The College of American Pathologists offers these templates to assist pathologists in providing clinically useful and relevant information when reporting results of biomarker testing. The College regards the reporting elements in the templates as important elements of the biomarker test report, but the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these templates as educational tools to assist pathologists in the useful reporting of relevant information. It did not issue them for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the templates might be used by hospitals, attorneys, payers, and others. The College cautions that use of the templates other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

Also see p. 157.

**TEMPLATE FOR REPORTING RESULTS OF BIOMARKER TESTING OF SPECIMENS FROM PATIENTS WITH NON–SMALL CELL CARCINOMA OF THE LUNG**

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

### BIOMARKER REPORTING TEMPLATE

**Lung**

Select a single response unless otherwise indicated.

Note: Use of this template is optional.

+ Data elements preceded by this symbol are not required.

### + SPECIMEN ADEQUACY

+ Adequacy of Sample for Testing (note A)
  + ___ Adequate
  + ___ Suboptimal (explain): _____________________________

Note: If “Adequate” not selected, please refer to original laboratory report for explanation.

### + RESULTS

+ **EGFR Mutational Analysis** (note B)
  + ___ No mutation detected (wild-type EGFR allele)
  + ___ Mutation identified (select all that apply)
+ __ Exon 18 Gly719*
+ __ Exon 19 deletion*
+ __ Exon 20 insertion**
+ __ Exon 20 Thr790Met***
+ __ Exon 21 Leu858Arg*
+ __ Other (specify)***:

* Cannot be determined (explain): ____________
* This EGFR-activation mutation is associated with response to EGFR tyrosine kinase inhibitors.
** This form of EGFR-activating mutation is generally associated with resistance to EGFR tyrosine kinase inhibitors although insertions at or before position 768 can be associated with sensitivity.
*** This mutation is typically secondary to other EGFR-activating mutations and is associated with acquired resistance to tyrosine kinase inhibitor therapy. If seen in untreated/pretreated patients, it may be present in the germline and indicate a hereditary cancer syndrome, in which case, genetic counseling is suggested.
**** There are limited data on response to EGFR tyrosine kinase inhibitors for many of the uncommon EGFR-activating mutations.

+ **ALK Rearrangement** (note C)
  + __ No rearrangement detected*
  + __ Rearrangement identified**
  + __ Cannot be determined (explain): ____________
  + Polyosmy
  + __ Present***

* Absence of ALK rearrangement in cancer cells suggests that this tumor is unlikely to respond to treatment with a targeted inhibitor, such as crizotinib.

** ALK rearrangement predicts response to therapy with a targeted inhibitor, such as crizotinib.

*** Polyosmy involving the ALK locus confirms that fluorescence in situ hybridization (FISH) scoring was carried out in tumor cells but has no significance regarding response to therapy with crizotinib.

+ **KRAS Mutational Analysis**
  + __ No mutation detected (wild-type KRAS allele)
  + __ Mutation identified* (select all that apply)
    + Codon 12
      + __ Gly12Cys (GGT>TGT)
      + __ Gly12Asp (GGT>GAT)
      + __ Gly12Val (GGT>GT)
      + __ Gly12Ser (GGT>AGT)
      + __ Gly12Ala (GGT>GCT)
    + __ Gly12Arg (GGT>CGT)
  + __ Specific codon 12 mutation not stated
  + __ Other codon 12 mutation (specify): ____________
  + __ Other codon 12 mutation (specify): ____________
  + __ Other codon 12 mutation (specify): ____________
  + __ Other codon 12 mutation (specify): ____________
  + __ Other codon 12 mutation (specify): ____________
  + __ Other codon 12 mutation (specify): ____________

+ __ Other (specify)***:

Note: Please specify in the “Comments” section if different testing methods were used for different exons.

+ **Methods**

+ **EGFR Exons Assessed** (select all that apply)
  + __ 18
  + __ 19
  + __ 20
  + __ 21

+ **EGFR Mutational Analysis Testing Method** (select all that apply)
  + __ Direct (Sanger) sequencing
  + __ Pyrosequencing
  + __ High-resolution melting analysis
  + __ Polymerase chain reaction (PCR), allele-specific hybridization
  + __ Real-time PCR
  + __ Next-generation (high-throughput) sequencing
  + __ Other (specify): ____________

Note: Please specify in the “Comments” section if different testing methods were used for different exons.

+ **ALK Rearrangement Testing Method** (select all that apply)
  + __ In situ hybridization (fluorescence [FISH] or chromogenic [CISH])
  + __ Reverse transcriptase polymerase chain reaction (RT-PCR)
  + __ Fusions identified (specify): ____________
  + __ Immunohistochemistry
    + __ 5A4 clone
    + __ D5F3 clone
    + __ Ventana ALK (D5F3) immunohistochemistry (IHC) assay
  + __ Next-generation (high-throughput) sequencing
  + __ Other (specify): ____________

+ **KRAS Codons Assessed** (select all that apply)
  + __ 12
  + __ 13
  + __ 61

+ **KRAS Mutational Analysis Testing Method** (select all that apply)
  + __ Direct (Sanger) sequencing
  + __ Pyrosequencing
  + __ High-resolution melting analysis
  + __ PCR, allele-specific hybridization
  + __ Real-time PCR
  + __ Next-generation (high-throughput) sequencing
  + __ Other (specify): ____________

Note: Please specify in the “Comments” section if different testing methods were used for different codons.

+ **Testing Method for Other Markers** (note E)
  + __ Specify: ____________

* No specific tyrosine kinase inhibitors have been approved for lung adenocarcinomas with KRAS mutations. In addition, KRAS mutations are typically mutually exclusive of EGFR and ALK alterations.
Note: Fixative type, time to fixation (cold ischemia time), and time of fixation should be reported, if applicable, in this template or in the original pathology report (note F).

EXPLANATORY NOTES

Background

As of 2013, more than one-half of lung adenocarcinomas contain one of a number of identifiable genetic alterations; some of those can be targeted by a specific therapeutic inhibitor that is approved either by the US Food and Drug Administration or in clinical trials. The National Comprehensive Cancer Network (NCCN) recommends testing for EGFR mutations and ALK rearrangements to guide therapy for all patients with recurrent or metastatic lung adenocarcinomas.1 The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) have prepared a joint guideline that provides a detailed description of the patient and specimen requirements and acceptable testing designs and strategies for the detection of these alterations; the reader is referred to that guideline for details that are beyond the scope of this document.

Briefly, approximately 20% to 30% of lung adenocarcinomas contain an EGFR-activating mutation that predicts response to therapy with EGFR tyrosine kinase inhibitors, such as erlotinib.3–8 Up to 90% of response to therapy with EGFR tyrosine kinase inhibitors, in the LREA motif of exon 19 or as a leucine to arginine EGFR-mutant contain an guideline for details that are beyond the scope of this document.

Common problems include:

- Improper fixation (see “Fixation” guidelines below).
- Low tumor content, as defined by the molecular diagnostics laboratory. The cutoff for acceptable tumor content depends on the method used by the laboratory. Samples with tumor content below the recommended cutoff may be falsely negative and should be reported as indeterminate if no mutations are detected.

A: Suboptimal Specimen Definition.—Suboptimal specimens may be defined as those with:

- Improper fixation (see “Fixation” guidelines below).
- Low tumor content, as defined by the molecular diagnostics laboratory. The cutoff for acceptable tumor content depends on the method used by the laboratory. Samples with tumor content below the recommended cutoff may be falsely negative and should be reported as indeterminate if no mutations are detected.

B: Other Mutations.—“Other” mutations include uncommon variants, including exon 19 insertions or other missense variants in the kinase domain of EGFR (exons 18–21) that are not listed above. Silent mutations that are known, common, single-nucleotide polymorphisms in the general population do not need to be included here.

C: Polysomy.—Polysomy (multiple copies) at the ALK locus is commonly found in lung adenocarcinoma and when present confirms that FISH has been performed in a tumor cell population. Current evidence suggests that it does not, however, predict response/resistance to targeted therapies.

D: Other Markers Tested.—“Other Markers Tested” should be used to report results from molecular assays not included here that may be relevant to lung cancer therapy. These assays may include, but are not limited to, detection of mutations in genes, such as BRAF, ERBB2, and PIK3CA; rearrangements involving ROS1 and RET genes; and MET copy number changes (see “Background” section above).

E: Testing Method for Other Markers.—This section should be completed if the “Other Markers Tested” section is filled out and should describe the type of analyses performed for alterations in genes other than EGFR, ALK, and KRAS, as detailed in note D.

F: Fixation.—Improper fixation can lead to failure to obtain results with PCR/sequencing-based assays or FISH. Common problems include:

- Procedures or fixation involving acid (eg, decalcification, Bouin) may degrade DNA.
- Fixation with heavy metals (eg, Zenker, B5, B+, zinc formalin) inhibits the enzymes used in PCR.
- Underfixation or overfixation. Fixation for at least 8 hours and less than 72 hours in buffered formalin is recommended; prolonged fixation, particularly in unbuffered formalin, degrades DNA.

We thank Jennifer Ruhl, MLIS, CTR, Surveillance, Epidemiology and End Results (SEER) Program, National Cancer Institute, Rockville, Maryland.

References


