
Natasha B. Leighl, Natasha Rekhtman, William A. Biermann, James Huang, Mari Mino-Kenudson, Suresh S. Ramalingam, Howard West, Sara Whitlock, and Mark R. Somerfield

Purpose
The College of American Pathologists (CAP), the International Society for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP) guideline on molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors was considered for endorsement.

Methods
American Society of Clinical Oncology (ASCO) staff reviewed the CAP/IASLC/AMP guideline for developmental rigor; an ASCO ad hoc review panel of experts reviewed the guideline content.

Results
The ASCO panel concurred that the recommendations are clear, thorough, and based on the most relevant scientific evidence in this content area and present options that will be acceptable to patients. The CAP/IASLC/AMP guideline comprises 37 recommendations (evidence grade A or B), expert consensus opinions, or suggestions that address the following five principal questions: (1) When should molecular testing be performed? (2) How should EGFR testing be performed? (3) How should ALK testing be performed? (4) Should other genes be routinely tested in lung adenocarcinoma? (5) How should molecular testing be implemented and operationalized?

Conclusion
The ASCO review panel endorses the CAP/IASLC/AMP guideline. This guideline represents an important advance toward standardization of EGFR and ALK testing practices and is of major clinical relevance in advancing the care of patients with lung cancer. In the Discussion section, the ASCO review panel highlights three evolving areas: advances in ALK testing methodology, considerations for selecting appropriate populations for molecular testing, and emergence of other targetable molecular alterations.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology
evidence-based recommendations for the molecular analysis of lung cancers for EGFR mutations and ALK rearrangements. The guideline addresses which patients and which samples should be tested, when testing should be performed, and which methods should be used.

OVERVIEW OF ASCO GUIDELINE ENDORSEMENT PROCESS

In 2006, the ASCO Board of Directors approved a policy and a set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations. The goal of the endorsement policy is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. Endorsement of guidelines will be considered in selected circumstances, either on request from related professional organizations at the discretion of the ASCO CPGC or when ASCO seeks to endorse the guideline of another organization in lieu of undertaking its own guideline on the same topic.

The guideline under endorsement consideration is reviewed and approved by the ASCO CPGC. The CPGC review includes two parts:

THE BOTTOM LINE

Molecular Testing for Selection of Patients With Lung Cancer for EGFR and ALK Tyrosine Kinase Inhibitors: CAP/IASLC/AMP

Guideline Questions
The guideline addressed five principle questions: (1) When should molecular testing for non–small-cell lung cancer (NSCLC) be performed? (2) How should epidermal growth factor receptor (EGFR) testing be performed? (3) How should anaplastic lymphoma kinase (ALK) testing be performed? (4) Should other genes be routinely tested in lung adenocarcinoma? (5) How should molecular testing of lung adenocarcinomas be implemented and operationalized?

Target Population
Patients with NSCLC.

Target Audience
Pathologists, surgeons, medical oncologists, radiation oncologists, interventional radiologists, respirologists, pathology technicians, oncology nurses, patients, and caregivers.

Recommendations
The major recommendation from the College of American Pathologists (CAP)/International Society for the Study of Lung Cancer (IASLC)/Association of Molecular Pathologists Guideline (AMP) guideline is to use testing for EGFR mutations and ALK rearrangements to guide patient selection for therapy with EGFR or ALK inhibitors, respectively, in all patients with advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component, irrespective of clinical characteristics (e.g., smoking history, sex, race, or other clinical factors). The guideline recommends that small tumor samples of other histologies, for which an adenocarcinoma component cannot be excluded because of sampling, can be considered for testing, particularly if clinical criteria are suggestive (e.g., younger age, lack of smoking history). Both primary tumors and metastatic lesions are suitable for testing. Methods for EGFR and ALK testing and minimal sample requirements should be validated by each laboratory. EGFR testing should detect mutations in samples composed of as few as 50% tumor cells, although sensitivity to detect mutations in samples containing >10% tumor cells is strongly encouraged. Sensitizing EGFR mutations with a population frequency of at least 1% should be reported. Laboratory turnaround times of 5 to 10 working days for EGFR and ALK results are recommended, with transport times of 3 days from day of request to an outside molecular facility and 24 hours within an institution. The following are not recommended as predictive assays for treatment selection: immunohistochemistry (IHC) for total EGFR, EGFR copy number, and ALK real-time polymerase chain reaction. The evolving role of IHC with antibodies to mutant EGFR and high-sensitivity ALK antibodies is discussed. Additional guidance is provided regarding specimen processing, testing validation, quality assurance, and result reporting.

Comments
The ASCO review panel endorses the CAP/IASLC/AMP guideline, which represents an important advance toward standardization of EGFR and ALK testing practices.

Additional Resources
Additional information including Methodology Supplement, evidence tables, and clinical tools and resources can be found at www.asco.org/endorsements/lungmarkers. Patient information is available there and at www.cancer.net. ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.
methodologic review and content review. The methodologic review is completed by a member of the CPGC Methodology Subcommittee and/or ASCO senior guideline staff using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. In addition to this methodologic review, ASCO staff conducts literature searches to identify relevant studies and additional systematic reviews, meta-analyses, and guidelines that have been published since the guideline under endorsement was completed.

The content review is completed by an ad hoc ASCO panel (Appendix Table A1, online only). The panel members are asked to complete an eight-item guideline endorsement content review form that assesses the perceived clarity and clinical utility of the recommendations and the degree to which the recommendations are consistent with the content reviewers’ interpretation of the available data on the topic in question. Final review and approval are completed by the ASCO CPGC after approval by the ASCO panel.

The ASCO panel and guidelines staff will work with their counterparts at the CAP, the IASLC, and the AMP to keep abreast of any substantive updates to the current CAP/IASLC/AMP lung cancer biomarkers issued by these groups. On the basis of the formal review of the CAP/IASLC/AMP update, ASCO will determine the need to update the ASCO endorsement. Additional details of the methods used for the development of this guideline endorsement are reported in an online-only Methodology Supplement available at http://www.asco.org/endorsements/lungmark-

Disclaimer

The clinical practice guidelines and other guidance published herein are provided by ASCO to assist providers with clinical decision making. The information therein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like must, must not, should, and should not indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be consid-

Guideline and Conflicts of Interest

The expert panel was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (procedures, summarized at http://www.asco.org/rwc). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the procedures, the majority of the members of the panel did not disclose any such relationships.

Clinical Questions and Target Population

The CAP/IASLC/AMP guideline addressed five principle questions and 14 corollary questions. The five principle questions asked were as follows: (1) When should molecular testing for non–small-cell lung cancer (NSCLC) be performed? (2) How should EGFR testing be performed? (3) How should ALK testing be performed? (4) Should other genes be routinely tested in lung adenocarcinoma? (5) How should molecular testing of lung adenocarcinomas be implemented and operationalized? The complete set of clinical questions and corresponding recommendations are listed in Table 1. The target population for the CAP/IASLC/AMP guideline is patients with NSCLC.

Summary of CAP/IASLC/AMP Guideline Development Methodology and Key Evidence

The CAP/IASLC/AMP guideline was developed by an author expert panel and a scientific advisory panel that included experts in molecular testing in NSCLC from pathology, oncology, and research and development. The literature search of Ovid MEDLINE, Ovid MEDLINE In-Proces & Other Nonindexed Citations, and the Wiley Cochrane Library spanned January 2004 through February 2012. Details of the search strategies and the study inclusion criteria and outcomes of interest are available at http://www.archivesofpathology.org/userimages/ContentEditor/1365017621306-2013-3-26_Supplemental_Digital%20Content.pdf.

The searches identified 127 studies for inclusion in the qualitative synthesis of the literature for the guideline. The expert author panel also solicited input and testimony from the nonwriting scientific advisory panel at a 1-day meeting. The CAP/IASLC/AMP panel reviewed data from randomized controlled trials of anti-EGFR or -ALK therapies in lung cancer and from unblinded trials that described test characteristics, outlined various methods, and defined quality assurance strategies for testing. The panel relied on expert consensus opinion to formulate recommendations for 20 of the 37 clinical questions, especially those related to technical aspects of testing that were supported by limited or no high-quality evidence.
Section I. When should molecular testing of lung cancers be performed?

Question 1: Which patients should be tested for EGFR mutations and ALK rearrangements?

1.1a: Recommendation: EGFR molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from this basis of clinical characteristics.

1.1b: Recommendation: ALK molecular testing should be used to select patients for ALK-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.2: Recommendation: In the setting of lung cancer resection specimens, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade. In the setting of fully excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers that lack any adenocarcinoma component, such as pure squamous cell carcinomas, pure small-cell carcinomas, or large-cell carcinomas lacking any IHC evidence of adenocarcinoma differentiation.

1.3: Recommendation: In the setting of more limited lung cancer specimens (biopsies, cytology) in which an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases that show squamous or small-cell histology, but clinical criteria (eg, younger age, lack of smoking history) may be useful in selecting a subset of these samples for testing.

1.4: Recommendation: To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.

1.5: Expert consensus opinion: For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested, but testing of multiple different areas within a single tumor is not necessary.

Question 2: When should a patient specimen be tested for EGFR mutation or ALK rearrangement?

2.1a: Recommendation: EGFR mutation testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the seventh edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.

2.1b: Suggestion: ALK rearrangement testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the seventh edition TNM staging system) and are suitable for therapy, or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.

2.2a: Expert consensus opinion: EGFR testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

2.2b: Expert consensus opinion: ALK testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

2.3: Recommendation: Tissue should be prioritized for EGFR and ALK testing.

Question 3: How rapidly should test results be available?

3.1: Expert consensus opinion: EGFR and ALK results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory.

3.2: Expert consensus opinion: Laboratories with average turnaround times beyond 2 weeks need to make available a more rapid test—either in-house or through a reference laboratory—in instances of clinical urgency.

3.3: Expert consensus opinion: Laboratory departments should establish processes to ensure that specimens that have a final histopathologic diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.

Section II. How should EGFR testing be performed?

Question 4: How should specimens be processed for EGFR mutation testing?

4.1: Expert consensus opinion: Pathologists should use FFPE specimens or fresh, frozen, or alcohol-fixed specimens for PCR-based EGFR mutation tests. Other tissue treatments (eg, acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for EGFR testing.

4.2: Expert consensus opinion: Cytologic samples are also suitable for EGFR and ALK testing, with cell blocks being preferred over smear preparations.

Question 5: What are the specimen requirements for EGFR testing?

5.1: Expert consensus opinion: Pathologists should determine the adequacy of specimens for EGFR testing by assessing cancer cell content and DNA quantity and quality.

5.2: Expert consensus opinion: Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.

5.3: Expert consensus opinion: A pathologist should assess the tumor content of each specimen and either perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment as needed.

Question 6: How should EGFR testing be performed?

6.1: Recommendation: Laboratories may use any validated EGFR testing method with sufficient performance characteristics.

6.2: 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.

6.3: Expert consensus opinion: Clinical EGFR mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.

6.4: Recommendation: IHC for total EGFR is not recommended for selection of EGFR TKI therapy.

6.5: Recommendation: EGFR copy number analysis (ie, FISH or chromogenic in situ hybridization) is not recommended for selection of EGFR TKI therapy.

Question 7: What is the role of KRAS analysis in selecting patients for targeted therapy with EGFR TKIs?

7.1: Recommendation: KRAS mutation testing is not recommended as a sole determinant of EGFR TKI therapy.

Question 8: What additional testing considerations are important in the setting of secondary or acquired EGFR TKI resistance?

8.1: Recommendation: If a laboratory performs testing on specimens from patients with acquired resistance to EGFR kinase inhibitors, such tests should be able to detect the secondary EGFR T790 M mutation in as few as 5% of cells.

(continued on following page)
Table 1. Summary of Recommendations From CAP/IASLC/AMP Molecular Testing Guideline for Selection of Patients With Lung Cancer for EGFR and ALK "TKIs" (continued)

<table>
<thead>
<tr>
<th>Section III: How should ALK testing be performed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 9: What methods should be used for ALK testing?</td>
</tr>
<tr>
<td>9.1: Recommendation: Laboratories should use an ALK FISH assay using dual-labeled break-apart probes for selecting patients for ALK TKI therapy; ALK IHC, if carefully validated, may be considered as a screening methodology to select specimens for ALK FISH testing.</td>
</tr>
<tr>
<td>9.2: Recommendation: RT-PCR is not recommended as an alternative to FISH for selecting patients for ALK inhibitor therapy.</td>
</tr>
<tr>
<td>9.3: Expert consensus opinion: A pathologist should be involved in the selection of sections for ALK FISH testing, by assessing tumor architecture, cytology, and specimen quality.</td>
</tr>
<tr>
<td>9.4: Expert consensus opinion: A pathologist should participate in the interpretation of ALK FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytomotechnicians or technologists with specialized training in solid tumor FISH analysis.</td>
</tr>
<tr>
<td>9.5: Expert consensus opinion: Testing for secondary mutations in ALK associated with acquired resistance to ALK inhibitors is not currently required for clinical management.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section IV. Should other genes be routinely tested in lung adenocarcinoma?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 10: Are other molecular markers suitable for testing in lung cancer?</td>
</tr>
<tr>
<td>10.1a: Recommendation: Testing for EGFR should be prioritized over other molecular markers in lung adenocarcinoma.</td>
</tr>
<tr>
<td>10.1b: Suggestion: After EGFR testing, testing for ALK should be prioritized over other proposed molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support testing guideline development at the present time.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section V. How should molecular testing of lung adenocarcinomas be implemented and operationalized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 11: Must all adenocarcinomas be tested for both EGFR and ALK?</td>
</tr>
<tr>
<td>11.1: Expert consensus opinion: Laboratories may implement testing algorithms to enhance the efficiency of molecular testing of lung adenocarcinomas, provided the overall turnaround time requirements are met.</td>
</tr>
<tr>
<td>Question 12: How should EGFR and ALK results be reported?</td>
</tr>
<tr>
<td>12.1: Expert consensus opinion: EGFR mutation testing reports and ALK FISH reports should include a results and interpretation section readily understandable by oncologists and by nonspecialist pathologists.</td>
</tr>
<tr>
<td>Question 13: How should EGFR and ALK testing be validated?</td>
</tr>
<tr>
<td>13.1: Expert consensus opinion: EGFR and ALK testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.</td>
</tr>
<tr>
<td>Question 14: How should quality assurance be maintained?</td>
</tr>
<tr>
<td>14.1: Expert consensus opinion: Laboratories should follow similar quality control and quality assurance policies and procedures for EGFR and ALK testing in lung cancers as for other clinical laboratory assays. In particular, laboratories performing EGFR and ALK testing for TKI therapy should enroll in proficiency testing, if available.</td>
</tr>
</tbody>
</table>

**Major Guideline Recommendations**

Table 1 lists the practice recommendations for the clinical questions addressed in the CAP/IASLC/AMP guideline; a summary of these recommendations is provided here:

**Which patients and which samples to test.** The guideline recommends that patients with a diagnosis of lung adenocarcinoma or mixed lung cancer with adenocarcinoma component be tested and that patients should not be excluded from testing on the basis of clinical characteristics, such as sex or smoking status. In fully resected lung cancer specimens, testing of pure squamous cell carcinoma or small-cell carcinoma is not recommended. In small samples (biopsies, cytology), these histologies may be included in testing for EGFR and ALK, because the possibility of a mixed tumor with an unsampled adenocarcinoma component cannot be excluded in limited samples; clinical characteristics (eg, lack of smoking history, younger age) may be useful in selecting a subset of small samples for testing. Less common tumors that may harbor EGFR and ALK, and which may be considered for testing, include large-cell carcinomas (particularly subset showing evidence of adenocarcinoma differentiation by immunohistochemistry [IHC]), sarcomatoid carcinomas, large-cell neuroendocrine carcinomas, and non–small-cell carcinomas not otherwise specified. Primary tumors or metastatic lesions are equally suitable for testing. Expert consensus was that each tumor may be tested for patients with multiple primary adenocarcinomas.

**Timing of testing.** Testing should be completed at the time of diagnosis of advanced disease or recurrence. For patients with earlier-stage (ie, I to III) disease who undergo surgical resection, expert consensus encourages testing at the time of diagnosis so that molecular information is available to an oncologist at the time of recurrence for a subset of patients who subsequently experience recurrence, although this decision is deferred to local laboratories and oncology teams.

**How should testing be performed?** The CAP/IASLC/AMP guideline is not prescriptive about specific testing platforms, but it emphasizes that the methodology and minimal specimen requirements be validated and quality assurance maintained in each laboratory. Expert consensus on preferred tissue processing for optimal EGFR and ALK testing is presented, including fixation techniques; it is emphasized that certain tissue treatments—such as decalcifying solutions—are not suitable for EGFR testing. Cytologic specimens are suitable for testing. Each laboratory should establish minimal cellularity requirements (proportion and number of tumor cells) during assay validation. Expert consensus is that laboratories should use an EGFR method that is able to detect mutations in sample with as low as 50% tumor cell content, although the ability to detect mutations in samples with tumor cell content ≥ 10% is strongly encouraged. For the detection of EGFR T790M acquired resistance mutation, the assays should have sufficient sensitivity to detect mutations in samples with ≥ 5% tumor cells. Expect consensus is that EGFR testing assays should be...
able to detect individual EGFR mutations with a reported frequency of $\geq 1\%$ of all EGFR mutations. It is noted that several methodologies, including IHC for total EGFR, EGFR copy number analysis, and ALK real-time polymerase chain reaction, are not recommended as predictive assays. IHC with EGFR mutation–specific antibodies has a high positive predictive value if scoring cutoffs are set stringently, but it has lower sensitivity, which necessitates testing of all IHC-negative cases. It is suggested that IHC for mutant EGFR may have a role in special circumstances, such as in samples deemed insufficient for molecular analysis. Lastly, IHC with highly sensitive ALK antibodies (DSF3, 5A4), if carefully validated, may be used as a screening method to select specimens for ALK fluorescent in situ hybridization (FISH) testing, and expert opinion is that tumors that are negative by ALK IHC need not be tested by FISH.

Testing for other genes. The CAP/IASLC/AMP guideline recommends prioritizing EGFR and ALK testing over other biomarkers, but it is noted that new important testing indications, notably ROS1 and RET rearrangements, emerged while the guideline was under development. Testing for KRAS mutations is not recommended as a sole determinant of EGFR-targeted therapy; however, testing for KRAS may be performed initially to exclude KRAS-mutated tumors from EGFR and ALK testing as part of a stepwise algorithm designed to maximize testing efficiency, recognizing that KRAS mutations are common (30%) in lung adenocarcinomas and mutually exclusive with EGFR and ALK.

Implementation and operationalization of testing. The guideline defers the decision on testing algorithms to local laboratories, provided that overall result turnaround time requirements are met. Expert consensus for testing turnaround time is that results should be available within 2 weeks (10 working days, with goal of 5 working days) of receiving the specimen in the testing laboratory. Pathology departments should establish a process wherein tissue (blocks or unstained slides) is sent to outside molecular laboratories within 3 days of receiving a request and to intramural molecular laboratories within 24 hours. Results should be reported in a format that is easily understood by oncologists and nonspecialist pathologists. The guideline includes detailed recommendations for the information that should be included in a molecular report. Expert consensus on test validation and quality assurance is provided.

The methodologic review of the CAP/IASLC/AMP guideline was completed independently by two ASCO guideline staff members using the Rigour of Development subscale from the AGREE II instrument, as discussed. Detailed results of the scoring for this guideline are available in the online Methodology Supplement at http://www.asco.org/endorsements/. Overall, the CAP/IASLC/AMP guideline scored high (83%) in terms of methodologic quality, with only minor deviations from the ideal as reflected in the AGREE II items.

METHODS AND RESULTS OF ASCO UPDATED LITERATURE SEARCH

A search for new evidence was conducted by ASCO guideline staff to identify relevant randomized clinical trials, systematic reviews, meta-analyses, and guidelines published since the CAP/IASLC/AMP guideline was completed. Following the strategies described in the CAP/IASLC/AMP guideline, the MEDLINE database was searched from February 2013 to September 19, 2013. The search was restricted to articles published in English, and the CAP/IASLC/AMP guideline inclusion criteria were applied to the review of the literature search results.

The updated search yielded 91 new records. A review of these results revealed no new evidence that would warrant substantive modification of the CAP/IASLC/AMP practice recommendations. Selected articles identified by individual panel members from personal files informed the comments of the ASCO ad hoc panel on the CAP/IASLC/AMP guideline recommendations.

The ASCO ad hoc panel reviewed the CAP/IASLC/AMP guideline and endorses the adoption of the guideline.

The ASCO ad hoc review panel identified three evolving areas that merit additional commentary: advances in ALK testing methodology, considerations for selecting appropriate populations for molecular testing, and emergence of other targetable molecular alterations. These areas are comprehensively addressed in the CAP/IASLC/AMP guideline but are briefly highlighted here for the benefit of the readership of this endorsement.

ALK Testing

The US Food and Drug Administration–approved ALK FISH assay is currently a prerequisite companion diagnostic for crizotinib treatment in the United States. However, as addressed in detail in the CAP/IASLC/AMP guideline, ALK IHC has been emerging as a highly specific, sensitive, rapid, and relatively inexpensive alternative method for the detection of ALK rearrangements, which circumvents several well-known limitations of ALK FISH, including labor intensiveness, high cost, requirement of a fluorescent microscope and specialized training, and a need for higher tumor cell numbers than IHC. Since the publication of the CAP/IASLC/AMP guideline, ALK IHC has continued to gain increasingly wide acceptance as the selection test for ALK inhibitors.7 It is suggested in the CAP/IASLC/AMP guideline that “ALK IHC, if carefully validated, may be considered as a screening methodology to select specimens for ALK FISH testing.” The ASCO panel wishes to highlight this evolution in ALK testing methodology and refers the readers to a recent comprehensive review of this area in the IASLC Atlas of ALK Testing in Lung Cancer.7

Testing in Early-Stage NSCLC

The CAP/IASLC/AMP expert consensus opinion is to encourage EGFR and ALK testing for all patients with early-stage (ie, I to III) carcinomas at diagnosis, with a note that “the decision to do so should be made locally by each laboratory, in collaboration with its oncology
To aid in this decision, the ASCO panel wishes to highlight potential considerations in the testing of patients with resected early-stage disease. The advantage of this approach is that it enables rapid initiation of treatment in patients who experience a recurrence, because molecular information is immediately available to the oncologist. This benefit must be balanced against the extra cost incurred by molecular testing of patients with early-stage disease who do not experience a relapse. If testing of such patients is implemented by local testing policies, it is important for oncologists to recall that the proven role for targeted therapies in EGFR-mutant or ALK-rearranged NSCLC at the present time is only in the setting of advanced-stage disease and to ensure that molecular results for patients with early-stage disease be used appropriately (eg, to initiate optimal therapy on lung cancer relapse or for enrollment onto clinical trials evaluating role of targeted therapies in adjuvant setting).

**Future Research: Emerging Targetable Molecular Alterations**

The CAP/IASLC/AMP guideline represents a great advance toward standardization of testing for EGFR and ALK alterations. An important consideration for the future of molecular testing in lung carcinoma is a growing number of other targetable molecular alterations, such as the recently identified RET and ROS1 rearrangements.

Future guidelines will be needed to address testing for these and other emerging alterations and strategies for testing of a growing number of biomarkers as they enter clinical practice, which challenges the practicality and feasibility of performing multiple separate assays for each individual alteration, particularly in limited tissue samples. In this regard, recent innovations in multigene testing methodologies (eg, next-generation sequencing) afford the capability of detecting multiple molecular alterations in a single assay and may hold significant promise in clinical testing.

---

**REFERENCES**


The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Natasha B. Leigh**
No relationships to disclose

**Natasha Rekhtman**
No relationships to disclose

**William A. Bierman**
Stock or Other Ownership: Genomic Health

**James Huang**
Research Funding: Bristol-Myers Squibb

**Mari Mino-Kenudson**
Consulting or Advisory Role: Agios Pharmaceuticals, Merrimack Pharmaceuticals

**Suresh S. Ramalingam**
Consulting or Advisory Role: Amgen You, ARIAD Pharmaceuticals, AVEO Pharmaceuticals, Boehringer Ingelheim, Celgene, AstraZeneca, Gilead Sciences, Novartis You, Genentech/Roche, Lilly/ImClone
Travel, Accommodations, Expenses: EMD Serono, Pfizer

**Howard West**
Honoraria: Foundation Medicine, Genentech/Roche, Celgene
Consulting or Advisory Role: Foundation Medicine, Genentech/Roche, Celgene

**Sara Whitlock**
No relationships to disclose

**Mark R. Somerfield**
No relationships to disclose
Acknowledgment

We thank Christopher G. Azzoli, MD, Ronald C. Chen, MD, MPH, and Gary H. Lyman, MD, MPH, and the Clinical Practice Guidelines Committee for their thoughtful reviews of and insightful comments on this guideline document. We also extend special thanks to Rose Z. Morrison and Sarah Temin for completing methodological reviews of the CAP/IASLC/AMP guideline.

Appendix

Table A1. Panel Members

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natasha B. Leighl, MD (co-chair)</td>
<td>Princess Margaret Cancer Centre, Toronto, Ontario, Canada</td>
</tr>
<tr>
<td>Natasha Rekhtman, MD, PhD (co-chair)</td>
<td>Memorial Sloan-Kettering Cancer Center, New York, NY</td>
</tr>
<tr>
<td>William A. Biermann, MD</td>
<td>Einstein Medical Center Montgomery, East Norriton, PA</td>
</tr>
<tr>
<td>James Huang, MD</td>
<td>Memorial Sloan-Kettering Cancer Center, New York, NY</td>
</tr>
<tr>
<td>Mari Mino-Kudson, MD</td>
<td>Massachusetts General Hospital and Harvard Medical School, Boston, MA</td>
</tr>
<tr>
<td>Suresh S. Ramalingam, MD</td>
<td>Winship Cancer Institute, Emory University, Atlanta, GA</td>
</tr>
<tr>
<td>Howard West, MD</td>
<td>Swedish Cancer Institute, Seattle, WA</td>
</tr>
<tr>
<td>Sara Whitlock (patient representative)</td>
<td>Free to Breathe, Madison, WI</td>
</tr>
</tbody>
</table>