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SPECIAL ARTICLE

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

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Context: In 2013, an evidence-based guideline was published by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology to set standards for the molecular analysis of lung cancers to guide treatment decisions with targeted inhibitors. New evidence has prompted an evaluation of additional laboratory technologies, targetable genes, patient populations, and tumor types for testing.

Objective: To systematically review and update the 2013 guideline to affirm its validity; to assess the evidence of new genetic discoveries, technologies, and therapies; and to issue an evidence-based update.

Design: The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology convened an expert panel to develop an evidence-based guideline to help define the key questions and literature search terms, review abstracts and full articles, and draft recommendations.

Results: Eighteen new recommendations were drafted. The panel also updated 3 recommendations from the 2013 guideline.

Conclusions: The 2013 guideline was largely reaffirmed with updated recommendations to allow testing of cytology samples, require improved assay sensitivity, and recommend against the use of immunohistochemistry for EGFR testing. Key new recommendations include *ROS1* testing for all adenocarcinoma

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patients; the inclusion of additional genes (*ERBB2, MET, BRAF, KRAS*, and *RET*) for laboratories that perform next-generation sequencing panels; immunohistochemistry as an alternative to fluorescence *in situ* hybridization for ALK and/or ROS1 testing; use of 5% sensitivity assays for *EGFR* T790M mutations in patients with secondary resistance to EGFR inhibitors; and the use of cell-free DNA to "rule in" targetable mutations when tissue is limited or hard to obtain. *(J Mol Diagn 2018, 20: 1—30; https://doi.org/10.1016/j.jmoldx.2017.11.004)*

Patients with advanced lung cancer have a poor prognosis, with a median survival of 1 year. However, for many patients whose tumors harbor certain specific molecular alterations (eg, activating alterations in the *EGFR, ALK*, and *ROS1* genes), particularly in lung adenocarcinoma, targeted tyrosine kinase inhibitor (TKI) therapy provides significant improvement in survival and quality. Accordingly, patients with the types of advanced lung cancer in which these targetable molecular alterations typically occur should receive the molecular testing required to identify them, and thereby receive appropriate targeted treatments. Importantly, this testing should extend beyond those molecular alterations for which targeted therapies are approved by regulatory agencies such as the US Food and Drug Administration (FDA) to include molecular alterations for which there is compelling evidence of effective investigational targeted therapies (and, more recently, immunotherapies) from published clinical trials.

In 2010, 3 professional societies—the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP)—recruited specialists in the biology, diagnosis, and treatment of lung cancer to form a joint working group to systematically assess the evidence supporting the clinical utility of molecular analysis of lung cancer samples. In 2013, this working group published an evidence-based guideline[1—3] for standard-of-care clinical practice concerning which lung cancer patients and samples should be tested, which genes should be tested, and how these tests should be designed, validated, and executed. This guideline was subsequently endorsed by the American Society of Clinical Oncology,[4] and has been cited in guidelines developed by numerous professional societies around the world.[5—26] However, the field has continued to advance rapidly, with the emergence of new genetic discoveries, new therapies, and new technologies, such that these same 3 organizations convened a second working group to systematically assess new evidence and to issue an evidence-based revision of the lung cancer molecular pathology practice guideline.

The revision focuses on new recommendations in 5 specific content areas: i) Which new genes should routinely be tested for alterations in lung cancers? ii) What methods are appropriate for lung cancer testing, with particular emphases on the use of immunohistochemistry (IHC) and next-generation sequencing (NGS)? iii) Is there a need to test patients with squamous cell, small cell, or other non-adenocarcinoma lung cancers? iv) What testing should be performed for patients with a targetable alteration who have progressed following initial response to appropriately targeted therapy? v) What is the role of testing circulating cell-free DNA (cfDNA) in lung cancer patient management? In addition, new evidence supporting the original 2013 guideline was reviewed and used to either modify the strength of those recommendations or change them entirely. Finally, a sixth question, regarding diagnostic support for the role of immunomodulatory therapies (eg, programmed death ligand-1 or PD-L1), emerged during the revision process. Although this topic was not subject to the systematic review of evidence, the expert panel decided to issue an opinion statement addressing this question, aware that separate efforts are currently underway to develop evidence-based recommendations regarding the use of biomarkers to select patients for immunomodulatory therapies.

One particular challenge for this evidence-based guideline revision was the rapid pace of discovery in this field. During the time between literature review and guideline drafting, major new discoveries were published and treatment advanced for *BRAF*-mutant lung cancers and for the use of immunotherapies. We expect that many additional advances will emerge in the fields of targeted therapy, cfDNA diagnostics, and immunotherapies in the near term. Although we make strong recommendations for the molecular biomarkers for which there was good evidence at the time we conducted our analysis, we also fully recognize the importance of emerging biomarkers to enable lung cancer patients to be eligible for clinical trials of investigational therapies. Accordingly, we have stratified the biomarkers in this guideline into 3 categories, rather than 2. 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 perform only single-gene assays. All remaining candidate biomarkers are investigational and are not appropriate for clinical use at this time.

Authors' disclosures of potential conflicts of interest and author contributions are found in the Appendix at the end of this article.

This guideline was developed through collaboration among the College of American Pathologists, the International Association for the Study of Lung Cancer, the Association for Molecular Pathology, and the American Society for Investigative Pathology and has been jointly published by invitation and consent in the *Archives of Pathology & Laboratory Medicine*, *Journal of Thoracic Oncology*, and *The Journal of Molecular Diagnostics*.