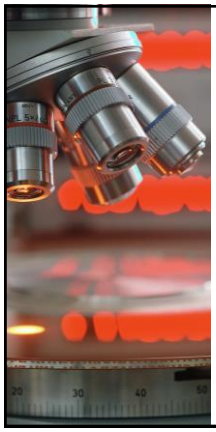

2015 Pulmonary Pathology Society
Biennial Meeting at San Francisco

Update on revisions to CAP/IASLC/AMP lung cancer biomarker guidelines

Yasushi Yatabe, MD, PhD.
Dept of Pathology and Molecular Diagnostics
Aichi Cancer Center

ORIGINAL ARTICLE

J Thorac Oncol. 2013;8:823-59

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

Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dhananjay Arun Chitale, MD; Sanja Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Juan-Sebastian Saldivar, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

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Co-chairs

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Summary of Recommendations

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 tyrosine kinase inhibitor therapy, patients with lung adenocarcinoma should not be excluded from testing based on clinical characteristics.

1.1b: Recommendation: ALK molecular testing should be used to select patients for ALK-targeted tyrosine kinase inhibitor therapy, patients with lung adenocarcinoma should not be excluded from testing based on 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 full 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 and pure small cell carcinomas.

1.3: Recommendation: In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (e.g., young 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: In 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.

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Summary of Recommendations

I. When should molecular testing of lung cancer be performed?
II. How should EGFR testing be performed?
III. How Should ALK testing be performed?
IV. Should other genes be routinely tested in lung adenocarcinomas?
V. How should molecular testing of lung adenocarcinomas be implemented and operationalized?

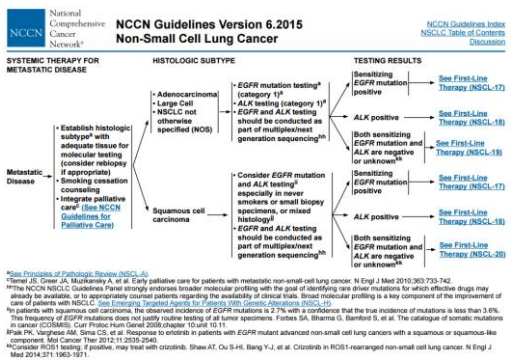
Key Questions

1. Which Patients Should Be Tested for *EGFR* Mutations and *ALK* Rearrangements?
2. When Should a Patient Specimen Be Tested for EGFR Mutation or ALK Rearrangement?
3. How Rapidly Should Test Results Be Available?
4. How Should Specimens Be Processed for EGFR Mutation Testing?
5. What Are the Specimen Requirements for EGFR Testing?
6. How Should EGFR Testing Be Performed?
7. What Is the Role of KRAS Analysis in Selecting Patients for Targeted Therapy With EGFR Tyrosine Kinase Inhibitors?
8. What Additional Testing Considerations Are Important in the Setting of Secondary or Acquired EGFR TKI Resistance?
9. How Should ALK Testing be Performed?
10. Are Other Molecular Markers Suitable for Testing in Lung Cancer?
11. Must All Adenocarcinomas be Tested for Both EGFR and ALK?
12. How Should EGFR and ALK Results Be Reported
13. How Should EGFR and ALK Results Be Reported?
14. How Shall Quality Assurance Be Maintained?

Pathologist-related recommendations

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 full 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 and pure small cell carcinomas.

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



Pathologist-related recommendations

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: In 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.

Pathologist-related recommendations

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, when needed.

⇩

10% or more tumor cells in the specimens for EGFR testing

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 employ (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.

Pathologist-related recommendations

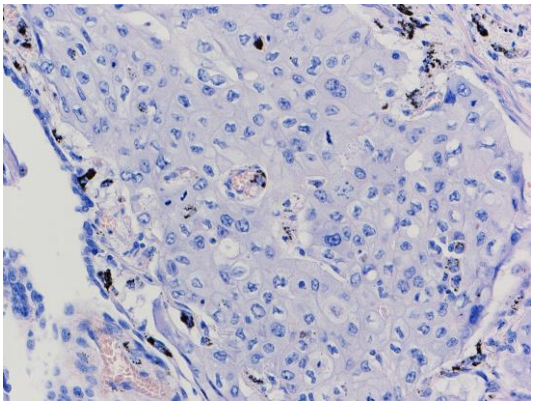
5.3: Expert consensus opinion: A pathologist should assess the tumor content of each specimen and either perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment, when needed.

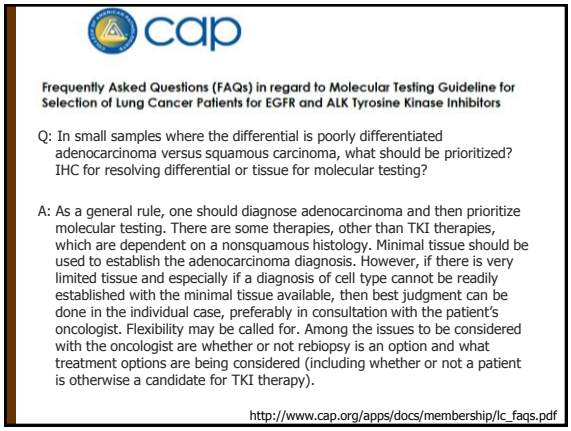
⇩

A pathologist should select the slides and participate in the interpretation for ALK FISH

9.3: Expert consensus opinion: A pathologist should be involved in the selection of sections for FISH testing, by assessing tumor architecture, cytology, and specimen quality.

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 cytogeneticists or technologists with specialized training in solid tumor FISH analysis.



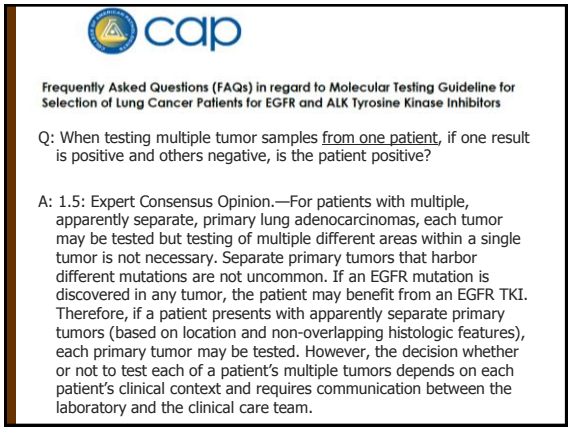


Frequently Asked Questions (FAQs) in regard to Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Q: In small samples where the differential is poorly differentiated adenocarcinoma versus squamous carcinoma, what should be prioritized? IHC for resolving differential or tissue for molecular testing?

A: As a general rule, one should diagnose adenocarcinoma and then prioritize molecular testing. There are some therapies, other than TKI therapies, which are dependent on a nonsquamous histology. Minimal tissue should be used to establish the adenocarcinoma diagnosis. However, if there is very limited tissue and especially if a diagnosis of cell type cannot be readily established with the minimal tissue available, then best judgment can be done in the individual case, preferably in consultation with the patient's oncologist. Flexibility may be called for. Among the issues to be considered with the oncologist are whether or not rebiopsy is an option and what treatment options are being considered (including whether or not a patient is otherwise a candidate for TKI therapy).

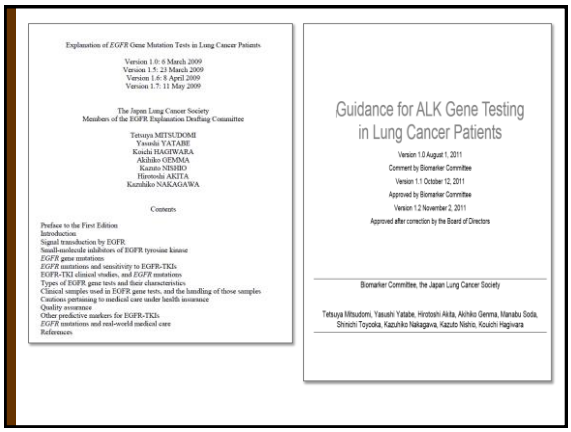
http://www.cap.org/apps/docs/membership/lc_faqs.pdf



Frequently Asked Questions (FAQs) in regard to Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Q: When testing multiple tumor samples from one patient, if one result is positive and others negative, is the patient positive?

A: 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. Separate primary tumors that harbor different mutations are not uncommon. If an EGFR mutation is discovered in any tumor, the patient may benefit from an EGFR TKI. Therefore, if a patient presents with apparently separate primary tumors (based on location and non-overlapping histologic features), each primary tumor may be tested. However, the decision whether or not to test each of a patient's multiple tumors depends on each patient's clinical context and requires communication between the laboratory and the clinical care team.



Explanation of *EGFR* Gene Mutation Tests in Lung Cancer Patients

Version 1.0: 6 March 2009
Version 1.5: 23 March 2009
Version 1.6: 8 April 2009
Version 1.7: 11 May 2009

The Japan Lung Cancer Society
Members of the EGFR Explanation Drafting Committee

Tetsuya MITSUDOMI
Yasushi YATABE
Koichi HAGIWARA
Akihiko GEMMA
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Contents

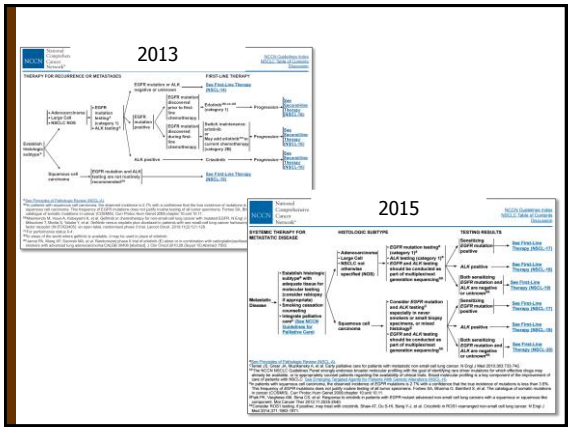
Preface to the First Edition
Introduction
Signal transduction by EGFR
Small-molecule inhibitors of EGFR tyrosine kinase
EGFR gene mutations
EGFR mutations and sensitivity to EGFR-TKIs
EGFR-TKI clinical studies, and *EGFR* mutations
Types of EGFR gene tests and their characteristics
Clinical samples used in EGFR gene tests, and the handling of those samples
Cautions pertaining to medical care under health insurance
Quality assurance
Other predictive markers for EGFR-TKIs
EGFR mutations and real-world medical care
References

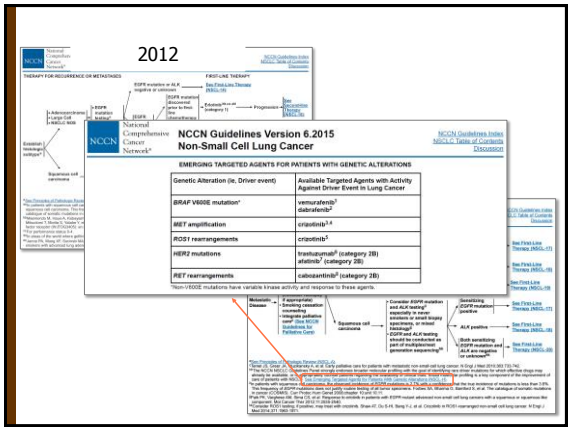
Guidance for ALK Gene Testing in Lung Cancer Patients

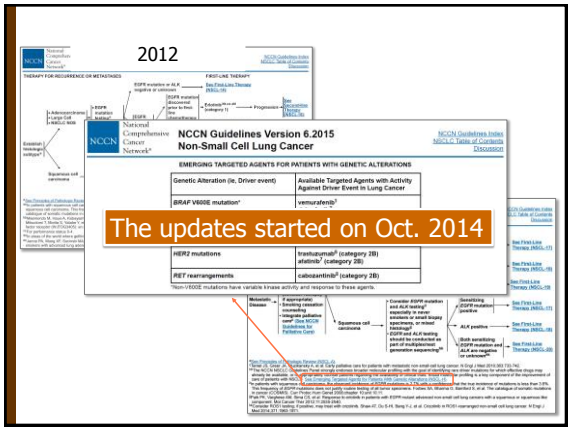
Version 1.0 August 1, 2011
Comment by Biomarker Committee
Version 1.1 October 12, 2011
Approved by Biomarker Committee
Version 1.2 November 2, 2011
Approved after correction by the Board of Directors

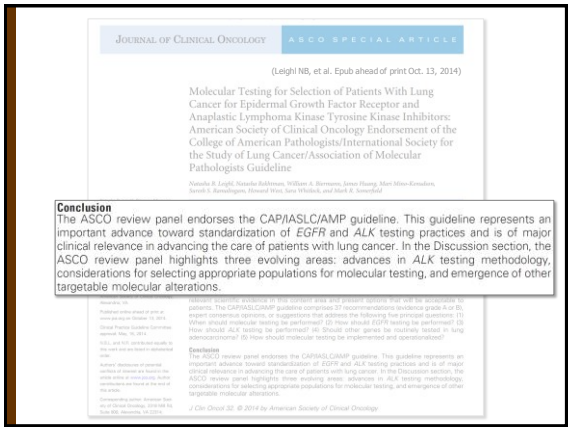
Biomarker Committee, the Japan Lung Cancer Society

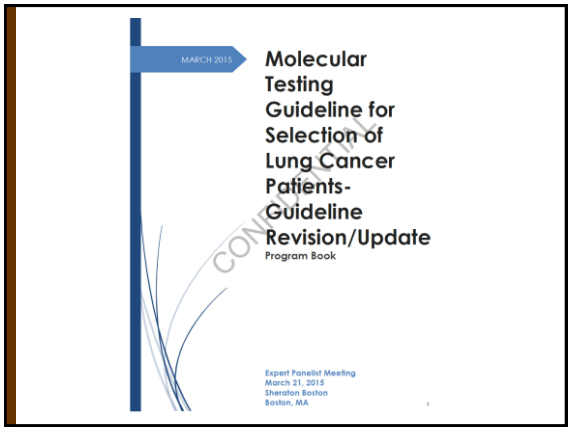
Tetsuya Mitsudomi, Yasushi Yatabe, Hirotoshi Akita, Akihiko Gemma, Manabu Soda, Shinichi Toyooka, Kazuhiko Nakagawa, Kazuto Nishio, Koichi Hagiwara





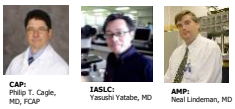






Panel members

CO-CHAIRS
Philip T. Cagle, MD,
Yasushi Yatabe, MD, PhD
Neal Lindeman, MD



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Two focuses

- Updates for EGFR and ALK testing
- Recommendations for the targetable genes, previously not addressed

Key questions

I. What other genes, previously not addressed, should be tested in lung adenocarcinoma?

II. Is immunohistochemistry reliable for screening for *ALK* translocations?

III. In patients who are undergoing treatment with targeted tyrosine kinase inhibitors, what are the types and rates of secondary resistance?

IV. Are there biomarkers that are predictive of clinical outcome in squamous and small cell carcinomas?

V. What are the clinical performance characteristics of circulating DNA/CTC in plasma when used for diagnosis of primary lung adenocarcinoma or relapse?

I. What other genes, previously not addressed, should be tested in lung adenocarcinoma?

1. ROS1
2. RET
3. MET
4. BRAF
5. HER2

   i. What demographic, histopathologic and clinical characteristics should be used to select patients?
   ii. Are there downstream improvements in clinical outcomes when individuals are tested for any alterations, compared to when individuals are not tested?
   iii. What are the clinical performance characteristics of the available assays, including, FISH, IHC and advanced sequencing?

6. NGS/multiplex assays:
   When conducting molecular testing of *ROS1*, *RET*, *MET*, *BRAF* and *HER2/ERBB2*, what technical validation experiments should be performed in order for an assay to be considered safe and reliable for use in patient care?

II. Is immunohistochemistry reliable for screening for ALK translocations?

7. When screening for ALK translocations, does IHC provide equivalent clinical performance characteristics when compared to FISH and RNA/DNA sequencing methods for ALK translocations?
8. When considering IHC antibodies for screening of ALK translocations, is there a difference in clinical performance characteristics for ALK1, 5A4, or D5F3 antibodies and/or detection platforms?
9. When comparing IHC techniques for screening of ALK translocations, do any emerging techniques (anchored PCR, ultrasensitive detection systems) provide superior clinical performance characteristics?
10. If potential ALK translocations are detected in patients by a sensitive IHC assay, are the clinical performance characteristic sufficient, or does the ALK translocation need to be confirmed by an orthogonal method?

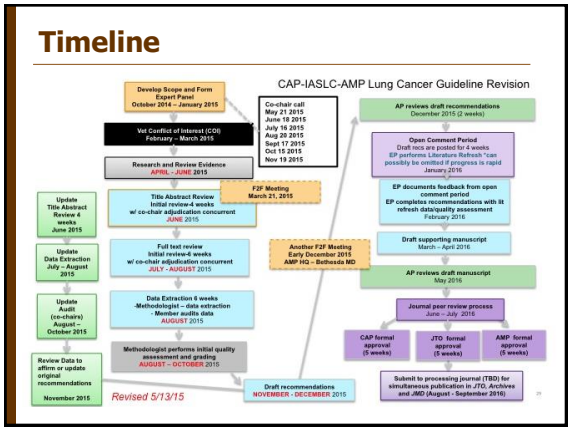
III. In patients who are undergoing treatment with targeted tyrosine kinase inhibitors, what are the types and rates of secondary resistance?

11. Does pre-treatment discovery of de novo resistance-related mutations improve clinical outcomes?
12. Does evaluation of rebiopsy specimen improve clinical outcomes?
13. When assessing the resistance-related mutations, what are the clinical performance characteristics of the emerging technologies, including rebiopsy, NGS, and circulating DNA/CTC?

Other Key questions

IV. Are there biomarkers that are predictive of clinical outcome in squamous and small cell carcinomas?

V. What are the clinical performance characteristics of circulating DNA/CTC in plasma when used for diagnosis of primary lung adenocarcinoma or relapse?


Timeline
CAP-IASLC-AMP Lung Cancer Guideline Revision
Develop Scope and Form Expert Panel October 2014 – January 2015
Vet Conflict of Interest (COI) February – March 2015
Research and Review Evidence APRIL – JUNE 2015
Co-chair call May 21 2015 June 18 2015 July 16 2015 Aug 20 2015 Sept 17 2015 Oct 15 2015 Nov 19 2015
F2F Meeting March 21, 2015
Update Title Abstract Review 4 weeks June 2015
Title Abstract Review Initial review-4 weeks w/ co-chair adjudication concurrent JUNE 2015
Update Data Extraction July – August 2015
Full text review Initial review-4 weeks w/ co-chair adjudication concurrent JULY - AUGUST 2015
Another F2F Meeting Early December 2015 AMP HQ – Bethesda MD
Update Audit (co-chairs) August – October 2015
Data Extraction 6 weeks -Methodologist – data extraction - Member audits data AUGUST 2015
Methodologist performs initial quality assessment and grading AUGUST – OCTOBER 2015
Review Data to affirm or update original recommendations November 2015
Revised 5/13/15
Draft recommendations NOVEMBER - DECEMBER 2015
AP reviews draft recommendations December 2015 (2 weeks)
Open Comment Period Draft recs are posted for 4 weeks EP performs Literature Refresh *can possibly be omitted if progress is rapid January 2016
EP documents feedback from open comment period EP completes recommendations with lit refresh data/quality assessment February 2016
Draft supporting manuscript March – April 2016
AP reviews draft manuscript May 2016
Journal peer review process June – July 2016
CAP formal approval (5 weeks)
JTO formal approval (5 weeks)
AMP formal approval (5 weeks)
Submit to processing journal (TBD) for simultaneous publication in JTO, Archives and JMD (August - September 2016)