COLLEGE of AMERICAN PATHOLOGISTS

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INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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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

What is the Purpose of the Guideline?

- **The guideline sets 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.**

- **Guideline 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.**

- **However, 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.**

Why Revise the Guideline?

The original guideline, *Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK 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,* was published in 2013.

There is a continuous, rapid flow of information and new evidence being published on:

- New therapies
- New biomarkers for targeted therapies
- Advances in current and new technologies

Existing guidelines must be updated periodically.

- National Guideline Clearinghouse: ≥5 years without an update is considered a guideline that is no longer current

Content of the Updated Guideline

New evidence supporting or refuting the original 2013 guideline was reviewed and used to reaffirm, modify the strength of, or change entirely the recommendations.

The revision focuses on new recommendations in five specific content areas:

1) Which new genes should be tested for lung cancer patients?
2) What methods should be used to perform molecular testing?
3) Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?
4) What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?
5) What is the role of testing for circulating cell free DNA for lung cancer patients?

Content of the Updated Guideline

- The role of diagnostic support for immunomodulatory therapies emerged after the revision process was significantly underway.

- While this topic was not subject to the systematic review of evidence, the expert panel issued an opinion statement regarding the use of biomarkers to select patients for immunomodulatory therapies.

Biomarker Categories

Biomarkers in this guideline are stratified into three categories:

- The first are "must test" biomarkers, which are standard-of-care for all patients with advanced lung cancer with an adenocarcinoma component who are being considered for an approved targeted therapy.

- Second are "should test" biomarkers, which are used to direct patients to clinical trials and which should be included in any large sequencing panel that is performed for lung cancer patients, but which are not required for laboratories that only perform single gene assays.

- All remaining candidate biomarkers are "investigational," and are therefore not recommended for routine clinical use at this time.

Grades for Strength of Recommendations

Designation	Recommendation	Rationale
Strong Recommendation	Recommend for or against a particular molecular testing practice for lung cancer (can include “must” or “should”).	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms.
Recommendation	Recommend for or against a particular molecular testing practice for lung cancer (can include “should” or “may”).	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation.
Expert Consensus Opinion	Recommend for or against a particular molecular testing practice for lung cancer (can include “should” or “may”).	Serious limitations in quality of evidence (inadequate [low, very low] or insufficient), balance of benefits and harms, values or costs but panel consensus is that a statement is necessary.
No Recommendation	No recommendation for or against a particular molecular testing practice for lung cancer.	Insufficient evidence or agreement of the balance of benefits and harms, values or costs to provide a consensus recommendation at this time.

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2013 vs 2018 Grades for Strength of Recommendations

Rationale	2013 Recommendation Designation	2018 Recommendation Designation
Convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms.	Recommendation	Strong Recommendation
Adequate (intermediate) or inadequate (low) quality of evidence with balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation.	Recommendation	Recommendation
Inadequate (low) or insufficient evidence with balance of benefits and harms, values or costs but panel consensus that a statement is necessary .	Suggestion	Expert Consensus Opinion
Inadequate (very low) or insufficient evidence quality evidence, with balance of benefits and harms, values or costs but panel consensus that a statement is necessary.	Expert Consensus Opinion	Expert Consensus Opinion
Insufficient evidence, confidence or agreement of the balance of benefits and harms, values or costs to provide a consensus recommendation at this time.	Expert Consensus Opinion	No Recommendation

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Reaffirmed 2013 Recommendation Statements

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.

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

Updated 2013 Recommendation Statements

Strong Recommendation: Physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients 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.

Recommendation: Pathologists may utilize either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.

Updated 2013 Recommendation Statements

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 total EGFR expression by IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.

Recommendation: Laboratories should not use *EGFR* mutation specific IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.

New Recommendation Statements

Key Question 1: Which new genes should be tested for lung cancer patients?

Strong Recommendation: *ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics.

Expert Consensus Opinion: *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: *RET* molecular testing is currently not indicated 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.

New Recommendation Statements

Key Question 1: Which new genes should be tested for lung cancer patients?

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)* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are 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*, and *ROS1* testing are 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*, and *ROS1* testing are negative.

New Recommendation Statements

Key Question 2: What methods should be used to perform molecular testing?

Expert Consensus Opinion: *ROS1* IHC may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive *ROS1* IHC results should be confirmed by a molecular or cytogenetic method.

Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to FISH for *ALK* testing.

Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, 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.

New Recommendation Statements

Key Question 3: 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 histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.

New Recommendation Statements

Key Question 4: 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 TKI, 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.

New Recommendation Statements

Key Question 5: 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.

New Recommendation Statements

Key Question 5: What is the role of testing for circulating cell-free DNA for lung cancer patients?

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.

Emerging Markers for Molecular Testing in Lung Cancer

Mitogen-Activated Protein Kinase Kinase 1 (*MEK1/MAP2K1*)
Fibroblast Growth Factor Receptor 1-4 (*FGFR 1-4*)
Neurotrophic Tyrosine Kinase, Receptor, Type 1 – 3 (*NTRK1-3*)
Neuregulin 1 (*NRG1*)
Ras-Like Without CAAX 1 (*RIT1*)
Neurofibromin 1 (*NF1*)
Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (*PIK3CA*)
AKT Serine/Threonine Kinase 1 (*AKT1*)
NRAS Proto-Oncogene, GTPase (*NRAS*)
Mechanistic Target Of Rapamycin (*MTOR*)
Tuberous Sclerosis 1 (*TSC1*)
Tuberous Sclerosis 2 (*TSC2*)
KIT Proto-Oncogene Receptor Tyrosine Kinase (*KIT*)
Platelet Derived Growth Factor Receptor Alpha (*PDGFRA*)
Discoidin Domain Receptor Tyrosine Kinase 2 (*DDR2*)

What is the role of testing to select patients for treatment with immunomodulatory therapies?

Opinion: Samples should be preserved for assessment of biomarkers that predict response to immunomodulatory therapies (e.g., *PD-1* and *PD-L1*), in accordance with the labeling requirements of the drugs under consideration.

Because of the lack of firm evidence supporting specific methodology or agents, we cannot make evidence-based recommendations regarding testing for these drugs in this guideline.

A subsequent practice guideline is being planned to focus specifically on evidence-based assessment of methods for selecting patients to receive immunomodulatory therapies.

Guideline Development Team

Co-Chairs

Philip T. Cagle, MD (CAP)

Yasushi Yatabe, MD, PhD (IASLC)

Neal I. Lindeman, MD (AMP)

Expert Panel Members

CAP: Keith Kerr, MD, Mary Beth Beasley, MD, Sanja Dacic, MD, PhD, & Eric Bernicker, MD

IASLC: Erik Thunnissen, MD, PhD, Marc Ladanyi, MD, Ming S. Tsao, MD, & Benjamin Solomon, MBBS, PhD

AMP: Dara L. Aisner, MD, PhD, Lynette Sholl, MD, Maria E. Arcila, MD & David J. Kwiatkowski, MD, PhD

Steering Committee

Jan A. Nowak, MD, PhD (CAP), Fred R. Hirsch, MD, PhD (IASLC),

Neal I. Lindeman, MD (AMP)

Advisory Panel Members

David Yankelevitz, MD
Mark G. Kris, MD
Anthony John Iafrate, MD, PhD
Tony Mok, MD
Charles A. Powell, MD
Dhananjay Chitale, MD
Timothy Allen, MD, JD
Pasi Jänne, MD, PhD
Lukas Bubendorf, MD
Juan-Sebastian Saldivar, MD
Antonio Marchetti, MD
Ed Cibas, MD
Paul A. Bunn, Jr. MD
Suresh Ramalingam, MD
Natasha Rekhtman, MD, PhD
Federico Cappuzzo, MD, PhD
Tetsuya Mitsudomi, MD
Yi-long Wu, MD
Bonnie Addario
Kim Norris
Julia Bridge, MD
Marina Nikiforova, MD
Marileila Varella Garcia, PhD

Staff

Christina Ventura, MLS (ASCP) - CAP
Lisa Fatheree, SCT(ASCP) – CAP
Carol Colasacco, MLIS, SCT(ASCP) - CAP
Murry Wynes, PhD - IASLC
Pia Hirsch - IASLC
Robyn Temple-Smolkin, PhD – AMP
Mrudula Pullambhatla, MS - AMP
Lesley Souter, PhD - Methodologist

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