Patient ID	Patient Name		Birth Date	Sex	Age
SA00154864	TESTING, MCLBP ABNORMAL		1988-10-17	M	34
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00154864	SA00154864	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		18 Oct 2022 07:30			

MayoComplete Liquid Biopsy Panel

Result

MCR

Reason for Referral: lung cancer

MSI-H status: not detected

The following alteration(s) was identified:
Gene: KRAS
DNA change: 35G>A
Amino acid change: G12D
Variant Allele Frequency: 1.5%
Reporting transcript: NM_033360

No other reportable alterations, gene amplifications, or fusions (translocations) were identified within the analyzed regions of the tested genes listed in the method description.

Interpretation

MCR

No evidence of microsatellite instability was detected. Additional testing on a tumor (tissue) sample is recommended.

GENE/VARIANT SUMMARY

KRAS G12D was identified

KRAS encodes the signaling protein K-Ras, a member of the Ras family; activating KRAS alterations may result in activation of downstream signaling pathways, including the Raf/MEK/ERK pathway [PMID:21993244, PMID:6320174]. KRAS mutations have been reported in 20–37% of lung adenocarcinoma samples analyzed [COSMIC (Nov 2021), cBioPortal for Cancer Genomics (Nov 2021)].

KRAS mutation has been associated with smoking in NSCLC patients; additionally, KRAS mutations have also been associated with adenocarcinoma histology and are generally mutually exclusive with EGFR mutations and ALK rearrangements [PMID:31711449, PMID:32729257, PMID:33758543, PMID:32607238, PMID:32619782, PMID:23729361, PMID:26992209, PMID:26208325, PMID:22605530, PMID:25738220, PMID:28179026, PMID:29600072].

Numerous studies have reported KRAS mutations to be associated with poor survival in NSCLC patients [PMID:27740967, PMID:30237741, PMID:2199829, PMID:18024870, PMID:1654209, PMID:33718025, PMID:33647504].

THERAPEUTIC IMPLICATIONS

Drug sensitivity: Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf/MEK/ERK and PI3K/Akt/mTOR [PMID:19372556, PMID:23443307]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [PMID:28492898, PMID:18390968, PMID:27338794, PMID:24915778, PMID:24746704, PMID:25322874, PMID:25722381, PMID:24444711]. One clinical approach for KRAS-positive tumors, based on synthetic lethal interactions that occur in the presence of a KRAS mutation and either diminished Cdk4 activity or diminished Bcl-2/Bcl-xL activity, is a treatment combination of MEK inhibition and either Cdk4/6 inhibition or Bcl-2/Bcl-xL inhibition [PMID:24496383, PMID:20609353, PMID:23475955, PMID:23245996]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors [PMID:31739184, PMID:29808006, PMID:29808009, PMID:23358651, PMID:27220963, PMID:27362227]. In addition, cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [PMID:31239544, PMID:29373830, PMID:24256730, PMID:26739882]. Studies analyzing KRAS mutation association with clinical benefit of PD-1/PD-L1 inhibitors to NSCLC patients have reported mixed results, with some studies reporting no significant association while other studies have reported that KRAS mutation correlated with improved clinical outcome of NSCLC patients treated with PD-1/PD-L1 inhibitors [PMID:34378081, PMID:33581492, PMID:34557415, PMID:30738221, PMID:34518623].

Drug resistance: In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies [PMID:32376853, PMID:16043828, PMID:18804418, PMID:19064407,

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

Patient ID	Patient Name		Birth Date	Sex	Age
SA00154864	TESTING, MCLBP ABNORMAL		1988-10-17	M	34
Order Number	Client Order Number	Ordering Physician	Report Notes		
SA00154864	SA00154864	CLIENT,CLIENT			
Account Information		Collected			
C7028846 DLMP Rochester		18 Oct 2022 07:30			

PMID:23538866, PMID:21163703, PMID:24024839, PMID:23404247, PMID:25155261].

Additional Information

MCR

Percent (%) of exons with sufficient coverage: 99.11

CLINICAL TRIALS

Possible clinical trials of benefit for this patient can be found at the following sites:
1) ClinicalTrials.gov: www.clinicaltrials.gov/ct2/search/advanced
2) Mayo Clinic: www.mayo.edu/research/clinical-trials/
3) National Cancer Institute: www.cancer.gov/clinicaltrials/search

Specimen

MCR

WB Whole Blood

Method

MCR

Blood samples are collected in Streck Cell-Free DNA BCT tubes and cell-free DNA (cfDNA) is then isolated from double spun plasma. Next generation sequencing is performed on the cfDNA using the PGDx Elio Plasma Resolve chemistry. The following variant types and molecular profiles were evaluated: microsatellite high instability (MSI-H) status, sequence variants in 33 genes (AKT1, ALK, APC, ARID1A, ATM, BRAF, BRCA1, BRCA2, BRIP1, CCND1, CD274, CDH1, CSF1R, EGFR, ERBB2, EZH2, FGFR1, FGFR2, HRAS, KIT, KRAS, MET, MYC, NRAS, NTRK1, PDGFRA, PIK3CA, POLD1, POLE, RAF1, RET, ROS1, TP53), gene amplification in 8 genes (CCND1, CD274, EGFR, ERBB2, FGFR2, KIT, MET, MYC), and fusions (translocations) involving 5 genes (ALK, FGFR2, NTRK1, RET, ROS1).

Variant nomenclature is based on build GRCh37 (hg19). For details about gene transcripts (GenBank accession numbers), targeted gene coverage and additional information on this test, see www.mayocliniclabs.com
(Test ID MCLBP)

Disclaimer

1 MCR

CLINICAL CORRELATIONS

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

Patients with a negative test result may still harbor a genomic alteration. Testing of a tissue specimen for mutations should be considered for patients with who have a negative result with this test.

Variant allele frequency (VAF) is the percentage of sequencing reads supporting a specific variant divided by the total sequencing reads at that position. In somatic testing, VAF should be interpreted in the context of several factors including, but not limited to: tumor heterogeneity/copy number status (ploidy, gains/losses, loss of heterozygosity) and sequencing artifact/ misalignment [PMID: 27144058, PMID: 29769535].

The limit of detection (LOD) for single nucleotide variants (SNVs) is 0.5% for hotspot mutations, 1% for other SNVs; 2.5% for deletion-insertions (delin), and 2 supporting reads for fusions. LOD for amplification is between 1.2–1.6 fold changes (2.4–3.2 copies) depending on specific genes and presence of sufficient SNPs for allelic imbalance assessment. LOD for microsatellite instability (MSI) is 2% tumor DNA. MSI status is classified as MSI-H detected (≥2 sites unstable), and MSI-H not detected (<2 sites unstable).

This test can be used to report gene amplifications but does not detect deletions or duplications.

The limit of detection of this assay for the detection mutations is influenced by the amount of cell-free DNA (cfDNA) in the blood. This is a biological variable that cannot be controlled.

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

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

MAYO CLINIC LABORATORIES

Patient ID	Patient Name		Birth Date	Sex	Age
SA00154864	TESTING, MCLBP ABNORMAL		1988-10-17	M	34
Order Number	Client Order Number	Ordering Physician	Report Notes		
SA00154864	SA00154864	CLIENT,CLIENT			
Account Information		Collected			
C7028846 DLMP Rochester		18 Oct 2022 07:30			

This test does not differentiate between tumor somatic alterations and CHIP (Clonal Hematopoiesis of Indeterminate Potential) mutations. Additional testing may be necessary to clarify the origin of mutations detected.

Rare polymorphisms may be present that could lead to false negative or false positive results.

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

Released By MCR

Gang Zheng, M.D., Ph.D.

Received: 18 Oct 2022 08:14 **Reported:** 20 Oct 2022 13:45

Laboratory Notes

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

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292