cancer biomarker molecular testing.
	Expert consensus opinion: Laboratories should employ, 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
	Strong Recommendation: Laboratories should not use EGFR expression by IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.
	Recommendation: Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection
	Recommendation: Pathologists and laboratories should not use EGFR copy number analysis (i.e., FISH or CISH) to select patients for EGFR-targeted tyrosine kinase inhibitor therapy
New 2018 Recommendations	
Which genes should be tested for lung cancer patients?	Recommendation: *ROS1* testing should be performed on all advanced lung adenocarcinoma patients, irrespective of clinical characteristics.
	Expert Consensus Opinion: ROS1 IHC may be used as a screening test in advanced lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.
	Expert Consensus Opinion: ***BRAF testing should be performed on all advanced lung adenocarcinoma patients, irrespective of clinical characteristics.***
	Expert Consensus Opinion: *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*, ***BRAF,*** and *ROS1* testing is negative.

Reprinted from 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. doi: 10.5858/arpa.2017-0388-CP, published online ahead of print November 2017, with permission from Archives of Pathology & Laboratory Medicine. Copyright 2017 College of American Pathologists.

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	Expert Consensus Opinion: *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,* ***BRAF,*** and *ROS1* testing is negative.
	Expert Consensus Opinion: *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*, ***BRAF,*** and *ROS1* testing is negative.
	Expert Consensus Opinion: *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,* ***BRAF,*** and *ROS1* testing is negative.
What methods should be used to perform molecular testing?	Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to FISH for ALK testing. *CAP/IASLC/AMP Qualifying Statement: ALK IHC is an acceptable* ***standard*** *alternative to FISH and treatment decisions can be made when IHC results are clearly positive, as manifested by strong granular cytoplasmic staining with/without membrane accentuation, or negative; however, weak staining can be challenging to interpret, and the specificity of weak staining relative to FISH should be determined in each laboratory during validation.*
	Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred ***where available*** over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK,* ***BRAF*** and *ROS1*.
	Expert Consensus Opinion: 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.
Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?	Expert Consensus Opinion: Physicians may use molecular biomarker testing in tumors with: a. ***an adenocarcinoma component;*** b. ***non-squamous, non-small cell histology;*** c. any non-small cell histology when clinical features indicate a higher probability of an oncogenic driver *(e.g. young age (<50 years); light or absent tobacco exposure).*

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What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?	Strong Recommendation: In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted tyrosine kinase inhibitor, physicians must use *EGFR* T790M mutational testing when selecting patients for third generation EGFR-targeted therapy.
	Recommendation: 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.
	No Recommendation: 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.
What is the role of testing for circulating, cell-free DNA, for lung cancer patients?	No Recommendation: There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma
	Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay to identify EGFR mutations.
	Expert Consensus Opinion: 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; testing of the tumor sample is recommended if the plasma result is negative.
	No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell (CTC) 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.

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