Test Definition: MCLNR

MayoComplete Lung Rearrangements, Rapid Test, Tumor

Overview

Useful For

Identifying lung tumors that may respond to targeted therapies by simultaneously assessing multiple genes involved in rearrangements resulting in fusion transcripts

Diagnosing and managing patients with lung cancer

Genetics Test Information

This test identifies specific gene fusions (rearrangements) involving the *ALK, ROS1*, and *RET* genes, *MET* exon 14 skipping, and expression imbalance for *ALK, ROS1, RET, NTRK1*, *NTRK2*, and *NTRK3* genes. See Targeted Genes and Methodology Details for MayoComplete Lung Rearrangements for details regarding the targeted gene regions evaluated by this test.

Expression imbalance assays have the benefit that provide an indication of the presence of a fusion not covered by the specific fusion panel.

This test is performed to evaluate gene fusions (rearrangements) within solid tumor, in particular lung cancer, specimens.

Additional Tests

Test Id	Reporting Name	Available Separately	Always Performed
SLIRV	Slide Review in MG	No	Yes

Testing Algorithm

When this test is ordered, slide review will always be performed at an additional charge.

Special Instructions

- Targeted Genes and Methodology Details for MayoComplete Lung Rearrangements

Highlights

This test evaluates formalin-fixed, paraffin-embedded tumor or cytology slides from patients with lung cancer for gene fusions (rearrangements) to identify candidates for targeted therapy.

Current data suggests that lung carcinomas with *ALK, ROS1, RET* rearrangements and *MET* exon 14 skipping may be sensitive to corresponding tyrosine kinase inhibitors.

Current data suggests that solid tumors with *NTRK* rearrangements may be sensitive to multikinase inhibitors.

Method Name

Polymerase Chain Reaction (PCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Multiple oncology (cancer) gene panels are available. For more information see Hematology, Oncology, and Hereditary Test Selection Guide.

Necessary Information

A pathology report (final or preliminary), at minimum containing the following information, **must accompany specimen for testing to be performed**:

1. Patient name
2. Block number-must be on all blocks, slides, and paperwork (can be handwritten on the paperwork)
3. Tissue collection date
4. Source of the tissue

Specimen Required

This assay requires at least 10% tumor nuclei.

-Preferred amount of tumor area with sufficient percent tumor nuclei: tissue 36 mm(2)
-Minimum amount of tumor area: tissue 18 mm(2)
-These amounts are cumulative over up to 10 unstained slides and must have adequate percent tumor nuclei.
-Tissue fixation: 10% neutral buffered formalin, not decalcified

Preferred: Submit 3, if available, or 2 of the following specimens.
Acceptable: Submit **at least one** of the following specimens.

Specimen Type: Tissue block
Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block with acceptable amount of tumor tissue.

Specimen Type: Tissue slide
Slides: 1 Hematoxylin and eosin-stained and 10 unstained
Collection Instructions:
Submit the followings slides:
1 Slide stained with hematoxylin and eosin
AND
10 Unstained, nonbaked slides with 5-micron thick sections of the tumor tissue.

Note: The total amount of required tumor nuclei can be obtained by scraping up to 10 slides from the same block.
Additional Information:
1. Hematoxylin and eosin-stained and unstained slides will not be returned.
2. Broken or cracked unstained slides will be rejected. Stained slides that were broken and repaired (ie, double mounted) at the client site will not be rejected, as, in most cases, they can still be reviewed under the microscope. However, due to the double mounting, digital scanning cannot be performed.

Specimen Type: Cytology slide (direct smears or ThinPrep)
Slides: 1 to 3 Slides
Collection Instructions: Submit 1 to 3 slides stained and coverslipped with a total of 5000 nucleated cells (preferred) or at least 3000 nucleated cells (minimum).
Note: Glass coverslips are preferred; plastic coverslips are acceptable but will result in longer turnaround times.
Additional Information:
1. Cytology slides will not be returned. An image of the slides will be stored per regulatory requirements.
2. Stained slides that were broken and repaired (ie, double mounted) at the client site will not be rejected, as, in most cases, they can still be reviewed under the microscope. However, due to the double mounting, digital scanning cannot be performed.

Forms

If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

See Specimen Required

Reject Due To

Broken or cracked unstained slides	Reject
Broken or cracked stained slides that cannot be repaired	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks.

Fusions involving the *NTRK1*, *NTRK2*, or *NTRK3* genes (ie, *NTRK* gene fusions) form through intra- and interchromosomal rearrangements. *NTRK* gene fusions lead to activation of downstream *MAPK*, *PIK*, and *STAT3* signaling pathways and act as oncogenic drivers of multiple types of pediatric and adult solid tumors. In solid tumors, the presence of an *NTRK* gene fusion is a biomarker for response to tropomyosin receptor kinase inhibitor therapy.

Lung cancers harboring *ALK* rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors but may be highly sensitive to ALK inhibitors, like Xalkori (crizotinib). The drug Xalkori works by blocking certain kinases, including those produced by the abnormal *ALK* gene. Clinical studies have demonstrated that Xalkori treatment of patients with tumors exhibiting *ALK* rearrangements can halt tumor progression or result in tumor regression.

RET rearrangements occur in approximately 2.5% to 10% of sporadic papillary thyroid cancer(1) and 1% to 3% of non-small cell lung cancer. The most prevalent fusions are *KIF5B* exon 15 - *RET* exon 12 and KIF5B exon 16 - *RET* exon 12, which represent over 75% of *RET* fusions.

ROS1 (c-ros oncogene 1), originally described in glioblastomas, has been identified as a potential relevant therapeutic target in lung adenocarcinoma. Crizotinib has shown in vitro activity and early evidence of clinical activity in *ROS1*-rearranged tumors.

Many cases of *METex14* alterations are found in lung adenocarcinomas, these events have a much higher incidence in pulmonary sarcomatoid carcinomas. Approximately 20% to 30% of sarcomatoid carcinomas harbor *METex14* alterations.

Reference Values

An interpretive report will be provided.

Interpretation

The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Cautions

This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

A negative result does not rule out the presence of a rearrangement (fusion) that may be present but below the limits of detection of this assay.

Gene fusions (rearrangements) and expression imbalance involving the *ALK, ROS1, RET, NTRK1, NTRK2*, and *NTRK3* genes only will be detected. This test does not detect point mutations, deletion-insertion mutations, large single or multiexon deletions or duplications, or genomic copy number variants in any of the genes tested.

Rare alterations (ie, polymorphisms) may be present that could lead to false-negative or false-positive results.

The presence or absence of a variant may not be predictive of response to therapy in all patients.

Test results should be interpreted in the context of clinical findings, tumor sampling, and other laboratory data. If results obtained do not match other clinical or laboratory findings, contact the laboratory for updated interpretation. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Reliable results are dependent on adequate specimen collection and processing. This test has been validated on cytology slides and formalin-fixed, paraffin-embedded tissues; other types of fixatives are discouraged. Improper treatment of tissues, such as decalcification, may cause polymerase chain reaction failure.

Broken or cracked unstained slides are not compatible with the instrumentation used in our performing laboratories and will be rejected. Additional material may be requested.

Attempts will be made to repair broken or cracked stained slides; however, if they are unable to be repaired (ie, shattered in transit), they will be rejected and discarded due to safety concerns.

Clinical Reference

1. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.Nat Med. 2013;19(11):1469-1472
2. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022, Accessed February 3, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
3. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94. doi:10.1056/NEJMoa1214886
4. Sehgal K, Patell R, Rangachari D, Costa DB. Targeting ROS1 rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors. Transl Cancer Res. 2018;7(Suppl 7):S779-S86. doi:10.21037/tcr.2018.08.11
5. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, et al. Efficacy of Selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383(9):813-24. doi:10.1056/NEJMoa2005653
6. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0
7. Frampton GM, Ali SM, Rosenzweig M, Chmielecki J, Lu X, Bauer TM, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015;5(8):850-9. doi:10.1158/2159-8290.CD-15-0285

Performance

Method Description

Qualitative detection using the Idylla GeneFusion Assay is performed to detect rearrangements (fusions) within the *ALK, ROS1* and *RET* genes, *MET* exon 14 skipping, and expression imbalance for *ALK, ROS1, RET, NTRK1, NTRK2* and *NTRK3*

genes. See Targeted Genes and Methodology Details for MayoComplete Lung Rearrangements for details regarding the targeted gene regions evaluated by this test.(Unpublished Mayo method)

A pathology review and macro dissection to enrich for tumor cells are performed prior to slide scraping.

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
4 to 8 days

Specimen Retention Time
Tissue blocks: Unused portions of blocks will be returned; Tissue slides: Hematoxylin and eosin-stained and unstained slides will not be returned. Unused slides are stored for at least 5 years; Extracted RNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81449

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MCLNR	MayoComplete Lung Rearrangements	73977-1

Result ID	Test Result Name	Result LOINC® Value
618280	Result	82939-0

618281	Interpretation	69047-9
618282	Additional Information	48767-8
618283	Specimen	31208-2
618284	Tissue ID	80398-1
618285	Method	85069-3
618286	Disclaimer	62364-5
618287	Released By	18771-6