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Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted 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 Clinical Practice Guideline Update.

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Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted 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 Clinical Practice Guideline Update

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G.P.K. and N.N. were Expert Panel co-chairs.

Clinical Practice Guideline Committee approval: October 2, 2017.

Editor's note: This American Society of Clinical Oncology clinical practice guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

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ASSOCIATED CONTENT



Appendix
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Methodology Supplement
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ABSTRACT

Purpose

In response to advances in the field, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recently updated their recommendations for molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors. ASCO has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

Methods

The molecular testing guideline was reviewed for developmental rigor by methodologists. Then an ASCO Expert Panel reviewed the content and the recommendations.

Results

The ASCO Expert Panel determined that the recommendations from the CAP/IASLC/AMP molecular testing guideline are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the guideline with minor modifications.

Recommendations

This update clarifies that any sample with adequate cellularity and preservation may be tested and that analytical methods must be able to detect mutation in a sample with as little as 20% cancer cells. It strongly recommends against evaluating epidermal growth factor receptor (EGFR) expression by immunohistochemistry for selection of patients for EGFR-targeted therapy. New for 2018 are recommendations for stand-alone ROS1 testing with additional confirmation testing in all patients with advanced lung adenocarcinoma, and RET, ERBB2 (HER2), KRAS, and MET testing as part of larger panels. ASCO also recommends stand-alone BRAF testing in patients with advanced lung adenocarcinoma. Recommendations are also provided for testing methods for lung cancers that have a nonadenocarcinoma non-small-cell component, for patients with targetable mutations who have relapsed on targeted therapy, and for testing the presence of circulating cell-free DNA. Additional information is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

Expected median survival for patients with advanced lung cancer is approximately 1 year; however,

treatment with targeted tyrosine kinase inhibitor (TKI) therapy can improve outcomes for patients who have certain molecular alterations that can be identified by molecular testing.¹ In 2013, the College of American Pathologists (CAP)/International

THE BOTTOM LINE

Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted 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 Clinical Practice Guideline Update

ASCO endorses the Updated Molecular Testing for the Selection of Patients With Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors Clinical Practice Guideline, with minor modifications suggested by the ASCO Expert Panel appearing in *bold italics*. Additional contextual information added from the CAP/IASLC/AMP guideline narrative is included in *italics*. A comparison of the CAP/IASLC/AMP and ASCO recommendations can be found in [Tables 1](#) and [2](#).

Guideline Question

Which patients with advanced lung cancer should be tested for biomarkers that indicate the likelihood of response to targeted tyrosine kinase inhibitors (TKIs)? Which samples and genes should be tested, and how should these tests be designed, validated, and executed?

Target Population

Patients with advanced lung cancer (ie, stage IV or other incurable lung cancer).

Target Audience

Medical or surgical oncologists, pathologists, thoracic surgeons, and specialists in pulmonary medicine or interventional radiology.

Methods: An Expert Panel was convened to endorse clinical practice guideline recommendations that were based on a systematic review of the medical literature.

Key Recommendations

2013 Recommendations that were reaffirmed or updated for 2018:

1. Expert Consensus Opinion: Pathologists may use either cell blocks or *smear* preparations as suitable specimens for lung cancer biomarker molecular testing.
2. Expert Consensus Opinion: Laboratories should use, 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.
3. Strong Recommendation: Laboratories should not use epidermal growth factor receptor (EGFR) expression by immunohistochemistry (IHC) testing to select patients for EGFR-targeted TKI therapy.
4. Recommendation: Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.
5. Recommendation: Pathologists and laboratories should not use EGFR copy number analysis (ie, fluorescent in situ hybridization or chemiluminescent in situ hybridization) to select patients for EGFR-targeted TKI therapy.

New 2018 Recommendations:

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

1. Recommendation: *ROS1* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
2. Expert Consensus Opinion: *ROS1* IHC may be used as a screening test in patients with advanced lung adenocarcinoma; however, positive *ROS1* IHC results should be confirmed by a molecular or cytogenetic method.
3. Expert Consensus Opinion: ***BRAF testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.***
4. Expert Consensus Opinion: *RET* molecular testing is not recommended 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*, ***BRAF***, and *ROS1* testing is negative.

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THE BOTTOM LINE (CONTINUED)

5. 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*) mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR*, *ALK*, ***BRAF***, and *ROS1* testing is negative.
6. 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*, ***BRAF***, and *ROS1* testing is negative.
7. 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*, ***BRAF***, and *ROS1* testing is negative.

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

8. Recommendation: IHC is an equivalent alternative to FISH for *ALK* testing.

CAP/IASLC/AMP Qualifying Statement: *ALK* IHC is an acceptable **standard** alternative to FISH, and treatment decisions can be made when IHC results are clearly positive, as manifested by strong granular cytoplasmic staining, with or without membrane accentuation, or negative; however, weak staining can be challenging to interpret, and the specificity of weak staining relative to FISH should be determined in each laboratory during validation.

9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred **where available** over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, ***BRAF***, and *ROS1*.
10. Expert Consensus Opinion: Laboratories should ensure that test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved by using an alternative method or sample.

Key Question 3: Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?

11. Expert Consensus Opinion: Physicians may use molecular biomarker testing in tumors with:
 - a. **an adenocarcinoma component;**
 - b. **nonsquamous, non–small-cell histology;**
 - c. any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver (eg, young age [< 50 years]; light or absent tobacco exposure).

Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?

12. Strong Recommendation: In patients with lung adenocarcinoma 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.
13. 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.
14. No Recommendation: There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for patients with lung adenocarcinoma with sensitizing *ALK* mutations who have progressed after treatment with an *ALK*-targeted TKI.

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

15. No Recommendation: There is currently insufficient evidence to support the use of cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma.
16. Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify *EGFR* mutations.
17. Expert Consensus Opinion: Physicians may use cfDNA methods to identify *EGFR* T790M mutations in patients with lung adenocarcinoma who have progression or secondary clinical resistance to *EGFR*-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative.
18. No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell 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.

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THE BOTTOM LINE (CONTINUED)

Additional Resources: More information, including a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

A link to the CAP/IASLC/AMP Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors can be found at <http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2017-0388-CP>

Recommendations reprinted from Lindeman NI, Cagle, PT, Aisner, DL, et al. 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. *Arch Pathol Lab Med*. doi: [10.5858/arpa.2017-0388-CP](https://doi.org/10.5858/arpa.2017-0388-CP), published online ahead of print November 2017, with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2017 College of American Pathologists.

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.

Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) issued a joint guideline for molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) TKIs.² ASCO endorsed that guideline,³ which included recommendations for selecting patients for testing, samples to be tested, and testing methodology. Because the field of molecular pathology and options for targeted therapy have advanced since the first edition was published, CAP/IASLC/AMP recently updated their guideline to incorporate new evidence related to molecular testing for selecting patients with lung cancer for treatment with targeted TKIs. The purpose of this update was to provide recommendations for an expanded list of biomarkers that should routinely be tested and to incorporate new evidence

for laboratory techniques, patient populations, and tumor types that should be tested. As a result of the update, the 2013 recommendations were largely reaffirmed, with the exception of a small number of statements that underwent minor modifications to incorporate new evidence. In addition, 18 new recommendations were developed by the CAP/IASLC/AMP Expert Panel (Appendix Table A1, online only).

The purpose of this ASCO guideline is to critically appraise and endorse the updated CAP/IASLC/AMP guideline on molecular testing for selection of patients with lung cancer for treatment with targeted TKIs. This endorsement reinforces the recommendations provided in the CAP/IASLC/AMP guideline and acknowledges the effort put forth by CAP/IASLC/AMP to produce an evidence-based guideline informing practitioners who care for

Table 1. Recommendations for Endorsement That Have Been Reaffirmed or Updated From the 2013 Version

CAP/IASLC/AMP Recommendation	ASCO Endorsed Recommendation (with modifications in bold italics)
Expert Consensus Opinion: Pathologists may use either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.	Expert Consensus Opinion: Pathologists may use either cell blocks or smear preparations as suitable specimens for lung cancer biomarker molecular testing.
Expert Consensus Opinion: Laboratories should use, 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.	Expert Consensus Opinion: Laboratories should use, 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 epidermal growth factor receptor (EGFR) expression by immunohistochemistry testing to select patients for EGFR-targeted tyrosine kinase inhibitor (TKI) therapy.	Strong Recommendation: Laboratories should not use EGFR expression by immunohistochemistry testing to select patients for EGFR-targeted TKI therapy.
Recommendation: Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.	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 (ie, fluorescent in situ hybridization or chemiluminescent in situ hybridization) to select patients for EGFR-targeted TKI therapy.	Recommendation: Pathologists and laboratories should not use EGFR copy number analysis (ie, fluorescent in situ hybridization or chemiluminescent in situ hybridization) to select patients for EGFR-targeted TKI therapy.

NOTE. Reprinted from Lindeman NI, Cagle, PT, Aisner, DL, et al. 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. *Arch Pathol Lab Med*. doi: [10.5858/arpa.2017-0388-CP](https://doi.org/10.5858/arpa.2017-0388-CP), published online ahead of print November 2017, with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2017 College of American Pathologists.

Molecular Testing for Patients With Lung Cancer

Table 2. Comparison of CAP/IASLC/AMP Recommendations and ASCO Endorsed Recommendations

CAP/IASLC/AMP Recommendation	ASCO Endorsed Recommendation (with modifications or qualifying statements in bold italics)
Key Question 1: Which genes should be tested for patients with lung cancer?	
Recommendation: <i>ROS1</i> testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.	<i>ROS1</i> testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
Expert Consensus Opinion: <i>ROS1</i> immunohistochemistry (IHC) may be used as a screening test in patients with advanced lung adenocarcinoma; however, positive <i>ROS1</i> IHC results should be confirmed by a molecular or cytogenetic method.	<i>ROS1</i> IHC may be used as a screening test in patients with advanced lung adenocarcinoma; however, positive <i>ROS1</i> IHC results should be confirmed by a molecular or cytogenetic method.
Expert Consensus Opinion: <i>BRAF</i> molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>BRAF</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> testing is negative.	<i>BRAF testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.</i>
Expert Consensus Opinion: <i>RET</i> molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>RET</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> testing is negative.	<i>RET</i> molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>RET</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , <i>BRAF</i> , and <i>ROS1</i> testing is negative.
Expert Consensus Opinion: <i>ERBB2 (HER2)</i> molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>ERBB2 (HER2)</i> mutation analysis as part of a larger testing panel performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> testing is negative.	<i>ERBB2 (HER2)</i> molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>ERBB2 (HER2)</i> mutation analysis as part of a larger testing panel performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , <i>BRAF</i> , and <i>ROS1</i> testing is negative.
Expert Consensus Opinion: <i>KRAS</i> molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include <i>KRAS</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> testing is negative.	<i>KRAS</i> molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include <i>KRAS</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , <i>BRAF</i> , and <i>ROS1</i> testing is negative.
Expert Consensus Opinion: <i>MET</i> molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>MET</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> testing is negative.	<i>MET</i> molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include <i>MET</i> as part of larger testing panels performed either initially or when routine <i>EGFR</i> , <i>ALK</i> , <i>BRAF</i> , and <i>ROS1</i> testing is negative.
Key Question 2: What methods should be used to perform molecular testing?	
Recommendation: IHC is an equivalent alternative to fluorescent in situ hybridization (FISH) for <i>ALK</i> testing.	IHC is an equivalent alternative to FISH for <i>ALK</i> testing. <i>CAP/IASLC/AMP Qualifying Statement: ALK IHC is an acceptable standard alternative to FISH, and treatment decisions can be made when IHC results are clearly positive, as manifested by strong granular cytoplasmic staining with or without membrane accentuation, or negative; however, weak staining can be challenging to interpret, and the specificity of weak staining relative to FISH should be determined in each laboratory during validation.</i>
Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond <i>EGFR</i> , <i>ALK</i> , and <i>ROS1</i> .	Multiplexed genetic sequencing panels are preferred, where available , over multiple single-gene tests to identify other treatment options beyond <i>EGFR</i> , <i>ALK</i> , <i>BRAF</i> , and <i>ROS1</i> .
Expert Consensus Opinion: Laboratories should ensure that test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved using an alternative method or sample.	Laboratories should ensure that test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved using an alternative method or sample.
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.	Physicians may use molecular biomarker testing in tumors with: a. an adenocarcinoma component; b. nonsquamous non–small-cell histology; c. any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver (eg, young age [< 50 years]; light or absent tobacco exposure).
Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?	

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Table 2. Comparison of CAP/IASLC/AMP Recommendations and ASCO Endorsed Recommendations (continued)

CAP/IASLC/AMP Recommendation	ASCO Endorsed Recommendation (with modifications or qualifying statements in bold italics)
Strong Recommendation: In patients with lung adenocarcinoma who harbor sensitizing <i>EGFR</i> mutations and have progressed after treatment with an EGFR-targeted tyrosine kinase inhibitor (TKI), physicians must use <i>EGFR</i> T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.	In patients with lung adenocarcinoma who harbor sensitizing <i>EGFR</i> mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use <i>EGFR</i> T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.
Recommendation: Laboratories testing for <i>EGFR</i> T790M mutation in patients with secondary clinical resistance to EGFR-targeted TKIs should deploy assays capable of detecting <i>EGFR</i> T790M mutations in as little as 5% of viable cells.	Laboratories testing for <i>EGFR</i> T790M mutation in patients with secondary clinical resistance to EGFR-targeted TKIs should deploy assays capable of detecting <i>EGFR</i> 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 <i>ALK</i> mutational status for patients with lung adenocarcinoma with sensitizing <i>ALK</i> mutations who have progressed after treatment with an <i>ALK</i> -targeted TKI.	There is currently insufficient evidence to support a recommendation for or against routine testing for <i>ALK</i> mutational status for patients with lung adenocarcinoma with sensitizing <i>ALK</i> mutations who have progressed after treatment with an <i>ALK</i> -targeted TKI.
Key Question 5: What is the role of testing for circulating cell-free DNA (cfDNA) for patients with lung cancer?	
No Recommendation: There is currently insufficient evidence to support the use of cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma.	There is currently insufficient evidence to support the use of 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 plasma cfDNA assay to identify EGFR mutations.	In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a plasma cfDNA assay to identify EGFR mutations.
Expert Consensus Opinion: Physicians may use plasma cfDNA methods to identify <i>EGFR</i> T790M mutations in patients with lung adenocarcinoma with progression or secondary clinical resistance to EGFR-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative.	Physicians may use plasma cfDNA methods to identify <i>EGFR</i> T790M mutations in patients with lung adenocarcinoma with progression or secondary clinical resistance to EGFR-targeted TKIs; 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 molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of <i>EGFR</i> or other mutations, or the identification of <i>EGFR</i> T790M mutations at the time of EGFR TKI resistance.	There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of <i>EGFR</i> or other mutations, or the identification of <i>EGFR</i> T790M mutations at the time of EGFR TKI resistance.
NOTE. Reprinted from Lindeman NI, Cagle PT, Aisner DL, et al. 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. <i>Arch Pathol Lab Med</i> . doi: 10.5858/arpa.2017-0388-CP, published online ahead of print November 2017, with permission from <i>Archives of Pathology & Laboratory Medicine</i> . Copyright 2017 College of American Pathologists. Abbreviations: AMP, Association for Molecular Pathology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer.	

patients with lung cancer. The CAP/IASLC/AMP recommendations are listed in the Bottom Line Box, with qualifying statements from the ASCO Endorsement Panel. The full CAP/IASLC/AMP guideline is available at <http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2017-0388-CP>.

OVERVIEW OF THE ASCO GUIDELINE ENDORSEMENT PROCESS

The American Society of Clinical Oncology (ASCO) has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodologic quality using the “Rigour of Development” subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (see Methodology Supplement for more detail.)

Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (“ASCO”) to assist providers in clinical decision making. The information therein should not be relied upon 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. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as 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

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include Employment; Leadership; Stock or Other Ownership; Honoraria, Consulting or Advisory Role; Speaker's Bureau; Research Funding; Patents, Royalties, Other Intellectual Property; Expert Testimony; Travel, Accommodations, Expenses; and Other Relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions: (1) Which new genes should be tested for in patients with lung cancer? (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 a targetable mutation who have relapsed on targeted therapy? (5) What is the role of testing for circulating cell-free DNA (cfDNA) for patients with lung cancer?

SUMMARY OF THE CAP/IASLC/AMP GUIDELINE DEVELOPMENT METHODOLOGY

The Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors was updated jointly by CAP, IASLC, and AMP. A systematic search of MEDLINE (Ovid Technologies, New York, NY) and PubMed from January 1, 2012, to June 27, 2016, was conducted. Additional searches were conducted in Scopus (Amsterdam, the Netherlands) to identify publications not indexed in MEDLINE. The clinicaltrials.gov Web site, guideline repository sites such as the National Guidelines Clearinghouse (guidelines.gov) and the Guidelines International Network (g-i-n.net), and other organizational Web sites were also searched. Details of the search strategies, the study inclusion criteria, and outcomes of interest are available

at <http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2017-0388-CP>. The searches identified 21 studies for inclusion in the guideline's update of the 2013 CAP/IASLC/AMP recommendations and 118 articles that met the inclusion criteria for the questions that were new to this update. The three participating organizations convened an Expert Panel that included practicing pathologists and oncologists with expertise in lung carcinoma, which met three times by teleconference and two times in person to develop the scope, draft recommendations, review and respond to solicited feedback, and assess the quality of evidence. The guideline draft was posted on the AMP Web site for an open comment period that took place between June 28, 2016, and August 2, 2016. Feedback from this process was incorporated into the draft guideline. Finally, each of the three organizations instituted a separate review process to approve the guideline.

METHODS AND RESULTS OF THE ASCO REVIEW

An initial methodology review of the Molecular Testing for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors was completed using the Rigour of Development subscale from the AGREE II instrument. Overall, the guideline scored 96% (Methodology Supplement). Detailed results of the scoring for this guideline are available upon request at guidelines@asco.org. Three content experts provided a preliminary ASCO review of the guideline. They found that the recommendations were well supported and suggested that the recommendations could be endorsed with the appropriate minor modifications. Each section, including the Introduction, Methods, Results, Recommendations, Conclusions, and Supplemental Material were clear and well referenced from the systematic review. After these initial methodology and content reviews, the ASCO Lung Biomarkers Endorsement Panel, which consisted of individuals with expertise in medical oncology, surgical oncology, pathology, pulmonology, radiology, and guideline development methodology, was formed and proceeded to meet via teleconference to review and discuss the Molecular Testing for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors guideline.

CAP/IASLC/AMP guideline development methods call for a review of the current guideline when practice-changing evidence is published or, at most, 4 years after publication. Because the ASCO Endorsement Panel was aware that the CAP/IASLC/AMP Expert Panel would be continuously monitoring the literature for signals that the guideline should be updated, the ASCO Panel chose not to conduct an additional review of the literature as part of this endorsement process. Therefore, the evidence base for this guideline is current to the final search date of the CAP/IASLC/AMP search strategy. However, the ASCO Endorsement Panel did consider the new US Food and Drug Administration (FDA) approval of stand-alone BRAF testing in 2017 during its endorsement process.

The Panel discussed each recommendation and agreed that the recommendations were generally clear, thorough, and based on the most relevant scientific evidence in this content area and that they present options that will be acceptable to patients. Overall, the ASCO Expert Panel agreed with the recommendations as stated in the guideline, with minor qualifications, which are outlined

in the Bottom Line Box and described in the Endorsement Recommendation section. All funding for the administration of the project was provided by ASCO.

This is the most recent information as of the publication date. For updates and the most recent information and to submit new evidence, please visit www.asco.org/thoracic-cancer-guidelines and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

ENDORSEMENT RECOMMENDATION

CAP/IASLC/AMP chose to update the joint guideline on molecular testing to incorporate advances in the field that have occurred since publication of the previous version.² ASCO endorses this update with minor modifications by the ASCO Expert Panel, as presented in the Bottom Line Box and discussed here. The ASCO Panel also included text from the CAP/IASLC/AMP narrative to provide context for two of the endorsed recommendations. A qualifying statement from the CAP/IASLC/AMP narrative was added to recommendation 8 on *ALK* immunohistochemistry (IHC) to clarify the significance of strong, negative, or weak granular cytoplasmic staining. The CAP/IASLC/AMP recommendation on *ALK* IHC was based on published evidence that tests based on the 5A4 and D5F3 monoclonal antibodies showed sensitivities and specificities ranging from 95% to 100%. For recommendation 11, the Panel also added text from the original CAP/IASLC/AMP document to provide clarification of clinical and pathologic factors that warrant molecular biomarker testing for oncogenic drivers, particularly in tumors with histologic components other than adenocarcinoma. In addition, in updated/modified recommendation 1, the ASCO Panel specifically indicated smear preparations as cytologic preparations other than cell blocks that, although not preferred, would be suitable as specimens for lung cancer biomarker testing. With regard to recommendation 17, in their discussions, the ASCO Panel also noted that for patients with *EGFR*-mutated non-small-cell lung cancer in whom cfDNA testing does not reveal a T790M mutation, direct tumor sampling may be helpful in identifying not only a T790M mutation but also other mechanisms of secondary resistance such as neuroendocrine differentiation or alternative genetic mutations.

The CAP/IASLC/AMP recommendation related to *BRAF* testing in patients with advanced adenocarcinoma was not endorsed by the ASCO Panel. When CAP/IASLC/AMP originally drafted updated recommendations, *BRAF* testing had not yet been approved by the FDA. However, the FDA has since granted approval for stand-alone *BRAF* testing. Therefore, the ASCO panel chose to incorporate this into the recommendations and to recommend *BRAF* testing for all patients with advanced lung adenocarcinoma. FDA approval was based on a 2016 phase II single-arm trial¹ showing a disease control rate (DCR) of 58% with second-line therapy with dabrafenib and a DCR of 75% with second-line therapy with dabrafenib plus trametinib in patients with stage IV non-small-cell lung cancer who had *BRAF* V600E mutations.⁴ The CAP/IASLC/AMP Expert Panel indicated awareness of the FDA approval in their guideline narrative and stated that they will most likely recommend stand-alone *BRAF* testing in the next iteration of their guideline. Following this modification to the CAP/IASLC/AMP recommendations, the ASCO Expert Panel also chose to add *BRAF* testing to the routine tests listed

in recommendations 4 through 7 for other molecular markers as well as to recommendation 9 for multiplexed genetic sequencing panels.

The Endorsement Panel agreed with the conclusions of the CAP/IASLC/AMP Expert Panel that there was adequate evidence to support the recommendation for *ROS1* testing in patients with advanced-stage adenocarcinoma.¹ *ROS1* testing has been approved by the FDA based on a 50-person phase I clinical trial that demonstrated a 72% response rate to targeted therapy with crizotinib in patients with *ROS1*-rearranged non-small-cell lung cancer.⁵ An additional 32-patient retrospective study demonstrated an 80% rate of response for patients with *ROS1*-rearranged non-small-cell lung cancer who were treated with crizotinib.⁶

The ASCO Expert Panel also noted that, as is true for all guidelines, the interpretation and implementation of some of the statements may be influenced by the geographic location and the practice setting (academic v community). This may particularly be true for the statements that lack robust evidence and are either primarily consensus opinions or for statements that have no recommendation for or against a particular issue. There was discussion within the Expert Panel and the ASCO Clinical Practice Guidelines Committee regarding the cost of multiplexed genomic sequencing panels, and it was concluded that multiplexed panels are likely to be more efficient in terms of cost and tumor tissue requirements. For patients in whom initial testing (multiplex or sequential) for *EGFR* and *BRAF* mutations as well as *ALK* and *ROS1* rearrangements or fusions is negative, further genomic testing may be considered depending upon the hospital/institutional and geographic setting, and a decision to this effect may be made after discussion with the patient. However, a detailed discussion of this aspect is beyond the scope of the current guideline and endorsement.

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners, survivors of cancer, and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ASCO and the Expert Panel are aware that CAP/IASLC/AMP is monitoring the literature for the latest substantive publications in the field of molecular testing and that they plan to update their guideline when new high-quality practice-changing evidence becomes available. One area of future research that was identified during the guideline review process was the consideration of rebiopsy after progression on an *ALK* inhibitor to identify secondary *ALK* mutations that might guide the use of next-generation *ALK* inhibitors. ASCO will continue to follow CAP/IASLC/AMP's guideline development updates on this topic and will incorporate future versions into our endorsement process as they become available.

ADDITIONAL RESOURCES

More information, including a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

Related ASCO Guidelines

- Molecular Testing for Selection of Patients With Lung Cancer for EGFR and ALK Tyrosine Kinase Inhibitors Guideline Endorsement³ (<http://ascopubs.org/doi/10.1200/jco.2014.57.3055>)
- Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer Update⁷ (<http://ascopubs.org/doi/10.1200/JCO.2017.74.6065>)
- Patient–Clinician Communication⁸ (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

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AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted 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 Clinical Practice Guideline Update**

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Appendix

Table A1. Guideline Expert Panel Membership

Name (designation)	Affiliation/Institution	Role/Area of Expertise
Gregory P. Kalemkerian, MD (co-chair)	University of Michigan, Ann Arbor, MI	Medical oncology
Navneet Narula, MD (co-chair)	Weill Cornell Medical College, New York, NY	Surgical pathology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology, Alexandria, VA	Health research methodology/ ASCO staff member
William Biermann, MD, MBA	Einstein Healthcare Network, East Norriton, PA	Practice Guidelines Implementation Network representative
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Martin Reck, MD, PhD	Lung Clinic Grosshansdorf, Grosshansdorf Germany	Thoracic oncology
Anjali Saqi, MD MBA	Columbia University Medical Center, New York, NY	Surgical pathology, cytopathology
Michael Simoff, MD	Henry Ford Hospital, Detroit, MI	Interventional pulmonary medicine
Navneet Singh, MBBS, MD, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Pulmonary medicine/thoracic medical oncology
Baskaran Sundaram, MD	Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA	Interventional thoracic radiology