

Molecular Testing for Selection of Patients With Lung Cancer for Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase 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 Guideline

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ABSTRACT

Purpose

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (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.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee (CPGC) identified a guideline for endorsement that addressed molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors. The target guideline was developed in 2013 as a joint product of the College of American

Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP).¹

RATIONALE AND PURPOSE

A growing body of research has demonstrated relationships between specific genomic alterations and response of advanced-stage lung cancer to targeted therapies. The CAP/IASLC/AMP guideline offers

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 devel-

oped 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 Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology 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 (eg, 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 (eg, 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 by 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 www.asco.org/endorsements/lungmarkers.

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 considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

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/rwi>). 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.

CAP/IASLC/AMP MOLECULAR TESTING GUIDELINE FOR SELECTION OF PATIENTS WITH LUNG CANCER FOR EGFR AND ALK TYROSINE KINASE INHIBITORS

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-Process & 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.

Table 1. Summary of Recommendations From CAP/IASLC/AMP Molecular Testing Guideline for Selection of Patients With Lung Cancer for EGFR and ALK TKIs*

| Recommendation |
|---|
| <p>Section I. When should molecular testing of lung cancers be performed?</p> <p>Question 1: Which patients should be tested for <i>EGFR</i> mutations and <i>ALK</i> rearrangements?</p> <p>1.1a: Recommendation: <i>EGFR</i> molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.</p> <p>1.1b: Recommendation: <i>ALK</i> 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.</p> <p>1.2: Recommendation: In the setting of lung cancer resection specimens, <i>EGFR</i> and <i>ALK</i> 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, <i>EGFR</i> and <i>ALK</i> 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.</p> <p>1.3: Recommendation: In the setting of more limited lung cancer specimens (biopsies, cytology) in which an adenocarcinoma component cannot be completely excluded, <i>EGFR</i> and <i>ALK</i> 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.</p> <p>1.4: Recommendation: To determine <i>EGFR</i> and <i>ALK</i> status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.</p> <p>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.</p> <p>Question 2: When should a patient specimen be tested for <i>EGFR</i> mutation or <i>ALK</i> rearrangement?</p> <p>2.1a: Recommendation: <i>EGFR</i> 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.</p> <p>2.1b: Suggestion: <i>ALK</i> 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.</p> <p>2.2a: Expert consensus opinion: <i>EGFR</i> 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.</p> <p>2.2b: Expert consensus opinion: <i>ALK</i> 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.</p> <p>2.3: Recommendation: Tissue should be prioritized for <i>EGFR</i> and <i>ALK</i> testing.</p> <p>Question 3: How rapidly should test results be available?</p> <p>3.1: Expert consensus opinion: <i>EGFR</i> and <i>ALK</i> results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory.</p> <p>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.</p> <p>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.</p> <p>Section II. How should <i>EGFR</i> testing be performed?</p> <p>Question 4: How should specimens be processed for <i>EGFR</i> mutation testing?</p> <p>4.1: Expert consensus opinion: Pathologists should use FFPE specimens or fresh, frozen, or alcohol-fixed specimens for PCR-based <i>EGFR</i> mutation tests. Other tissue treatments (eg, acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for <i>EGFR</i> testing.</p> <p>4.2: Expert consensus opinion: Cytologic samples are also suitable for <i>EGFR</i> and <i>ALK</i> testing, with cell blocks being preferred over smear preparations.</p> <p>Question 5: What are the specimen requirements for <i>EGFR</i> testing?</p> <p>5.1: Expert consensus opinion: Pathologists should determine the adequacy of specimens for <i>EGFR</i> testing by assessing cancer cell content and DNA quantity and quality.</p> <p>5.2: Expert consensus opinion: Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.</p> <p>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.</p> <p>Question 6: How should <i>EGFR</i> testing be performed?</p> <p>6.1: Recommendation: Laboratories may use any validated <i>EGFR</i> testing method with sufficient performance characteristics.</p> <p>6.2: Expert consensus opinion: Laboratories should use <i>EGFR</i> 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.</p> <p>6.3: Expert consensus opinion: Clinical <i>EGFR</i> mutation testing should be able to detect all individual <i>EGFR</i> mutations that have been reported with a frequency of at least 1% of <i>EGFR</i>-mutated lung adenocarcinomas.</p> <p>6.4: Recommendation: IHC for total EGFR is not recommended for selection of EGFR TKI therapy.</p> <p>6.5: Recommendation: <i>EGFR</i> copy number analysis (ie, FISH or chromogenic in situ hybridization) is not recommended for selection of EGFR TKI therapy.</p> <p>Question 7: What is the role of <i>KRAS</i> analysis in selecting patients for targeted therapy with EGFR TKIs?</p> <p>7.1: Recommendation: <i>KRAS</i> mutation testing is not recommended as a sole determinant of EGFR TKI therapy.</p> <p>Question 8: What additional testing considerations are important in the setting of secondary or acquired EGFR TKI resistance?</p> <p>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 <i>EGFR</i> T790 M mutation in as few as 5% of cells.</p> <p style="text-align: center;">(continued on following page)</p> |

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)

| Recommendation |
|--|
| <p>Section III. How should <i>ALK</i> testing be performed?</p> <p>Question 9: What methods should be used for <i>ALK</i> testing?</p> <p>9.1: Recommendation: Laboratories should use an <i>ALK</i> FISH assay using dual-labeled break-apart probes for selecting patients for ALK TKI therapy; <i>ALK</i> IHC, if carefully validated, may be considered as a screening methodology to select specimens for <i>ALK</i> FISH testing.</p> <p>9.2: Recommendation: RT-PCR is not recommended as an alternative to FISH for selecting patients for ALK inhibitor therapy.</p> <p>9.3: Expert consensus opinion: A pathologist should be involved in the selection of sections for <i>ALK</i> FISH testing, by assessing tumor architecture, cytology, and specimen quality.</p> <p>9.4: Expert consensus opinion: A pathologist should participate in the interpretation of <i>ALK</i> FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.</p> <p>9.5: Expert consensus opinion: Testing for secondary mutations in <i>ALK</i> associated with acquired resistance to ALK inhibitors is not currently required for clinical management.</p> |
| <p>Section IV. Should other genes be routinely tested in lung adenocarcinoma?</p> <p>Question 10: Are other molecular markers suitable for testing in lung cancer?</p> <p>10.1a: Recommendation: Testing for <i>EGFR</i> should be prioritized over other molecular markers in lung adenocarcinoma.</p> <p>10.1b: Suggestion: After <i>EGFR</i> testing, testing for <i>ALK</i> 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.</p> |
| <p>Section V. How should molecular testing of lung adenocarcinomas be implemented and operationalized?</p> <p>Question 11: Must all adenocarcinomas be tested for both <i>EGFR</i> and <i>ALK</i>?</p> <p>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.</p> <p>Question 12: How should <i>EGFR</i> and <i>ALK</i> results be reported?</p> <p>12.1: Expert consensus opinion: <i>EGFR</i> mutation testing reports and <i>ALK</i> FISH reports should include a results and interpretation section readily understandable by oncologists and by nonspecialist pathologists.</p> <p>Question 13: How should <i>EGFR</i> and <i>ALK</i> testing be validated?</p> <p>13.1: Expert consensus opinion: <i>EGFR</i> and <i>ALK</i> testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.</p> <p>Question 14: How should quality assurance be maintained?</p> <p>14.1: Expert consensus opinion: Laboratories should follow similar quality control and quality assurance policies and procedures for <i>EGFR</i> and <i>ALK</i> testing in lung cancers as for other clinical laboratory assays. In particular, laboratories performing <i>EGFR</i> and <i>ALK</i> testing for TKI therapy should enroll in proficiency testing, if available.</p> |

Abbreviations: AMP, Association for Molecular Pathology; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence in situ hybridization; IASLC, International Association for the Study of Lung Cancer; PCR, polymerase chain reaction; RT, reverse transcription; TKI, tyrosine kinase inhibitor.
 *Reprinted with permission.¹

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 $\geq 10\%$ is strongly encouraged. For the detection of *EGFR* T790M acquired resistance mutation, the assays should have sufficient sensitivity to detect mutations in samples with $\geq 5\%$ tumor cells. Expert 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 (D5F3, 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.

RESULTS OF ASCO METHODOLOGIC REVIEW

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/lungmarkers>. 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.

RESULTS OF ASCO CONTENT REVIEW

The ASCO ad hoc panel reviewed the CAP/IASLC/AMP guideline and concurs that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients, clinicians, and pathologists.

ENDORSEMENT RECOMMENDATION

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

DISCUSSION POINTS

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.² 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.”^{1(p846)} 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*.²

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

team.”^{1(p838)} 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 altera-

tions, such as the recently identified *RET* and *ROS1* rearrangements.³ 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 sequencing⁴) afford the capability of detecting multiple molecular alterations in a single assay and may hold significant promise in clinical testing.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Lindeman NI, Cagle PT, Beasley MB, et al: Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: Guideline from the College of American

Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med 137:828-860, 2013

2. Tsao MS, Hirsh FR, Yatabe Y (eds): IASLC Atlas of ALK Testing in Lung Cancer. Aurora, CO, International Association for the Study of Lung

Cancer, 2013

3. Gainor JF, Shaw AT: Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist 18:865-875, 2013

4. Collins FS, Hamburg MA: First FDA authorization for next-generation sequencer. N Engl J Med 369:2369-2371, 2013

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Molecular Testing for Selection of Patients With Lung Cancer for Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase 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 Guideline

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Appendix

Table A1. Panel Members

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|--|---|
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