TECHNICAL NOTICE
THE MEDICAL FOUNDATION

Non-Small Cell Lung Carcinoma Panel by FISH (ALK, RET, ROS1, MET) **Effective date: 5/1/2018**

Test Code: 36035

Department: Flow Cytometry / Molecular Pathology

Test Mnemonic: LUNG FISH 2

CPT Code(s): 88374×4

Test Includes: Tissue based FISH tests include technical and professional components which are billed either as global charges or as separate TC and PC charges depending upon the place of service.

Test Synonyms: Lung Cancer FISH Panel • NSCLC FISH • ALK • RET • ROS1 • MET

Also See:

36269 Non-Small Cell Lung Carcinoma Mutation Analysis Panel (BRAF, EFGR, and KRAS) with ALK, RET, ROS1 and MET by FISH if Indicated
36176 ALK Gene Rearrangement by FISH
36277 ROS1 Gene Rearrangement by FISH
36278 RET Gene Rearrangement by FISH
36279 MET Gene Amplification by FISH

Patient Prep: **NOTICE: Genetic tests are often subject to limited coverage and / or prior-authorization requirements. Consult the patient's medical insurance provider before ordering this test.**

Spec Collect: Tumor tissue.

Spec Process:
Formalin fix and paraffin embedded tissue block containing viable tumor. Neutral buffered formalin is the preferred fixative and tissue should be sectioned and fixed as soon as possible after surgery for best tissue preservation. In selecting the paraffin blocks, submit the largest area of tumor available that shows the least degeneration or necrosis. Preservation of nuclear detail can help assess quality of fixation. Tissue block should show at least 20 percent nucleated tumor cells. Single small biopsy or cytology cell block may be acceptable depending on the amount of tumor tissue present.

Spec Store Transport:
Room temperature. Also acceptable: Refrigerated. Avoid excessive heat (greater than 55°C). Ship in cooled container during summer months.

Spec Stability: Room temperature: Indefinitely. Refrigerated: Indefinitely. Frozen: Unacceptable

Spec Reject: Insufficient well preserved tumor cells in submitted tissue block. Specimens processed in alternative fixatives (alcohol, Prefer®) or heavy metal fixatives (B-4 or B-5). Decalcified specimens.

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Joyce Simpson, M.D. • *Medical Director*

Spec Remarks: Include surgical pathology report. Tissue block will be returned after testing.

Use:
Detection of relevant ALK, ROS1, RET fusion and MET gene amplification in primary pulmonary adenocarcinoma or mixed carcinoma with an adenocarcinoma component, regardless of histologic grade. Testing should be considered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV TNM staging system) who are suitable for therapy, or at the time of recurrence or progression in patients who originally presented with lower-stage disease.

Clinical Significance:

ALK gene rearrangement
Approximately 3–7% of lung tumors harbor *ALK* gene rearrangement, which results in impaired apoptosis, and abnormal cell proliferation. The most common *ALK* fusion in NSCLC is *EML4-ALK*, which arises from fusion between the 5' end of the EML4 gene and the 3' end of the ALK gene on chromosome 2p23. ALK fusions are more commonly found in young age, never or light smokers. Patients with *ALK*-positive NSCLC have been shown to respond to the *ALK* kinase inhibitor XALKORI® (crizotinib), the first FDA-approved *ALK* TKI.

ROS1 gene rearrangement
ROS1 gene rearrangements, detected in 1-2% of NSCLC, share with *ALK* rearrangements a similar biological defect, predominant histology (adenocarcinoma), and patient demographic profile (younger age, non-smoker, and increased frequency of Asian ethnicity). ROS1 gene rearrangements are most often mutually exclusive from *EGFR* mutations, *KRAS* mutations, and *ALK* rearrangements. Recent clinical studies have shown that patients with advanced NSCLC harboring *ROS1* rearrangements are also sensitive to crizotinib (XALKORI®) treatment

RET gene rearrangement
RET gene rearrangements have been identified in 1-2% of lung adenocarcinoma, RET gene rearrangements are associated with adenocarcinoma, light/never smokers, and younger patients, and are mainly non-overlapping with other oncogenic aberrations (e.g. *ALK*- and *ROS1* rearrangements, etc.). Recent clinical studies showed inhibition of RET with multiple kinase inhibitors in RET overexpressing cells. The evaluation of *RET* gene rearrangements could be applicable in clinical practice to detect NSCLC patients that may be response to cabozantinib and vandetanib.

Met gene amplification
Clinically, *MET* gene amplification has been associated with poor prognosis in patients with NSCLC, and is detected in 2-4% of previously untreated NSCLC patients. Patients with MET gene amplification who have progressed on chemotherapy may benefit from MET targeted therapy (e.g. MET inhibitor crizotinib or cabozantinib) as next-line therapy. However MET amplification is often acquired as a resistance mutation following EGFR tyrosine kinase inhibitor therapy.

Methodology:

ALK, ROS1 and RET gene rearrangement detection by fluorescence in situ hybridization (FISH) method utilizes dual color, break-apart rearrangement probes in the ALK (2p23.2), ROS1 (6q22.1), and RET (10q11.21) genes. These probes are designed to detected a break apart in the gene(s), but do not identify any specific fusion partner. Analysis for MET gene amplification was performed using the fluorescent probes targeting the MET (7q31.2) gene and the chromosome 7 centromere (CEP7). Cells were evaluated from regions of tumor on sections from a paraffin-embedded tissue block identified on histopathologic review of a matching H&E stained section. The normal cutoff is 15% for ALK, ROS1 and RET assay. For MET assay a MET/CEP7 ratio of 2.0 or greater or an average number of MET signal per cell of 5.0 or greater indicates amplification of the MET gene locus.

This test was developed using an analyte specific reagent. Its performance characteristics were determined by the South Bend Medical Foundation Laboratory. This test has not been cleared or approved by the U.S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. The Medical Foundation is certified under CLIA as qualified to perform high complexity clinical laboratory testing.

Additional Test Info: Lab Tests Online

Day Run: Once per week

Time Reported: 7-10 days

Test Type: GENETIC

REFERENCES

1. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. 2012 CAP Archives of Pathology & Laboratory Medicine.
2. NCCN Clinical Practice Guidelines in Oncology™. Non-small cell lung cancer. v 2.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf . Accessed July 22, 2010.
3. Molecular analysis-based treatment strategies from the management of non-small cell lung cancer. *J Thorac Oncol*. 2009; 4:s 1029-s1039
4. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013; 368(25):2385.
5. XALKORI® (crizotinib) package insert. New York, NY: Pfizer; 2012
6. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. *J Clin Oncol* 30, 2012 (suppl; abstr 7508)
7. *RET* Fusion Genes in Non–Small-Cell Lung Cancer. *J Clin* Oncol 2012, 30: 4439-4441
8. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov.* 2013; 3(6):630.
9. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. *J Thorac Oncol*. 2013; 8(5):e43.

Please direct comments or questions regarding this notice to Albert Huho, M.D. (ahuho@sbmf.org), Qing Li, Ph.D. (qli@sbmf.org), Kevin Maggert (kmaggert@sbmf.org) or South Bend Medical Foundation (574) 234-4176 or (800) 544-0925.