Read, Interpret, and Communicate Test Results

Effective interpretation of epidermal growth factor receptor (EGFR) mutation test results both at diagnosis and at disease progression will help health care providers set patient expectations and prescribe the most appropriate treatment for patients with metastatic non–small cell lung cancer (NSCLC). Open and accurate communication with your patients is essential to their understanding of their disease and treatment.

There are 4 key areas that will be discussed in this section, each with information that may help you interpret and communicate the results of an EGFR mutation test:

- **Guidelines for reporting test results**
- **Interpreting test reports**
- **Treatment options based on mutation status**
- **Discussing mutation status and treatment with patients**

Guidelines for reporting EGFR mutation test results[1]

When it comes to identifying mutations in the EGFR gene, there are many tests to choose from. Whichever test is chosen by your practice team, the testing laboratory is responsible for communicating the results clearly and effectively to the treating physician. The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) have recommended the following components be included for the complete reporting of EGFR mutation testing.

Guidelines for Reporting EGFR Mutation Testing Results

Results	Interpretation
Names of clinically significant mutations identified	Assessment of a tumor's likelihood to respond to targeted therapy based on mutation
Histopathologic assessment of tumor content for the tumor tested	Requirements for repeat testing if needed
Reason for assay failure (if needed)	

Interpreting EGFR mutation test reports[1,2]

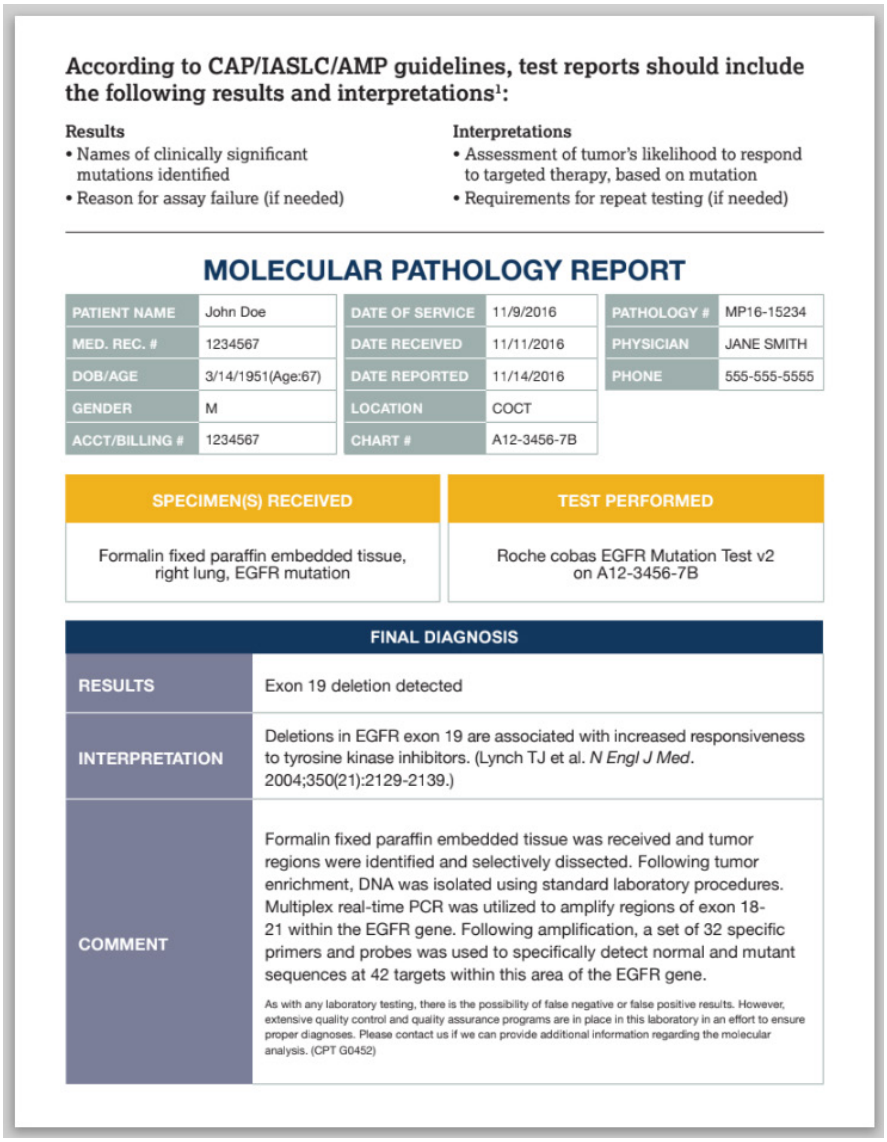
NSCLC tumors are heterogeneous, meaning that different cells within the tumor may contain different mutations, or some may not contain a mutation at all.[2] The test for EGFR mutations in NSCLC may show that tumors harbor multiple mutations, especially at disease progression.[3] A tumor may show both an EGFR sensitizing mutation (eg, L858R point mutation or exon 19 deletion) and a T790M resistance mutation.[2]

Some screening methodologies may identify novel EGFR mutations for which there will be no clinical or preclinical data to guide treatment decisions.

Depending upon the test and laboratory, results of EGFR mutation tests may vary.

- One example—the cobas® EGFR Mutation Test v2—reports an EGFR T790M mutation as "detected" or "not detected" and can detect at least a 5% mutation level in the sample[3]

Sample Molecular Pathology Report



According to CAP/IASLC/AMP guidelines, test reports should include the following results and interpretations[1]:

Results
- Names of clinically significant mutations identified
- Reason for assay failure (if needed)

Interpretations
- Assessment of tumor's likelihood to respond to targeted therapy, based on mutation
- Requirements for repeat testing (if needed)

MOLECULAR PATHOLOGY REPORT

PATIENT NAME	John Doe	DATE OF SERVICE	11/9/2016	PATHOLOGY #	MP16-15234
MED. REC. #	1234567	DATE RECEIVED	11/11/2016	PHYSICIAN	JANE SMITH
DOB/AGE	3/14/1951(Age:67)	DATE REPORTED	11/14/2016	PHONE	555-555-5555
GENDER	M	LOCATION	COCT		
ACCT/BILLING #	1234567	CHART #	A12-3456-7B		

SPECIMEN(S) RECEIVED	TEST PERFORMED
Formalin fixed paraffin embedded tissue, right lung, EGFR mutation	Roche cobas EGFR Mutation Test v2 on A12-3456-7B

FINAL DIAGNOSIS	
RESULTS	Exon 19 deletion detected
INTERPRETATION	Deletions in EGFR exon 19 are associated with increased responsiveness to tyrosine kinase inhibitors. (Lynch TJ et al. *N Engl J Med*. 2004;350(21):2129-2139.)
COMMENT	Formalin fixed paraffin embedded tissue was received and tumor regions were identified and selectively dissected. Following tumor enrichment, DNA was isolated using standard laboratory procedures. Multiplex real-time PCR was utilized to amplify regions of exon 18-21 within the EGFR gene. Following amplification, a set of 32 specific primers and probes was used to specifically detect normal and mutant sequences at 42 targets within this area of the EGFR gene. As with any laboratory testing, there is the possibility of false negative or false positive results. However, extensive quality control and quality assurance programs are in place in this laboratory in an effort to ensure proper diagnoses. Please contact us if we can provide additional information regarding the molecular analysis. (CPT G0452)

- Other tests may report EGFR mutations as a percentage (eg, 15%) detected in the sample[4]
- Based on the results of the mutation test, the health care provider must decide how to proceed with a treatment plan

Contact your pathologist or preferred testing laboratory with any questions you may have about EGFR testing.

Identification of EGFR mutations may help guide treatment decisions both at initial diagnosis of NSCLC and at disease progression[5]

- A test result showing the presence of an EGFR mutation can indicate if a patient is eligible for treatment with an EGFR tyrosine kinase inhibitor (EGFR-TKI) at diagnosis
- A positive result for an EGFR T790M mutation at disease progression may help guide subsequent treatment decisions
- Negative plasma test results should be retested with tissue

Communicating EGFR mutation status with patients

Discussion of test results and treatment plans with your patients is essential. An oncologist will often communicate the initial test results and the treatment options/plan, and a nurse or nurse navigator will discuss those results in greater detail with the patient.

Discussing EGFR mutation testing at diagnosis

Patients and family members or caregivers should understand the role and results of an EGFR mutation test at initial diagnosis, including:

- EGFR sensitizing mutations are common in patients with NSCLC, occurring in[5-7]:
  - 7% to 20% of patients in Western populations
  - 30% to 50% of patients in Asian populations
- The most common EGFR sensitizing mutations are the exon 19 deletion and the L858R point mutation[5]
- Available treatment options and treatment plans[5]

Reminder: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for all actionable biomarkers at diagnosis of NSCLC, including EGFR, BRAF, and ROS1 mutations, ALK rearrangements, and PD-L1 expression.[5]

Discussing the need to retest at progression and available testing procedures

Patients and caregivers should understand that some tumor cells may develop drug resistance to first-line EGFR-TKI therapy at disease progression.[2]

Retesting can offer insight into the mechanisms of resistance to initial therapy with an EGFR-TKI.

Drug resistance to a first-line EGFR-TKI is often associated with an acquired EGFR mutation.2 Obtaining a biopsy for testing at progression may include:

Tissue-based samples

Plasma-based samples

Reminder: A new sample is required to test for EGFR T790M mutations at the time of progression.

Describing test results at progression

Patients and caregivers should be aware that the EGFR T790M mutation is the most common mutation that confers resistance to first- or second-generation EGFR-TKI therapy.[8]

The presence of an EGFR T790M mutation may mean that the patient will have to assess their treatment plan.[5]

It is important to note that 49% to 63% of patients become resistant to first- or second-generation EGFR-TKIs due to the EGFR T790M mutation, meaning that up to 37% of your patients will not have the EGFR T790M mutation.[8-12] Alternate treatment options for patients without a T790M mutation should be discussed. Negative plasma test results should be retested with tissue.

ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase.

The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References: 1. 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*. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP. **2.** Sacher AG, Jänne PA, Oxnard GR. Management of acquired resistance to epidermal growth factor receptor kinase inhibitors in patients with advanced non-small cell lung cancer. *Cancer*. 2014;120(15):2289-2298. **3.** cobas® EGFR Mutation Test v2 [package insert]. Indianapolis, IN: Roche Diagnostics; 2015. **4.** Guardant Health. How Guardant360 works. http://www.guardanthealth.com/guardant360/#how-it-works. Accessed February 21, 2018. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed March 14, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **6.** Sekine I, Yamamoto N, Nishio K, Saijo N. Emerging ethnic differences in lung cancer therapy. *Br J Cancer*. 2008;99(11):1757-1762. doi: 10.1038/sj.bjc.6604721. **7.** Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014;9(2):154-162. doi:10.1097/JTO.0000000000000033. **8.** Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240-2247. 9. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17(6):1616-1622. **10.** Sun JM, Ahn MJ, Choi YL, Ahn JS, Park K. Clinical implications of T790M mutation in patients with acquired resistance to EGFR tyrosine kinase inhibitors. *Lung Cancer*. 2013;82(2):294-298. **11.** Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26. doi:10.1126/scitranslmed.3002003. **12.** Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. *Eur Respir Rev*. 2014;23(133):356-366.