Keshav Sarda MOLECULAR QUEST HEALTHCARE PVT LTD PLAT NO 28 29 SECTOR 18 P GURGAON Gurgaon Haryana	DOB: 24/04/1953 Age: 65Y Gender: M PID: QD2205525 Physician:DR.SANTOSH	Molecular Quest Healthcare Pvt. Ltd. 28-29, Electronic City,Sec-18,Udyog Vihar, Phase-04 Gurgaon Haryana Phone: 8588869342

Order#	Collected Date/Time	Reported Date/Time	Status
2270147	11/05/2018	15/06/2018 08:12 PM	Final Report

Order Comments

Medical Oncologist ? Dr. Amish Vora
Molecular Oncologist ? Dr. Amit Verma

Test	Within Range	Out of Range	Biological Ref Range	Units
WATSON GENOMICS FROM QUEST DIAGNOSTICS, CORE	See Attached Report.			

end of report for Keshav Sarda, Order No #2270147, Acc No # 180546852

Dr Anurag Bansal M.D., Associate Director - Medical

Date and Time of Order Received in the Lab: 15/05/2018 02:09 PM

H - High, L - Low, VH - Very High, VL - Very Low, A - Clinically Abnormal, PA - Panic Abnormal

2270147

PATIENT INFORMATION
SARDA,KESHAV

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

DOB: 04/24/1953 Age: 65
SEX: M

ORDERING PHYSICIAN
A VORA/A VERMA
CLIENT INFORMATION
55001
QUEST DIAGNOSTICS INDIA PVT LTD
A17, INFO CITY, GURGAON
SECTOR 34
HARYANA INDIA 122001,

SPECIMEN INFORMATION
SPECIMEN: 83173413
REQUISITION: 550010033418
LAB REF NO:

ID: 2270147

COLLECTED: 05/11/2018 00:00
RECEIVED: 05/24/2018 01:05
REPORTED: 06/14/2018 22:33

Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE				EZ
Tumor Tissue Type:	ADENOCARCINOMA			
Block ID:	18011098			
Diagnosis:	COADREAD METASTATIC POORLY DIFFERENTIATED ADENOCA-HINDGUT			
Source	ABDOMINAL WALL			
Paired Blood Submitted	YES			
Report Germline Consent	NO			
Overall Interpretation	SEE BELOW			

Diagnosis: Colorectal Adenocarcinoma

The following clinically significant results were found in this specimen:

1- KRAS wildtype
2- NRAS wildtype
3- TP53 R175H

KRAS and NRAS SUMMARY
Both KRAS and NRAS are wildtype (not mutated) in this sample. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy.

TP53 SUMMARY
The TP53 R175H mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA.

MSI SUMMARY
The tumor/normal pair samples were examined for microsatellite instability using 5 mononucleotide markers (Bat25, Bat26, NR21, NR24 and NR27). Results indicate microsatellite stable pattern (MSS). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the MSI Stable tumor. Pre-clinical and clinical evidence are not available for this indication.

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Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE (Continued)				
Overall Interpretation (Continued)				
Tumor mutation burden (TMB) for this case is 6 non-synonymous variants per MB coding sequence. In contrast, MSS tumors which in general carry a low TMB are expected to have 12 non-synonymous variants per MB coding sequence (95% Confidence Interval 12-18) and MSI-High tumors which in general carry a high TMB are expected to have 48 non-synonymous variants per MB coding sequence (95% Confidence Interval 42-66). Published literature supports that higher TMB in tumors can help predict response to immunotherapies in certain cancer indications.				
Gene Name #1	SEE BELOW			
	KRAS			
Mutation #1	SEE BELOW			
	wildtype			
Alteration Type #1	SEE BELOW			
	WILDTYPE			
Mutation Frequency #1	SEE BELOW		% Frequency	
	0			
Tumor Type Drugs #1	YES			
Non-Tumor Type Drugs #1	NO			
Clinical Trials #1	NO			
Watson Genomics,Core 2				EZ
Gene Name #2	SEE BELOW			
	NRAS			
Mutation #2	SEE BELOW			
	wildtype			
Alteration Type #2	SEE BELOW			
	WILDTYPE			
Mutation Frequency #2	SEE BELOW		% Frequency	
	0			
Tumor Type Drugs #2	YES			
Non-Tumor Type Drugs #2	NO			
Clinical Trials #2	NO			
Watson Genomics,Core 3				EZ
Gene Name #3	SEE BELOW			
	TP53			
Mutation #3	SEE BELOW			
	R175H			
Alteration Type #3	SEE BELOW			
	MISSENSE MUTATION			

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Test Name	In Range	Out of Range	Reference Range	Lab
Watson Genomics,Core 3 (Continued)				
Mutation Frequency #3	SEE BELOW		% Frequency	
	10			
Tumor Type Drugs #3	NO			
Non-Tumor Type Drugs #3	NO			
Clinical Trials #3	YES			
Interacting Mutations				EZ
Interacting Mutations	SEE BELOW			
	None			
Additional Mutations	SEE BELOW			
	None			
Clinical Impact 1				EZ
Gene Function #1	SEE BELOW			

BACKGROUND

KRAS is a GDP/GTP-binding protein with intrinsic GTPase activity that acts as intracellular signal transducer. KRAS is usually tethered to cell membranes and an early molecule in many signal transduction pathways. The protein alternates between an inactive form bound to GDP and an active form bound to GTP. It is activated by receptor tyrosine kinases and a guanine nucleotide-exchange factor (GEF), which then stimulates the RAF-MEK-MAPK pathway. KRAS is inactivated by a GTPase-activating protein (GAP). KRAS is one of the most frequently mutated genes in human cancer. The most common oncogenic Ras mutation found in tumors is an amino acid change from Gly12 to Asp12 (G12D or another amino acid). This mutation prevents the inactivation of the RAS protein. The transforming capacity of KRAS mutants is associated with different degrees of aggressiveness depending on the location of the variant within the protein and the amino acid substation. Codon 12 mutations are more resistant to cell death and have more oncogenic and transforming potential than codon 13 variants (PMID: 11118062). Furthermore, different variants can signal through different downstream effector pathways (PMID: 16679305). Aside from mutations within the highly conserved P-loop (amino acids 10 to 17), switch 1 and switch 2 mutations can also increase the basal activity of KRAS.

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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 1 (Continued)				
Mutation Effect on Gene #1	SEE BELOW			

MUTATION EFFECT
No clinically significant mutation was found in KRAS

NCCN
GUIDELINES

Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.

STANDARD THERAPEUTIC IMPLICATIONS

The absence of a mutation in the RAS genes is clinically important because it expands approved treatments available to treat this tumor. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy. Expression levels of the ligands epiregulin and amphiregulin may allow for further selection of patients, and retrospective data analysis suggest that high expression of epiregulin and amphiregulin is associated with response and low expression is associated with no benefit (PMID: 19738126, 26867820).

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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 1 (Continued)				
FDA Tumor Drugs #1	SEE BELOW			

PANITUMUMAB,Colorectal Carcinoma
The approval is based on the results of a single, open label study that enrolled 463 patients with metastatic CRC. Patients were randomly assigned to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg intravenously, every other week. All patients were required to have disease progression following one or more chemotherapy regimens containing a fluoropyrimidine, irinotecan, and oxaliplatin. The mean PFS was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone. There were 19 partial responses (8%) among the 231 patients randomly assigned to panitumumab, the median response duration was 17 weeks. There was no difference in OS between the two study arms. Approximately 75% of patients in the BSC alone arm crossed over to receive panitumumab after a determination of disease progression by the study investigator. Most patients" tumors exhibited EGFR expression in 10% of tumor cells with no evidence of a correlation between either the proportion of cells expressing EGFR or the intensity of EGFR expression (PMID: 17475878). Efficacy was also shown in a phase 3 trial, which assessed the treatment effect of panitumumab plus best supportive care (BSC) vs BSC on OS in 377 patients with chemo-refractory wild-type KRAS exon 2 mCRC. In wild-type RAS mCRC, median OS for panitumumab plus BSC was 10.0 vs 6.9 months for BSC. Patients with RAS mutations did not benefit from panitumumab (PMID: 27736842).

CETUXIMAB,Colorectal Carcinoma
The approval was based on retrospective analyses of tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies, CA225025 and EMR 62 202-047 (OPUS), according to KRAS mutation status. The addition of cetuximab to chemotherapy or best supportive care (BSC) resulted in improved OS, PFS, and ORR in patients with KRAS wild-type tumors, whereas there was no benefit, or even potential harm, in patients with KRAS mutant tumors. CRYSTAL was an open-label trial in patients with mCRC who had not received prior chemotherapy for metastatic disease. KRAS mutation status was available from 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI alone. The median PFS for patients with wild type tumors treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with cetuximab plus FOLFIRI was 8.9 months compared to 8.1 months in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab (PMID: 27722750). Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors: CA225025 was an open-label randomized trial that compared cetuximab plus best supportive care (BSC) with BSC alone in patients with previously treated mCRC. The median OS was 8.6 versus 5.0 months in the cetuximab plus BSC and BSC groups in patients wild type tumors, respectively. The median PFS was 3.8 and 1.9 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared

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Clinical Impact 1 (Continued)				
FDA Tumor Drugs #1 (Continued)				
cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315), ORR was 57% in patients treated with cetuximab plus FOLFOX-4 compared to 34% in patients treated with FOLFOX-4. The median PFS was 8.3 compared with 7.2 months and median OS was 22.8 versus 18.5 months. In the KRAS mutant subgroup (N=136/315), no improvements in OS, PFS, or ORR were observed in patients treated with cetuximab plus FOLFOX-4 compared with patients treated with FOLFOX-4 alone (PMID: 21228335).				
FDA Non-Tumor Drugs #1	SEE BELOW			
	None			
Clinical Trials #1	SEE BELOW			
	None			
Companion Diagnostics #1	SEE BELOW			
	None			
Clinical Impact 2				EZ
Gene Function #2	SEE BELOW			

BACKGROUND
NRAS is a guanine-nucleotide binding protein that cycles between the active (GTP-bound) and inactive (GDP-bound) form. It functions as a molecular switch mediating signals from ligand activated receptor tyrosine kinases (RTK) to the nucleus through a complex network of downstream signaling cascades. NRAS mutations are by far the predominant alteration among RAS genes in Melanoma found in approximately 15% of all tumors (PMID: 16291983). The most common mutation occurs in codon 61, followed by codon 12 and 13. Mutations in NRAS are also associated with up to 6% of CRC (PMID: 20736745), AML (PMID: 23634996), Multiple Myeloma (PMID: 24434212) and few

cases of adenocarcinoma of the lung (PMID: 12460918).

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Clinical Impact 2 (Continued)				
Mutation Effect on Gene #2	SEE BELOW			

MUTATION EFFECT
No clinically significant mutation was found in NRAS

NCCN
GUIDELINES
Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.

STANDARD THERAPEUTIC IMPLICATIONS
CETUXIMAB
PANITUMUMAB

FDA Tumor Drugs #2	SEE BELOW			

PANITUMUMAB,Colorectal Carcinoma
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CETUXIMAB,Colorectal Carcinoma
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Clinical Impact 2 (Continued)
FDA Tumor Drugs #2 (Continued)
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FDA Non-Tumor Drugs #2 SEE BELOW

None

Clinical Trials #2 SEE BELOW

None

Companion Diagnostics #2 SEE BELOW

None

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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 3				EZ
Gene Function #3	SEE BELOW			

BACKGROUND
The transcription factor TP53 regulates a large number of genes that control tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis, whilst the activation of TP53 often leads to apoptosis. Activation of TP53 begins through a number of mechanisms including phosphorylation by ATM, ATR, CHK1 and MAPKs. The TP53 tumor suppressor gene regulates more than 100 genes that control critical tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis. It is the most frequently altered gene in human cancers and missense mutations that are associated with an aggressive phenotype occur in more than 50% of cancers.

Mutation Effect on Gene #3	SEE BELOW			

MUTATION EFFECT
loss-of-function mutation.

The TP53 R175H mutation is known to be oncogenic. The R175H mutation is one of the most common alterations of TP53 with more than 320 entries in the COSMIC database. The histidine substitution at codon 175 results in unfolding of the DNA-binding domain and loss of transcriptional activity (PMID: 8510927, 17401432), while the mutant protein has gained the ability to bind to and inhibit P63 and P73 (PMID: 27589690) in addition to having a dominant negative effect on wild type TP53 (PMID: 8633021, 9364015, 10519380). It is significantly less thermodynamically stable and completely denatured at 37C. Furthermore, it lacks wild-type TP53 function and is unable to induce cell cycle arrest or apoptosis. R175H is most commonly associated with CRC, PDAC, breast carcinoma, adenocarcinoma of the esophagus and stomach, as well as HNSCC. The germline variant has been associated with Li-Fraumeni syndrome (LFS) and hereditary cancer-predisposing syndrome (PMID: 9047394, 18511570) and classified as causative for these disorders (ClinVar). The germline variant of this mutation has been associated with a hereditary cancer predisposing syndrome (ClinVar). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA.

NCCN GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

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Clinical Impact 3 (Continued)				
FDA Tumor Drugs #3	SEE BELOW			
	None			
FDA Non-Tumor Drugs #3	SEE BELOW			
	None			
Clinical Trials #3	SEE BELOW			

CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE
NCT02576444, Phase 2
TITLE:
A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

NCT01748825, Phase 1
TITLE: A Phase I Study of Single-agent AZD1775 (MK-1775), a Wee1 Inhibitor, in Patients With Advanced Refractory Solid Tumors

NCT02095132, Phase 1 or 2
TITLE: A Phase 1/2 Study of AZD1775 (MK-1775) in Combination With Oral Irinotecan in Children, Adolescents, and Young Adults With Relapsed or Refractory Solid Tumors

NCT02354547, Phase 1
TITLE: A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children With Refractory or Recurrent Solid Tumors

NCT02617277, Phase 1
TITLE: A Phase I Study Assessing the Safety, Tolerability and Pharmacokinetics of AZD1775 in Combination With MEDI4736 in Patients With Advanced Solid Tumours

NCT03313557, Phase 1
TITLE: An Open-label, Non-randomised, Multicentre Study to Allow Continued Access to and Assess the Safety and Tolerability of AZD1775 for Patients Enrolled in AZD1775 Clinical Pharmacology Studies

INVESTIGATIONAL THERAPEUTIC IMPLICATIONS

P53-directed therapies are currently in early phase trials, based on preclinical studies

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Clinical Impact 3 (Continued)
Clinical Trials #3 (Continued)
aiming to restore wildtype p53 function or to inhibit the downstream function of oncogenic mutant p53 (PMID: 24651012). Despite the substantial body of research on p53, restoring its function within cancer cells is a challenging task and difficult to translate into clinical benefit. Nonetheless, multiple strategies have been utilized in an attempt to restore p53 function in cancer cells. These strategies include impairing the activity of p53 regulators, restoring wildtype activity to p53 mutant forms or mimicking p53 downstream function, however, as of yet, none of these approaches have successfully translated into advanced clinical trials (PMID: 20463003, 16690321).

TRANSFERRIN RECEPTOR-TARGETED LIPOSOMAL P53 CDNA

Highest level of evidence: 3B
Clinical activity of this Drug was demonstrated in afirst-in-man Phase I clinical trial in 11 patients with refractory disease. Minimal side effects were observed and seven patients demonstrated SD. One patient with adenoid cystic carcinoma had his status changed from unresectable to resectable after one treatment cycle. The median survival was 340 days (PMID: 23609015). Combination therapy with docetaxel was tested in 14 patients with advanced cancers. The combination treatment was well-tolerated and clinical activity in 12 patients evaluable for analysis was observed. Three of these patients achieved PR with tumor reductions of -47%, -51%, and -79%. Two other patients had SD with significant shrinkage of tumor volumes of 25% and 16% (PMID: 27357628).

AZD1775

Highest level of evidence: 3B
In a phase II study of AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line platinum based therapy, the ORR was 43%, including one patient (5%) with a prolonged CR. Median PFS and OS were 5.3 months and 12.6 months, respectively, with two patients having ongoing response for more than 31 and 42 months at data cutoff (PMID: 27998224).

LEVELS OF EVIDENCE
Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies
Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN)
Level 2B: Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended

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Clinical Impact 3 (Continued)				
Clinical Trials #3 (Continued) as standard of care by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN				
Companion Diagnostics #3	SEE BELOW			
	None			
Gene Regions Passing QC				EZ
Gene Regions Passing QC	SEE BELOW			
In this specimen, 868 of 900 regions (>96%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 32 of 900 regions (<4%) was not optimal and the risk of a false-negative result at those regions cannot be ruled out. Details can be provided upon request.				
This data was reviewed and interpreted by Anatole Ghazalpour, PhD, FACMG				
Always Statement	SEE BELOW			
This Watson Genomics from Quest Core test is designed to detect mutations present in any FFPE tissue from solid tumors. The test is designed to detect single nucleotide variants (SNVs) and small insertions/deletions (In/Dels) as well as whole gene copy number alterations and translocations in a select group of genes. Results of the test should be correlated with clinical findings. The genes (listed below) were selected based on actionability of mutations identified in those genes using currently available evidence from national and international guidelines and literature. Actionability is defined as information a clinician might find useful to aid in diagnosis, prognosis and/or treatment strategy for a patient. Results of the test should be correlated with clinical findings. Clinical trial information provided in this report is solely for informational purposes for the physician and does not constitute any endorsement or a recommendation for enrollment of patients in any trial by Quest Diagnostics, its affiliates, or its employees. Only mutations present in the interrogated regions of the genes are reported. The test does not identify mutations present outside the interrogated regions. Normal population variations, promoter and intronic variations (with the exception of the TERT promoter and splice site variants) as well as synonymous single nucleotide polymorphisms (SNPs) are not included in this report. This test has an analytical sensitivity for detecting 5% SNVs and 5%				

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Test Name	In Range	Out of Range	Reference Range	Lab

Gene Regions Passing QC (Continued)
Always Statement (Continued)

INDEL mutated sequences in a background of non-mutated DNA sequence; two-fold or higher gene amplifications; and homozygous gene deletions.
Insertion/Deletion detection is limited to 10 base insertion and 15 base deletion. Translocation detection is limited to a set of specified acceptor genes at 20% analytical sensitivity. The performance characteristics of the test can change based on adequacy of tumor tissue or pre-analytical variables. (This test was validated on FFPE tissue and whole blood).
The genes tested include: AKT1, AKT2, ALK, AR, AURKA, BAP1, BRAF, BRCA1, BRCA2, CDKN2A, CDKN2B, CTNNB1, DDR2, EGFR, EP300, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, HRAS, IDH1, JAK2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, MYC, MYCN, NRAS, NTRK1, PDGFRA, PDGFRB, PIK3CA, PTCH1, PTEN, RET, ROS1, TERT, TMPRSS2, TP53, TSC1, VHL. The genes tested for translocations include ALK, BRAF, EGFR, FGFR2, FGFR3, NTRK1, RET, ROS1, and TMPRSS2.

Microsatellite instability and/or hypermutated phenotype can be reported if identified.
This test was not designed for comprehensive germline mutation analysis or for circulating tumor DNA mutation analysis. When patient consent is provided, and where warranted, limited information is included about whether an alteration detected in the BRCA1, BRCA2, CDKN2A, PTEN, RET, TP53 or VHL genes in the tissue is of germline origin, but this information should be confirmed with specialized germline testing in consultation with a clinician and genetic counseling, if appropriate. Genetic counseling is available at 1.866.GENE.INFO (1.866.436.3463).
The Watson Genomics from Quest Diagnostics name and logo are registered trademarks owned by IBM, and used by Quest under license. IBM makes available to Quest certain information to assist Quest in providing this service. This report provided by Quest, is the sole responsibility of Quest, and no relationship is created between the patient or referring physician/institution and IBM or its employees.

For additional information, please refer to
http://education.QuestDiagnostics.com/faq/FAQ155
(This link is being provided for informational/educational purposes only.)

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/14/2018 22:33

PATIENT INFORMATION
SARDA,KESHAV

DOB: 04/24/1953 Age: 65
SEX: M
ID: 2270147

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab
Gene Regions Passing QC (Continued)				
Publications	SEE BELOW			

Please visit http://ncbi.nlm.nih.gov and enter the PMID number to retrieve reference(s) cited in patient report.

Please visit http://clinicaltrials.gov and enter NCT number to retrieve further information about trials cited in this report.

For more information about the Watson test please visit https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name ibm-watson--genomics-from-quest-diagnostics/watson-genomics-for-physicians

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Performing Laboratory Information:

EZ Quest Diagnostics Nichols Institute 33608 Ortega Hwy San Juan Capistrano CA 92675
Laboratory Director: I Maramica MD, PhD, MBA

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Report Status: Final

SARDA, KESHAV

Patient Information	Specimen Information	Client Information
SARDA, KESHAV **DOB: 04/24/1953 AGE: 65** Gender: M Phone: NG Patient ID: 83173413	Specimen: 83173413 Requisition: Lab Ref #: 2270147 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/14/2018 / 22:33 PDT	Client #: 55001 A VORA/A VERMA QUEST DIAGNOSTICS INDIA PVT LT Attn: A17, INFO CITY, GURGAON SECTOR 34 HARYANA INDIA 122001

IBM Watson™ Genomics from Quest Diagnostics®

OVERALL INTERPRETATION Lab: EZ

Diagnosis: Colorectal Adenocarcinoma

The following clinically significant results were found in this specimen:

1- KRAS wildtype 2- NRAS wildtype 3- TP53 R175H

KRAS and NRAS SUMMARY Both KRAS and NRAS are wildtype (not mutated) in this sample. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy.

TP53 SUMMARY

The TP53 R175H mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA.

MSI SUMMARY

The tumor/normal pair samples were examined for microsatellite instability using 5 mononucleotide markers (Bat25, Bat26, NR21, NR24 and NR27). Results indicate microsatellite stable pattern (MSS). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the MSI Stable tumor. Pre-clinical and clinical evidence are not available for this indication.

Tumor mutation burden (TMB) for this case is 6 non-synonymous variants per MB coding sequence. In contrast, MSS tumors which in general carry a low TMB are expected to have 12 non-synonymous variants per MB coding sequence (95% Confidence Interval 12-18) and MSI-High tumors which in general carry a high TMB are expected to have 48 non-synonymous variants per MB coding sequence (95% Confidence Interval 42-66). Published literature supports that higher TMB in tumors can help predict response to immunotherapies in certain cancer indications.

CLINICIAN PROVIDED INFORMATION Lab: EZ

Diagnosis:	METASTATIC POORLY DIFFERENTIATED ADENOCA-HINDGUT				
Tumor-Tissue Type:	ADENOCARCINOMA	**Specimen Source**	ABDOMINAL WALL		
Block/Specimen ID	18011098	**Paired Blood Submitted:**	YES	**Report Germline Consent:**	NO

RESULT SUMMARY Lab: EZ

Gene Name	Mutation	Alteration Type	Mutation Frequency	Tumor Type Drugs	Non-Tumor Type Drugs	Clinical Trials
KRAS	wildtype	WILDTYPE	0 % Frequency	YES	NO	NO
NRAS	wildtype	WILDTYPE	0 % Frequency	YES	NO	NO
TP53	R175H	MISSENSE MUTATION	10 % Frequency	NO	NO	YES

ADDITIONAL MUTATIONS Lab: EZ

None

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INTERACTING MUTATIONS **Lab: EZ**

None

KRAS wildtype CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** KRAS is a GDP/GTP-binding protein with intrinsic GTPase activity that acts as intracellular signal transducer. KRAS is usually tethered to cell membranes and an early molecule in many signal transduction pathways. The protein alternates between an inactive form bound to GDP and an active form bound to GTP. It is activated by receptor tyrosine kinases and a guanine nucleotide-exchange factor (GEF), which then stimulates the RAF-MEK-MAPK pathway. KRAS is inactivated by a GTPase-activating protein (GAP). KRAS is one of the most frequently mutated genes in human cancer. The most common oncogenic Ras mutation found in tumors is an amino acid change from Gly12 to Asp12 (G12D or another amino acid). This mutation prevents the inactivation of the RAS protein. The transforming capacity of KRAS mutants is associated with different degrees of aggressiveness depending on the location of the variant within the protein and the amino acid substation. Codon 12 mutations are more resistant to cell death and have more oncogenic and transforming potential than codon 13 variants (PMID: 11118062). Furthermore, different variants can signal through different downstream effector pathways (PMID: 16679305). Aside from mutations within the highly conserved P-loop (amino acids 10 to 17), switch 1 and switch 2 mutations can also increase the basal activity of KRAS.
Mutation Effect on Gene	**MUTATION EFFECT** No clinically significant mutation was found in KRAS NCCN GUIDELINES Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab. **STANDARD THERAPEUTIC IMPLICATIONS** The absence of a mutation in the RAS genes is clinically important because it expands approved treatments available to treat this tumor. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy. Expression levels of the ligands epiregulin and amphiregulin may allow for further selection of patients, and retrospective data analysis suggest that high expression of epiregulin and amphiregulin is associated with response and low expression is associated with no benefit (PMID: 19738126, 26867820).
FDA Approved Drugs in Tumor Type	PANITUMUMAB,Colorectal Carcinoma The approval is based on the results of a single, open label study that enrolled 463 patients with metastatic CRC. Patients were randomly assigned to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg intravenously, every other week. All patients were required to have disease progression following one or more chemotherapy regimens containing a fluoropyrimidine, irinotecan, and oxaliplatin. The mean PFS was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone. There were 19 partial responses (8%) among the 231 patients randomly assigned to panitumumab, the median response duration was 17 weeks. There was no difference in OS between the two study arms. Approximately 75% of patients in the BSC

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KRAS wildtype CLINICAL IMPLICATIONS **Lab: EZ**

	alone arm crossed over to receive panitumumab after a determination of disease progression by the study investigator. Most patients" tumors exhibited EGFR expression in 10% of tumor cells with no evidence of a correlation between either the proportion of cells expressing EGFR or the intensity of EGFR expression (PMID: 17475878). Efficacy was also shown in a phase 3 trial, which assessed the treatment effect of panitumumab plus best supportive care (BSC) vs BSC on OS in 377 patients with chemo-refractory wild-type KRAS exon 2 mCRC. In wild-type RAS mCRC, median OS for panitumumab plus BSC was 10.0 vs 6.9 months for BSC. Patients with RAS mutations did not benefit from panitumumab (PMID: 27736842). CETUXIMAB,Colorectal Carcinoma The approval was based on retrospective analyses of tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies, CA225025 and EMR 62 202-047 (OPUS), according to KRAS mutation status. The addition of cetuximab to chemotherapy or best supportive care (BSC) resulted in improved OS, PFS, and ORR in patients with KRAS wild-type tumors, whereas there was no benefit, or even potential harm, in patients with KRAS mutant tumors. CRYSTAL was an open-label trial in patients with mCRC who had not received prior chemotherapy for metastatic disease. KRAS mutation status was available from 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI alone. The median PFS for patients with wild type tumors treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with cetuximab plus FOLFIRI was 8.9 months compared to 8.1 months in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab (PMID: 27722750). Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors: CA225025 was an open-label randomized trial that compared cetuximab plus best supportive care (BSC) with BSC alone in patients with previously treated mCRC. The median OS was 8.6 versus 5.0 months in the cetuximab plus BSC and BSC groups in patients wild type tumors, respectively. The median PFS was 3.8 and 1.9 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315), ORR was 57% in patients treated with cetuximab plus FOLFOX-4 compared to 34% in patients treated with FOLFOX-4. The median PFS was 8.3 compared with 7.2 months and median OS was 22.8 versus 18.5 months. In the KRAS mutant subgroup (N=136/315), no improvements in OS, PFS, or ORR were observed in patients treated with cetuximab plus FOLFOX-4 compared with patients treated with FOLFOX-4 alone (PMID: 21228335).
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	None
Companion Diagnostics	None

NRAS wildtype CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND**

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NRAS wildtype CLINICAL IMPLICATIONS **Lab: EZ**

	NRAS is a guanine-nucleotide binding protein that cycles between the active (GTP-bound) and inactive (GDP-bound) form. It functions as a molecular switch mediating signals from ligand activated receptor tyrosine kinases (RTK) to the nucleus through a complex network of downstream signaling cascades. NRAS mutations are by far the predominant alteration among RAS genes in Melanoma found in approximately 15% of all tumors (PMID: 16291983). The most common mutation occurs in codon 61, followed by codon 12 and 13. Mutations in NRAS are also associated with up to 6% of CRC (PMID: 20736745), AML (PMID: 23634996), Multiple Myeloma (PMID: 24434212) and few cases of adenocarcinoma of the lung (PMID: 12460918).
Mutation Effect on Gene	**MUTATION EFFECT** No clinically significant mutation was found in NRAS NCCN GUIDELINES Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab. **STANDARD THERAPEUTIC IMPLICATIONS** **CETUXIMAB** PANITUMUMAB
FDA Approved Drugs in Tumor Type	PANITUMUMAB,Colorectal Carcinoma The approval is based on the results of a single, open label study that enrolled 463 patients with metastatic CRC. Patients were randomly assigned to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg intravenously, every other week. All patients were required to have disease progression following one or more chemotherapy regimens containing a fluoropyrimidine, irinotecan, and oxaliplatin. The mean PFS was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone. There were 19 partial responses (8%) among the 231 patients randomly assigned to panitumumab, the median response duration was 17 weeks. There was no difference in OS between the two study arms. Approximately 75% of patients in the BSC alone arm crossed over to receive panitumumab after a determination of disease progression by the study investigator. Most patients" tumors exhibited EGFR expression in 10% of tumor cells with no evidence of a correlation between either the proportion of cells expressing EGFR or the intensity of EGFR expression (PMID: 17475878). Efficacy was also shown in a phase 3 trial, which assessed the treatment effect of panitumumab plus best supportive care (BSC) vs BSC on OS in 377 patients with chemo-refractory wild-type KRAS exon 2 mCRC. In wild-type RAS mCRC, median OS for panitumumab plus BSC was 10.0 vs 6.9 months for BSC. Patients with RAS mutations did not benefit from panitumumab (PMID: 27736842). CETUXIMAB,Colorectal Carcinoma The approval was based on retrospective analyses of tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies, CA225025 and EMR 62 202-047 (OPUS), according to KRAS mutation status. The addition of cetuximab to chemotherapy or best supportive care (BSC) resulted in improved OS, PFS, and ORR in patients with KRAS wild-type tumors, whereas there was no benefit, or even potential harm, in patients with KRAS mutant tumors. CRYSTAL was an open-label trial in patients with mCRC who had not received prior chemotherapy for metastatic disease. KRAS mutation status was available from 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median

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NRAS wildtype CLINICAL IMPLICATIONS **Lab: EZ**

	OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI alone. The median PFS for patients with wild type tumors treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with cetuximab plus FOLFIRI was 8.9 months compared to 8.1 months in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab (PMID: 27722750). Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors: CA225025 was an open-label randomized trial that compared cetuximab plus best supportive care (BSC) with BSC alone in patients with previously treated mCRC. The median OS was 8.6 versus 5.0 months in the cetuximab plus BSC and BSC groups in patients wild type tumors, respectively. The median PFS was 3.8 and 1.9 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315), ORR was 57% in patients treated with cetuximab plus FOLFOX-4 compared to 34% in patients treated with FOLFOX-4. The median PFS was 8.3 compared with 7.2 months and median OS was 22.8 versus 18.5 months. In the KRAS mutant subgroup (N=136/315), no improvements in OS, PFS, or ORR were observed in patients treated with cetuximab plus FOLFOX-4 compared with patients treated with FOLFOX-4 alone (PMID: 21228335).
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	None
Companion Diagnostics	None

TP53 R175H CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** The transcription factor TP53 regulates a large number of genes that control tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis, whilst the activation of TP53 often leads to apoptosis. Activation of TP53 begins through a number of mechanisms including phosphorylation by ATM, ATR, CHK1 and MAPKs. The TP53 tumor suppressor gene regulates more than 100 genes that control critical tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis. It is the most frequently altered gene in human cancers and missense mutations that are associated with an aggressive phenotype occur in more than 50% of cancers.
Mutation Effect on Gene	**MUTATION EFFECT** loss-of-function mutation. The TP53 R175H mutation is known to be oncogenic. The R175H mutation is one of the most common alterations of TP53 with more than 320 entries in the COSMIC database. The histidine substitution at codon 175 results in unfolding of the DNA-binding domain and loss of transcriptional activity (PMID: 8510927, 17401432), while the mutant protein has gained the ability to bind to and inhibit P63 and P73 (PMID: 27589690) in addition to having a dominant negative effect on wild type TP53 (PMID: 8633021, 9364015, 10519380). It is

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TP53 R175H CLINICAL IMPLICATIONS **Lab: EZ**

	significantly less thermodynamically stable and completely denatured at 37C. Furthermore, it lacks wild-type TP53 function and is unable to induce cell cycle arrest or apoptosis. R175H is most commonly associated with CRC, PDAC, breast carcinoma, adenocarcinoma of the esophagus and stomach, as well as HNSCC. The germline variant has been associated with Li-Fraumeni syndrome (LFS) and hereditary cancer-predisposing syndrome (PMID: 9047394, 18511570) and classified as causative for these disorders (ClinVar). The germline variant of this mutation has been associated with a hereditary cancer predisposing syndrome (ClinVar). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA. **NCCN GUIDELINES** none **STANDARD THERAPEUTIC IMPLICATIONS** none
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE NCT02576444, Phase 2 TITLE: A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors NCT01748825, Phase 1 TITLE: A Phase I Study of Single-agent AZD1775 (MK-1775), a Wee1 Inhibitor, in Patients With Advanced Refractory Solid Tumors NCT02095132, Phase 1 or 2 TITLE: A Phase 1/2 Study of AZD1775 (MK-1775) in Combination With Oral Irinotecan in Children, Adolescents, and Young Adults With Relapsed or Refractory Solid Tumors NCT02354547, Phase 1 TITLE: A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children With Refractory or Recurrent Solid Tumors NCT02617277, Phase 1 TITLE: A Phase I Study Assessing the Safety, Tolerability and Pharmacokinetics of AZD1775 in Combination With MEDI4736 in Patients With Advanced Solid Tumours NCT03313557, Phase 1 TITLE: An Open-label, Non-randomised, Multicentre Study to Allow Continued Access to and Assess the Safety and Tolerability of AZD1775 for Patients Enrolled in AZD1775 Clinical Pharmacology Studies **INVESTIGATIONAL THERAPEUTIC IMPLICATIONS**

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TP53 R175H CLINICAL IMPLICATIONS **Lab: EZ**

	P53-directed therapies are currently in early phase trials, based on preclinical studies aiming to restore wildtype p53 function or to inhibit the downstream function of oncogenic mutant p53 (PMID: 24651012). Despite the substantial body of research on p53, restoring its function within cancer cells is a challenging task and difficult to translate into clinical benefit. Nonetheless, multiple strategies have been utilized in an attempt to restore p53 function in cancer cells. These strategies include impairing the activity of p53 regulators, restoring wildtype activity to p53 mutant forms or mimicking p53 downstream function, however, as of yet, none of these approaches have successfully translated into advanced clinical trials (PMID: 20463003, 16690321). TRANSFERRIN RECEPTOR-TARGETED LIPOSOMAL P53 CDNA Highest level of evidence: 3B Clinical activity of this Drug was demonstrated in afirst-in-man Phase I clinical trial in 11 patients with refractory disease. Minimal side effects were observed and seven patients demonstrated SD. One patient with adenoid cystic carcinoma had his status changed from unresectable to resectable after one treatment cycle. The median survival was 340 days (PMID: 23609015). Combination therapy with docetaxel was tested in 14 patients with advanced cancers. The combination treatment was well-tolerated and clinical activity in 12 patients evaluable for analysis was observed. Three of these patients achieved PR with tumor reductions of -47%, -51%, and -79%. Two other patients had SD with significant shrinkage of tumor volumes of 25% and 16% (PMID: 27357628). AZD1775 Highest level of evidence: 3B In a phase II study of AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line platinum based therapy, the ORR was 43%, including one patient (5%) with a prolonged CR. Median PFS and OS were 5.3 months and 12.6 months, respectively, with two patients having ongoing response for more than 31 and 42 months at data cutoff (PMID: 27998224). **LEVELS OF EVIDENCE** Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN) Level 2B: Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended as standard of care by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN
Companion Diagnostics	None

PUBLICATIONS **Lab: EZ**

Please visit http://ncbi.nlm.nih.gov and enter the PMID number to retrieve reference(s) cited in patient report.

Please visit http://clinicaltrials.gov and enter NCT number to retrieve further information about trials cited in this report.

For more information about the Watson test please visit https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name ibm-watson--genomics-from-quest-diagnostics/watson-genomics-for-physicians

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ADDITIONAL INFORMATION

Lab: EZ

This Watson Genomics from Quest Core test is designed to detect mutations present in any FFPE tissue from solid tumors. The test is designed to detect single nucleotide variants (SNVs) and small insertions/deletions (In/Dels) as well as whole gene copy number alterations and translocations in a select group of genes. Results of the test should be correlated with clinical findings. The genes (listed below) were selected based on actionability of mutations identified in those genes using currently available evidence from national and international guidelines and literature. Actionability is defined as information a clinician might find useful to aid in diagnosis, prognosis and/or treatment strategy for a patient. Results of the test should be correlated with clinical findings. Clinical trial information provided in this report is solely for informational purposes for the physician and does not constitute any endorsement or a recommendation for enrollment of patients in any trial by Quest Diagnostics, its affiliates, or its employees. Only mutations present in the interrogated regions of the genes are reported. The test does not identify mutations present outside the interrogated regions. Normal population variations, promoter and intronic variations (with the exception of the TERT promoter and splice site variants) as well as synonymous single nucleotide polymorphisms (SNPs) are not included in this report. This test has an analytical sensitivity for detecting 5% SNVs and 5% INDEL mutated sequences in a background of non-mutated DNA sequence; two-fold or higher gene amplifications; and homozygous gene deletions. Insertion/Deletion detection is limited to 10 base insertion and 15 base deletion. Translocation detection is limited to a set of specified acceptor genes at 20% analytical sensitivity. The performance characteristics of the test can change based on adequacy of tumor tissue or pre-analytical variables. (This test was validated on FFPE tissue and whole blood). The genes tested include: AKT1, AKT2, ALK, AR, AURKA, BAP1, BRAF, BRCA1, BRCA2, CDKN2A, CDKN2B, CTNNB1, DDR2, EGFR, EP300, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, HRAS, IDH1, JAK2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, MYC, MYCN, NRAS, NTRK1, PDGFRA, PDGFRB, PIK3CA, PTCH1, PTEN, RET, ROS1, TERT, TMPRSS2, TP53, TSC1, VHL. The genes tested for translocations include ALK, BRAF, EGFR, FGFR2, FGFR3, NTRK1, RET, ROS1, and TMPRSS2.

Microsatellite instability and/or hypermutated phenotype can be reported if identified. This test was not designed for comprehensive germline mutation analysis or for circulating tumor DNA mutation analysis. When patient consent is provided, and where warranted, limited information is included about whether an alteration detected in the BRCA1, BRCA2, CDKN2A, PTEN, RET, TP53 or VHL genes in the tissue is of germline origin, but this information should be confirmed with specialized germline testing in consultation with a clinician and genetic counseling, if appropriate. Genetic counseling is available at 1.866.GENE.INFO (1.866.436.3463). The Watson Genomics from Quest Diagnostics name and logo are registered trademarks owned by IBM, and used by Quest under license. IBM makes available to Quest certain information to assist Quest in providing this service. This report provided by Quest, is the sole responsibility of Quest, and no relationship is created between the patient or referring physician/institution and IBM or its employees.

For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ155 (This link is being provided for informational/educational purposes only.)

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute, San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

GENE REGIONS PASSING QC

Lab: EZ

In this specimen, 868 of 900 regions (>96%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 32 of 900 regions (<4%) was not optimal and the risk of a false-negative result at those regions cannot be ruled out. Details can be provided upon request.

This data was reviewed and interpreted by Anatole Ghazalpour, PhD, FACMG

PERFORMING SITE:

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This is supplemental to your standard report.