PBM
PATHOLOGISTS BIO-MEDICAL LABORATORIES, L.L.P.

Date: 09/02/2016
Order Date: 08/22/2016
Specimen Number: TEST
Report Version: 1

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COLON**SEQ**: Final Report

Patient Information	Specimen Information	Physician Information
Name: TEST PATIENT	**Type:** Lymph node, left cervical	**Institution:** Test Account
DOB: 01/02/1234 **Gender** Male	**Collected:** 08/19/2016	**Referring Physician:** Dr. Test Case
MRN: TEST123456	**Received:** 08/22/2016	**Final Reviewer:** Benton Middleman, MD
Disease Type: Colorectal Cancer	**Block ID:** Test-1234	**Genomic Analyst:** Michael Weindel, MD
Diagnosis: Metastatic adenocarcinoma		

Summary of Findings

This specimen is positive for a mutation in the KRAS gene. Multiple studies have demonstrated that patients with metastatic colorectal cancer whose tumors harbor mutations in KRAS or NRAS exons 2, 3, or 4 predict lack of response to anti-EGFR antibody therapy given in combination with chemotherapy (Ciardiello et al. 2014; Douillard et al. 2013; Schwartzberg et al. 2014; Peeters et al. 2014; Stintzing et al. 2014; Tejpar et al. 2014).

*** Molecular - Electronically Signed Out by Kristen Champion, PhD, FACMG on 08/29/2016

*** Final Approval - Electronically Signed Out by Benton Middleman, MD on 08/29/2016

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Patient Information	Specimen Information	Physician Information
Name: Test Patient **DOB:** 01/02/1234 **Gender:** Male **MRN:** TEST123456 **Disease Type:** Colorectal Cancer **Diagnosis:** Metastatic adenocarcinoma	**Type:** Lymph node, left cervical **Collected:** 08/19/2016 **Received:** 08/22/2016 **Block ID:** Test-1234	**Institution:** Test Account **Referring Physician:** Dr. Test Case **Final Reviewer:** Kristen Champion, PhD, FACMG **Genomic Analyst:** Michael Weindel, MD

SUMMARY

Clinical Information:

Metastatic adenocarcinoma

Results Interpretation:

This specimen is positive for a mutation in the KRAS gene. Multiple studies have demonstrated that patients with metastatic colorectal cancer whose tumors harbor mutations in KRAS or NRAS exons 2, 3, or 4 predict lack of response to anti-EGFR antibody therapy given in combination with chemotherapy (Ciardiello et al. 2014; Douillard et al. 2013; Schwartzberg et al. 2014; Peeters et al. 2014; Stintzing et al. 2014; Tejpar et al. 2014).

Genes Tested With Alterations: KRAS

Genes Tested Without Alterations: BRAF, NRAS, PIK3CA, PTEN

Gene Regions That Failed Testing: None

DRUG RESPONSE

Drugs Associated With Sensitivity For Patient's Tumor Type, Based on Genomic Analysis

Drug(s)	Response to Drug Based on Biomarkers (Source)	Related Biomarker(s)	Indication of the Drug Response	Drug Class	Drug FDA-Approved for Patient's Tumor Type	Additional Information
None						

Drugs Associated With Resistance, Based on Genomic Analysis

Drug(s)	Response to Drug Based on Biomarkers (Source)	Related Biomarker(s)	Indication of the Drug Response	Drug Class	Drug FDA-Approved for Patient's Tumor Type	Additional Information
Cetuximab	Primary resistance (FDA, NCCN, ASCO, MCG)	KRAS G12V	Colorectal Cancer	Therapeutic Antibodies	Yes	
Panitumumab	Primary resistance (FDA, NCCN, ASCO, MCG)	KRAS G12V	Colorectal Cancer	Therapeutic Antibodies	Yes	

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Drugs Associated With Sensitivity For Other Tumor Types, Based on Genomic Analysis						
Drug(s)	**Response to Drug Based on Biomarkers (Source)**	**Related Biomarker(s)**	**Indication of the Drug Response**	**Drug Class**	**Drug FDA-Approved for Patient's Tumor Type**	**Additional Information**
None						

SOURCES:
FDA: US Food and Drug Administration (www.fda.gov), **NCCN**: National Comprehensive Cancer Network (www.nccn.org), **ASCO**: American Society of Clinical Oncology (www.asco.org), **MCG**: My Cancer Genome (www.mycancergenome.org)

GENETIC ALTERATIONS

Detected Alterations of Known or Potential Pathogenicity					
Gene	**Gene Alteration**	**Significance**	**Therapeutic Implications***	**Additional Information**	**Methodology**
KRAS	G12V c.35G>T	Pathogenic	Associated with drug response; Potentially relevant clinical trials	COSMIC: COSM520 Allele Frequency: 0.0% dbSNP: rs121913529	Mutational Analysis

Detected Alterations of Uncertain Significance					
Gene	**Gene Alteration**	**Significance**	**Therapeutic Implications***	**Additional Information**	**Methodology**
None					

Detected Alterations Known to be Benign or Likely to be Benign					
Gene	**Gene Alteration**	**Significance**	**Therapeutic Implications***	**Additional Information**	**Methodology**
None					

***Therapeutic Implications:** Associated with drug response = related to drug sensitivity or resistance as described in Drug Response section of this report; Potentially relevant clinical trials = gene is related to a trial in the Clinical Trials section of this report
COSMIC: Mutation ID in the Catalogue Of Somatic Mutations in Cancer (http://cancer.sanger.ac.uk/)
Allele Frequency: Allele frequency of the alteration in the 1000 Genomes Project (http://www.1000genomes.org/)
dbSNP: RS number of alteration in dbSNP database (http://www.ncbi.nlm.nih.gov/SNP)

CLINICAL TRIALS

Overview of Clinical Trials That May Be Relevant Based On Results Of The Tumor Profile	
Trial Phase	**Number of Open, Enrolling Trials**
Phase 2	3
Phase 1/Phase 2	1
Phase 1	11

For a full list of clinical trials which may be relevant for your patient, please follow this link to the US Government Clinical Trials website: Full List of Clinical Trials on www.clinicaltrials.gov

Below are potentially relevant targeted clinical trials for your patient based on the results of the tumor profile only.

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Potentially Relevant US Oncology Directed Clinical Trials			
Phase	**Trial Title**	**Genes**	**Location**
None			

Sample of Other Potentially Relevant Clinical Trials			
Phase	**Trial Title**	**Genes**	**Location**
Phase 1	Phase 1 Study of MGD007 in Relapsed/Refractory Metastatic Colorectal Carcinoma (NCT02248805)	KRAS	North Carolina
Phase 2	Phase 2a Study of BAX69 and 5-FU /Leucovorin or Panitumumab Versus Standard of Care in Subjects With Metastatic Colorectal Cancer (NCT02448810)	KRAS	Texas
Phase 1	Recombinant Albumin Fusion Protein sEphB4-HSA in Treating Patients With Metastatic or Recurrent Solid Tumors (NCT01642342)	KRAS	California
Phase 1	A Phase 1 Study Evaluating CB-5083 in Subjects With Advanced Solid Tumors (NCT02243917)	KRAS	Colorado
Phase 1	A Trial of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers (NCT02613650)	KRAS	Utah

ALTERATION DETAILS

KRAS Description:

KRAS (Kirsten rat sarcoma viral oncogene homolog) encodes for the GTPase KRas protein, one of three human RAS proteins. RAS proteins are small GTPases that are central mediators downstream of growth factor receptor signaling and therefore critical for cell proliferation, survival, and differentiation. KRAS is implicated in the pathogenesis of several cancers.

G12V
Frequency of KRAS mutations in ovarian cancer: 14% (COSMIC)
Frequency of G12V mutations in KRAS-mutated ovarian cancer: 37% (COSMIC)
Frequency of KRAS mutations in thyroid cancer: 3% (COSMIC)
Frequency of G12V mutations in KRAS-mutated thyroid cancer: 6.6% (COSMIC)
Frequency of KRAS mutations in lung adenocarcinoma: 15-25% (Brose et al. 2002, Riely et al. 2008)
Frequency of G12V mutations in KRAS-mutated lung adenocarcinoma: 20% (COSMIC)
Frequency of KRAS mutations in colorectal cancer: 40% (Amado et al. 2008; Faulkner et al. 2010; Neumann et al. 2009)
Frequency of G12V mutations in KRAS-mutated colorectal cancer: 21.9-24.4% (COSMIC; Faulkner et al. 2010)

References:
http://www.mycancergenome.org/content/disease/ovarian-cancer/kras/37
http://www.mycancergenome.org/content/disease/thyroid-cancer/kras/37
http://www.mycancergenome.org/content/disease/lung-cancer/kras/37
http://www.mycancergenome.org/content/disease/colorectal-cancer/kras/37

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TEST DETAILS

This test utilizes a multiplexed genotyping panel to detect somatic hotspot mutations within 5 cancer-related genes.

Biomarkers Tested by Mutational Analysis:

BRAF (NM_004333.4)	KRAS (NM_033360.3)	NRAS (NM_002524.3)	PIK3CA (NM_006218.2)	PTEN (NM_000314.4)

Methodology

The ColonSEQ cancer panel consists of a genotyping panel to detect somatic hotspot mutations within 5 cancer-related genes. DNA is isolated from micro-dissected tumor tissue. The genotyping panel utilizes multiplexed genotyping by the SNaPshot(R) method (Life Technologies) to detect 48 different recurrent mutations across 5 different genes implicated in colorectal cancer (CRC). The SNaPshot(R) technology consists of a multiplexed PCR step, followed by a single-base extension sequencing reaction in which allele-specific fluorescently-labeled probes interrogate each loci of interest. These different-sized probes are subsequently resolved by electrophoresis and analyzed by an automated DNA sequencer. This assay is capable of detecting the following pathogenic mutations: BRAF (p.V600E); KRAS (p.G12C/S/R/V/A/D, p.G13C/S/R/D/A, p.Q61R/K/L/H, p.K117N, p.A146T/P/V); NRAS (p.G12C/S/A/D/V, p.G13R/C/D/V, p.Q61K/L/R); PIK3CA (p.E542K, p.E545K/Q/A/G/V, p.Q546K/E/P/R/L, p.H1047R/L); PTEN (p.R233X). The term "pathogenic" is used here to describe a sequence variant previously reported and recognized to be pathogenic (i.e. variant is reported in a curated mutational database with well-established in *vitro* or in *vivo* functional evidence that is supportive of a deleterious effect on the gene or gene product). Clinically actionable variants will be reported and interpreted utilizing the GenomOncology software powered by the My Cancer Genome(TM) personalized cancer medicine knowledge-base.

Intended Use

The ColonSEQ cancer panel is intended to be used for the molecular genotyping of tumors from patients with colorectal cancer in order to help predict response to targeted therapies and prioritize treatment. Results from this test may also be useful in some cases as a prognostic indicator. Approximately 60-70% of colorectal tumor specimens are expected to be positive for one or more mutations on this assay according to the current mutational databases (COSMIC, TCGA). The results of this test should be interpreted in the context of the patient's clinical findings and other laboratory data.

Limitations

The ColonSEQ cancer panel is designed to detect somatic hotspot mutations within 5 cancer-related genes. Mutations occurring within regions of these genes that are not targeted by the assay specific design will not be detected. The absence of mutation does not rule out the possibility that other mutations that are not targeted by this assay may be present. The limit of detection of the genotyping assay (the minimum percentage of mutant DNA that can be detected in a background of wild-type) is approximately 5 percent.

Laboratory test results should always be considered in the context of clinical observations and epidemiologic data. This test was developed and its performance characteristics determined by med fusion. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

Technical services performed at: med fusion, 2501 South State Highway 121, Bld 12 Lewisville, TX 75067 CLIA#45D2004217
Professional services performed at: Pathologists Bio-Medical Lab, 3600 Gaston Ave, Suite 261, Dallas, TX 75246