

## CAP Pathology and Laboratory Quality Center, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

### KEY MESSAGES

- The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) have updated and revised their 2013 evidence-based **"Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors."**
- The **"Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors"** continues to set evidence-based standards for clinical molecular testing of non-small cell lung cancers (NSCLC) that effectively guides targeted therapy and treatment.
- Rapid advancements in the understanding of lung cancer, and corresponding growth in available molecularly-targeted therapies, make this guideline revision essential to guide optimal patient care. NSCLC patients whose tumors harbor specific molecular alterations may be candidates for targeted tyrosine kinase inhibitor (TKI) therapy, which may improve survival and quality of life.
- The updated guideline strengthens or reaffirms of the majority of the 2013 recommendations for patients with lung adenocarcinoma, and also recommends testing for some new genes. Most notably:
  - Testing for *ROS1* mutations is new and strongly recommended for all lung cancer patients regardless of clinical characteristics.
  - Multiplexed genetic sequencing panels (e.g. NGS) are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*, however single gene assays are still acceptable. 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.
  - When NGS is performed, several other genes are also recommended – *BRAF*, *ERBB2*, *MET*, *RET*, and *KRAS*. However, these genes are not essential when only single gene tests are performed. Note: *BRAF* had late-breaking early evidence, which we expect to mature to a stronger recommendation for inclusion as a single gene assay, as well, in the near future.
  - Testing in relapse is required for *EGFR* (T790M), but not for *ALK*, as the differential sensitivities of second-line ALK inhibitors in the setting of specific acquired mutations in *ALK* has not yet sufficiently matured and is still investigational.
  - Testing for *EGFR* T790M in relapse may be done by biopsy or cell-free circulating DNA. However cell-free DNA is not appropriate for initial diagnosis at this time, unless a tissue or cytology sample cannot be obtained.
  - Previous recommendations, otherwise, were largely reinforced, with some strengthening of evidence that has led to strengthening of the original recommendations. Most notable changes:
    - Inclusion of IHC for ALK as an alternative to FISH;
    - Inclusion of any cytology sample with adequate cancer content, as opposed to recommending cell blocks.

- Opinion is expressed that samples should also be set aside for assays to predict response to immunotherapy (e.g., PD-L1 IHC), but no specific recommendations about how to predict this treatment response were made, and will be the subject of an upcoming guideline.
- The updated lung cancer testing guideline also addresses other key clinical concerns, including molecular testing for lung cancers that do not have an adenocarcinoma component.
- An international, multi-disciplinary panel of expert authors, appointed by each of the organizations, included pathologists, oncologists, pulmonologists, a methodologist, laboratory scientists, and patient representatives, worked collaboratively to develop the guideline through an evidence-based process following Institute of Medicine standards for guideline development, which included:
  - Extensive review of relevant published literature.
  - Feedback on draft guidance, garnered through an open comment period to allow for input from scientists, clinicians, government agencies, other non-profit organizations, patients, patient advocates, and members of the public.
  - Revisions based on open comment period feedback, which authors considered in writing the final guideline.
  - Stringent organizational review of all collaborating organizations.
  - Rigorous scientific peer review process for publication.
- Patients battling lung cancer will benefit as their clinicians review and adopt this guideline. Stakeholders around the world are encouraged to review the guideline and implement recommendations.
- The CAP Pathology and Laboratory Quality Center, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology collaboratively developed this evidence-based guideline, consensus statements, clinical tools and resources related to the practice of lung cancer pathology and laboratory medicine, oncology, and molecular diagnostics. Through this work, these organizations and their members continually educate stakeholders and advance the quality of diagnostic medicine to improve lung cancer patient outcomes.
- 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 updates in the future.