Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision
2016 Draft Recommendations – CONFIDENTIAL

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Draft statements are not valid as of August 2, 2016.

	BIOMARKER SELECTION	
#	**2016 Draft Recommendation Statement**	**Associated 2013 Original Reaffirmed Recommendation Number *OR* New Recommendation Statement in 2016**
1	**Strong Recommendation:** Physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients at the time of diagnosis for patients presenting with advanced stage disease or at progression in patients who originally presented with lower stage disease but were not previously tested.	**2.1a: Recommendation:** *EGFR* mutation testing should be ordered at the time of diagnosis for patients presenting with advanced stage disease (stage IV according to the 7th edition Tumor Node Metastasis (TNM) staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested. **2.1b: Suggestion:** *ALK* rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.
2	**Expert Consensus Opinion:** Molecular testing of tumors at diagnosis from patients presenting with early stage disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its multidisciplinary oncology team.	**2.2a: Expert consensus opinion:** *EGFR* testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

		2.2b: Expert consensus opinion: *ALK* testing of tumors at diagnosis from patients presenting 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.
3	**Strong Recommendation:** Physicians may use *EGFR* and *ALK* testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.	**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.
4	**Strong recommendation:** Physicians must use *EGFR* molecular testing to select lung adenocarcinoma patients for EGFR-targeted therapy, irrespective of clinical characteristics or when adenocarcinoma cannot be excluded.	**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.
5	**Strong Recommendation:** In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted tyrosine kinase inhibitor, physicians must use *EGFR* T790M mutational testing when selecting patients for third generation EGFR-targeted therapy.	New Recommendation Statement
6	**Strong Recommendation:** Physicians must use *ALK* testing to select lung adenocarcinoma patients for ALK-targeted therapy irrespective of clinical characteristics or when adenocarcinoma cannot be excluded.	**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.

7	**Recommendation:** Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.	**1.4: Recommendation:** To determine *EGFR* and *ALK* status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.
8	**No Recommendation:** There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for lung adenocarcinoma patients with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted tyrosine kinase inhibitor.	New Recommendation Statement
9	**Recommendation:** Physicians should use *ROS1* molecular or cytogenetic testing on all lung adenocarcinoma patients, irrespective of clinical characteristics, when selecting patients for ROS1-targeted therapy.	New Recommendation Statement
10	**Expert Consensus Opinion:** *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. As part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative, it is appropriate to include *BRAF* in the panel done as an initial test or to identify other treatment options.	New Recommendation Statement
11	**Expert Consensus Opinion:** *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. As part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative, it is appropriate to include *RET* in the panel done as an initial test or to identify other treatment options.	New Recommendation Statement
12	**Expert Consensus Opinion:** *ERBB2* (*HER2*) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. As part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative, it is appropriate to include *ERBB2* (*HER2*) in the panel done as an initial test or to identify other treatment options. Note: There is insufficient evidence to recommend IHC or FISH testing for *ERBB2* (*HER2*) amplification or expression status to guide selection of therapy in lung adenocarcinoma patients.	New Recommendation Statement

13	**Expert Consensus Opinion:** *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. As part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative, it is appropriate to include *KRAS* in the panel done as an initial test or to identify other treatment options.	New Recommendation Statement
14	**Expert Consensus Opinion:** *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. As part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative, it is appropriate to include *MET* in the panel done as an initial test or to identify other treatment options.	New Recommendation Statement
15	**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.	New Recommendation Statement

	PRE-ANALYTICAL	
#	**2016 Draft Recommendation Statement**	**Associated 2013 Original Reaffirmed Recommendation Number *OR* New Recommendation Statement in 2016**
1	**Recommendation:** Pathologists and laboratories should utilize tissue sparing techniques to preserve tumor tissue for diagnosis and to enable subsequent lung cancer biomarker testing.	**2.3: Recommendation:** Tissue should be prioritized for *EGFR* and *ALK* testing.
2	**Expert consensus opinion:** Pathologists should select samples for lung cancer biomarker testing.	**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.
3	**Expert consensus opinion:** Pathologists should assess the tumor content of each specimen. When indicated, pathologists should directly perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment.	**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.
4	**Expert consensus opinion:** Pathologists should determine the adequacy of specimens for lung cancer biomarker molecular testing by assessing cancer cell content, tissue preservation, and nucleic acid quantity and quality.	**5.1: Expert consensus opinion:** Pathologists should determine the adequacy of specimens for *EGFR* testing by assessing cancer cell content and DNA quantity and quality.
5	**Recommendation:** Pathologists should use formalin-fixed, paraffin-embedded specimens or fresh, frozen, or alcohol-fixed specimens for	**4.1. Expert consensus opinion:** Pathologists should use formalin-fixed, paraffin-embedded specimens or fresh, frozen, or alcohol-

	lung cancer biomarker molecular testing. Other tissue treatments, such as acidic or heavy metal fixatives, or acid decalcifying solutions, should be avoided in specimens destined for molecular testing.	fixed specimens for PCR-based EGFR mutation tests. Other tissue treatments (eg, acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for EGFR testing.
6	**Recommendation:** Pathologists may utilize either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.	**4.2 Expert consensus opinion:** Cytologic samples are also suitable for *EGFR* and *ALK* testing, with cell blocks being preferred over smear preparations.
7	**Expert consensus opinion:** In patients with multiple, apparently separate, primary lung adenocarcinomas, laboratories may test each tumor, but testing of multiple different areas within a single tumor is not necessary.	**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.
8	**Expert consensus opinion:** In laboratories with average turnaround times beyond two weeks, the laboratory should ensure that a more rapid in-house or reference laboratory testing option is available for specimens from patients with advanced stage lung cancer.	**3.2. Expert consensus opinion:** Laboratories with average turnaround times beyond two weeks need to make available a more rapid test–either in house or through a reference laboratory–in instances of clinical urgency.
9	**Expert consensus opinion:** Laboratories should have lung cancer biomarker testing results available for oncology team review within two weeks (10 working days) of receiving the specimen in the testing laboratory.	**3.1: Expert consensus opinion:** *EGFR* and *ALK* results should be available within two weeks (10 working days) of receiving the specimen in the testing laboratory.
10	**Expert Consensus Opinion:** Laboratories should establish processes to ensure that specimens that have a histopathological diagnosis are sent to the molecular pathology laboratory within 3 working days of receiving requests.	**3.3. Expert consensus opinion:** Laboratory departments should establish processes to ensure that specimens that have a final histopathological diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.

	ANALYTICAL	
#	**2016 Draft Recommendation Statement**	**Associated 2013 Original Reaffirmed Recommendation Number *OR* New Recommendation Statement in 2016**
1	**Expert Consensus Opinion:** Clinical *EGFR* mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.	**6.3 Expert consensus opinion:** Clinical *EGFR* mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of *EGFR*-mutated lung adenocarcinomas.

2	**Expert consensus opinion:** Laboratories should employ, 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.	**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.
3	**Strong Recommendation:** Laboratories should not use total *EGFR* expression by IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.	**6.4. Recommendation:** Immunohistochemistry for total *EGFR* is not recommended for selection of EGFR TKI therapy
4	**Recommendation:** Pathologists and laboratories should not use *EGFR* copy number analysis (*i.e.*, FISH or CISH) to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.	**6.5. Recommendation:** *EGFR* copy number analysis (ie, FISH or CISH) is NOT recommended for selection of EGFR TKI therapy.
5	**Expert Consensus Opinion:** In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may utilize a mutation-specific IHC assay for EGFR testing.	New Recommendation Statement
6	**Recommendation:** Laboratories testing for *EGFR* T790M mutation in patients with acquired resistance to EGFR-targeted kinase inhibitors should deploy assays capable of detecting EGFR T790M mutations in as little as 4% of viable cells (2% of *EGFR* alleles).	New Recommendation Statement
7	**Recommendation:** When performing ALK testing, physicians can utilize IHC as an equivalent alternative to FISH.	New Recommendation Statement
8	**Expert consensus opinion:** Pathologists should participate in the interpretation of FISH, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.	**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.
9	**No Recommendation:** There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.	New Recommendation Statement

10	**Expert Consensus Opinion:** Physicians may use *ROS1* IHC as a screening test in lung adenocarcinoma patients; however, positive *ROS1* IHC results should be confirmed by a molecular or cytogenetic method.	New Recommendation Statement
11	**No Recommendation:** There is currently insufficient evidence to recommend IHC or FISH testing for *ERBB2* (*HER2*) amplification or expression status to guide selection of therapy in lung adenocarcinoma patients.	New Recommendation Statement
12	**Recommendation:** In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay for *EGFR*.	New Recommendation Statement
13	**Expert Consensus Opinion:** Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or acquired resistance to EGFR-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.	New Recommendation Statement
14	**No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell (CTC) molecular methods for the diagnosis of primary lung adenocarcinoma.**	New Recommendation Statement
15	**Expert Consensus Opinion:** Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*.	New Recommendation Statement

	POST-ANALYTICAL	
#	**2016 Draft Recommendation Statement**	**Associated 2013 Original Reaffirmed Recommendation Number *OR* New Recommendation Statement in 2016**
1	**Recommendation:** Pathologists and laboratories should ensure that lung cancer biomarker testing reports of all types include both results and interpretation sections readily understandable by clinical oncologists and by non-specialist pathologists.	**12.1: Expert consensus opinion:** *EGFR* mutation testing reports and ALK FISH reports should include a results and interpretation section readily understandable by clinical oncologists and by nonspecialist pathologists.
2	**Expert Consensus Opinion:** Laboratories should ensure test results that are unexpected, discordant, equivocal, or otherwise of low confidence are be confirmed or resolved using an alternative method or sample.	New Recommendation Statement

	VALIDATION & QUALITY	

#	2016 Draft Recommendation Statement	Associated 2013 Original Reaffirmed Recommendation Number *OR* New Recommendation Statement in 2016
1	**Expert consensus opinion:** Laboratories should establish laboratory-specific requirements for the minimum proportion and number of cancer cells needed for mutation detection during validation.	**5.2. Expert consensus opinion:** Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.
2	**Strong recommendation:** Laboratories must use clinically validated lung cancer biomarker testing methods with appropriate performance characteristics, following standardized best practice guidelines for each technology.	**13.1: Expert consensus opinion:** *EGFR* and *ALK* testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.
3	**Strong Recommendation:** Laboratories should ensure that lung cancer biomarker testing follows similar quality control and quality assurance policies and procedures as for other clinical laboratory assays.	**14.1. Expert consensus opinion:** Laboratories should follow similar quality control and quality assurance policies and procedures for *EGFR* and *ALK* testing in lung cancers as for other clinical laboratory assays. In particular, Laboratories performing *EGFR* and *ALK* testing for TKI therapy should enroll in proficiency testing, if available.