Kabedi Kayembe Gurgaon Haryana	DOB: 15/05/1981 Age: 36Y Gender: F PID: QD2206789 Physician:Dr. Amish Vora/ Dr. Amit Verma	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
2270146	11/05/2018	07/06/2018 12:52 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 Kabedi Kayembe, Order No #2270146, Acc No # 180554234

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

Date and Time of Order Received in the Lab: 16/05/2018 05:09 PM

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

2270146

QUEST DIAGNOSTICS INCORPORATED

SPECIMEN INFORMATION
SPECIMEN: 83173411
REQUISITION: 550010033416
LAB REF NO:

COLLECTED: 05/11/2018 00:00
RECEIVED: 05/23/2018 16:32
REPORTED: 06/06/2018 19:28

PATIENT INFORMATION
KAYEMBE,KABEDI

DOB: 05/15/1981 Age: 36
SEX: F

ID: 2270146

REPORT STATUS **Final**

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

Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE				EZ
Tumor Tissue Type:	DUCTAL CARCINOMA			
Block ID:	S/2971/17			
Diagnosis:	BRCA INVASIVE DUCTAL CARCINOMA			
Source	BREAST			
Paired Blood Submitted	YES			
Report Germline Consent	NO			
Overall Interpretation	SEE BELOW			

Diagnosis: Breast Invasive Ductal Carcinoma

The following clinically significant alterations were found in this specimen:

1- TP53 I195fs
2- DDR2 amplification
3- NTRK1 amplification

** no other significant alteration was found in the genes tested

TP53 SUMMARY
The TP53 I195fs mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring TP53 pathogenic mutation. There is clinical evidence that such mutations confer sensitivity to AZD1775.

DDR2 SUMMARY
The DDR2 Amplification is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the DDR2 amplification. There is clinical evidence that the DDR2 amplification confers sensitivity to Nilotinib.

NTRK1 SUMMARY
The NTRK1 Amplification is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the NTRK1 amplification. Pre-clinical and clinical evidence are not available for this indication.

MSI SUMMARY

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 19:28

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KAYEMBE,KABEDI

DOB: 05/15/1981 Age: 36
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ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE (Continued)				
Overall Interpretation (Continued)				
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 Ductal Breast 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.				
Gene Name #1	SEE BELOW			
	TP53			
Mutation #1	SEE BELOW			
	I195fs			
Alteration Type #1	SEE BELOW			
	FRAMESHIFT			
Mutation Frequency #1	SEE BELOW		% Frequency	
	52			
Tumor Type Drugs #1	NO			
Non-Tumor Type Drugs #1	NO			
Clinical Trials #1	YES			
Watson Genomics,Core 2				EZ
Gene Name #2	SEE BELOW			
	DDR2			
Mutation #2	SEE BELOW			
	Amplification			
Alteration Type #2	SEE BELOW			
	CNV			
Mutation Frequency #2	SEE BELOW		% Frequency	
	Ratio 2.5X			
Tumor Type Drugs #2	NO			
Non-Tumor Type Drugs #2	YES			
Clinical Trials #2	YES			

QUEST DIAGNOSTICS INCORPORATED

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Test Name	In Range	Out of Range	Reference Range	Lab
Watson Genomics,Core 3				EZ
Gene Name #3	SEE BELOW			
	NTRK1			
Mutation #3	SEE BELOW			
	Amplification			
Alteration Type #3	SEE BELOW			
	CNV			
Mutation Frequency #3	SEE BELOW		% Frequency	
	Ratio 2X			
Tumor Type Drugs #3	NO			
Non-Tumor Type Drugs #3	NO			
Clinical Trials #3	NO			
Interacting Mutations				EZ
Interacting Mutations	SEE BELOW			
	None			
Additional Mutations	SEE BELOW			
	None			
Clinical Impact 1				EZ
Gene Function #1	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.

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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
loss-of-function mutation.

The TP53 I195fs mutation is known to be oncogenic. Truncating mutations, which disrupt the DNA-binding domain or oligodimerization domain of the protein are predicted to be inactivating (PMID: 11900253, 11753428, 16007150). Inactivation of TP53 can confer cells additive growth and survival advantages, such as increased proliferation, evasion of apoptosis, and chemoresistance (PMID: 11156366, 19691397). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring TP53 pathogenic mutation. There is clinical evidence that such mutations confer sensitivity to AZD1775.

NCCN GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

FDA Tumor Drugs #1	SEE BELOW			
	None			
FDA Non-Tumor Drugs #1	SEE BELOW			
	None			

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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 1 (Continued)				
Clinical Trials #1	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

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 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).

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%,

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Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 1 (Continued)
Clinical Trials #1 (Continued)
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 #1 SEE BELOW

None

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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 2				EZ
Gene Function #2	SEE BELOW			

BACKGROUND
DDR2 is a widely expressed tyrosine kinase and the cell surface receptor for fibrillar collagen that regulates cell differentiation, remodeling of the extracellular matrix, cell migration and cell proliferation. It is required for normal bone development and regulates osteoblast differentiation and chondrocyte maturation via a signaling pathway that involves MAP kinases and leads to the activation of the transcription factor RUNX2. In addition, DDR2 is also involved in cutaneous wound healing promoting fibroblast migration and proliferation. DDR2 plays a key role in cancer progression by regulating the interactions of tumor cells with their surrounding collagen matrix (PMID: 22366781). DDR2 is amplified in a wide variety of cancer types and activating mutations have been reported in NSCLC cancer that are associated with sensitivity to dasatinib (PMID: 22328973, 23932362, 26206333).

Mutation Effect on Gene #2	SEE BELOW			

MUTATION EFFECT
copy number alteration (amplification)

The DDR2
amplification is known to be oncogenic. DDR2 amplification is observed at low frequency in multiple tumor types, including bladder cancer, nerve sheath tumors, adrenocortical and ampullary carcinomas and uterine sarcomas (cBioPortal, Zehir, A et al. Nature Medicine, 2017). The amplification of DDR2 has also been detected in liposarcomas (PMID: 24505276, 28099935). Elevated expression levels of DDR2 have been detected in hepatocellular carcinoma cell lines and clinical specimens. In vitro studies have shown that DDR2 regulates the epithelial-to-mesenchymal process (PMID: 26362312) indicating a possible oncogenic role for DDR2 amplification. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the DDR2 amplification. There is clinical evidence that the DDR2 amplification confers sensitivity to Nilotinib.

NCCN
GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

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ORDERING PHYSICIAN
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Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 2 (Continued)				
FDA Tumor Drugs #2	SEE BELOW			
	None			
FDA Non-Tumor Drugs #2	SEE BELOW			

DASATINIB
Acute Lymphoblastic Leukemia, Chronic Myeloid Leukemia

IMATINIB
Acute Lymphoblastic Leukemia, Chronic Eosinophilic Leukemia, Not Otherwise Specified, Chronic Myeloid Leukemia, Dermatofibrosarcoma Protuberans, Gastrointestinal Stromal Tumor, Mastocytosis/Hypereosinophilic Syndrome, Myelodysplastic Syndromes, Myeloproliferative Neoplasm, Systemic Mastocytosis

NILOTINIB
Chronic Myeloid Leukemia

Clinical Trials #2	SEE BELOW			

CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE
NCT01471106, Phase 2
TITLE:
Phase II Short-term Adjuvant Therapy and Biomarker Studies With Targeted Agents in Women With Estrogen Receptor Negative Breast Cancer

NCT01738139,
Phase 1
TITLE: A Phase I Trial of Ipilimumab (Immunotherapy) and Imatinib Mesylate (c-Kit Inhibitor) in Patients With Advanced Malignancies

NCT02379416, Phase 1
TITLE: Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults With Refractory Solid Tumors

NCT02791334,
Phase 1
TITLE: A Phase 1a/1b Study of a Novel Anti-PD-L1 Checkpoint Antibody (LY3300054) Administered Alone or in Combination With Other Agents in Advanced Refractory Solid Tumors (Phase 1a/1b Anti-PD-L1 Combinations in Tumors-PACT)

NCT03292536, Phase 1
TITLE: An Exploratory Phase 1B Study to Assess the Effects of Merestinib on Bone Metastases in Subjects With Breast Cancer

PATIENT INFORMATION
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Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 2 (Continued)
Clinical Trials #2 (Continued)

INVESTIGATIONAL THERAPEUTIC IMPLICATIONS

NILOTINIB

Highest level
of evidence: 3B
An orally bioavailable aminopyrimidine-derivative Bcr-Abl tyrosine kinase inhibitor with antineoplastic activity. Designed to overcome Imatinib resistance, Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of the Abl protein of the Bcr-Abl fusion protein, resulting in the inhibition of the Bcr-Abl-mediated proliferation of Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukemia (CML) cells. This agent also inhibits the receptor tyrosine kinases platelet-derived growth factor receptor (PDGF-R) and c-kit, a receptor tyrosine kinase mutated and constitutively activated in most Gastrointestinal Stromal Tumors (GISTs). With a binding mode that is energetically more favorable than that of Imatinib, Nilotinib has been shown to have an approximately 20-fold increased potency in kinase and proliferation assays compared to Imatinib.

IMATINIB

Highest level
of evidence: 4
An antineoplastic agent that inhibits the Bcr-Abl fusion protein tyrosine kinase, an abnormal enzyme produced by Chronic Myeloid Leukemia cells that contain the Philadelphia chromosome. Imatinib also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF)/c-kit, the SCF/c-kit receptor tyrosine kinase is activated in Gastrointestinal Stromal Tumor (GIST). This agent inhibits proliferation and induces apoptosis in cells that overexpress these oncoproteins.

MERESTINIB

Highest level of evidence: 4
Inhibition of DDR2 by
Merestinib has been demonstrated in biochemical assays resulting in inhibition of kinase activity (PMID: 23275061).

DASATINIB

Highest level of evidence:

PATIENT INFORMATION
KAYEMBE,KABEDI

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

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Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 2 (Continued)
Clinical Trials #2 (Continued)
4
Preclinical studies in vitro have shown that Dasatinib binds to DDR2 blocks its activity and inhibits cell proliferation and tumor growth in cell and animal models of DDR2-driven cancer (PMID: 27434411, 26206333, 18938156). In addition, a patient with Lung Squamous Cell Carcinoma harboring a DDR2 had a positive response to the treatment with Dasatinib (PMID: 23932362).

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 #2 SEE BELOW

None

PATIENT INFORMATION
KAYEMBE,KABEDI

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

BACKGROUND
NTRK1 is a neurotrophic transmembrane receptor that is present on neural cells. It is the high affinity receptor for nerve growth factor (NGF) and ligand binding results in autophosphorylation and activation of the MAPK pathway. NTRK1 is involved in differentiation and survival of neurons as well as the control of gene expression of enzymes that play a role in neurotransmitter synthesis. MPRIP-NTRK1 and CD74-NTRK1 fusions have been identified in NSCLC (PMID: 24162815). Somatic rearrangements of the gene are also observed in a fraction of papillary thyroid cancer cases (PMID: 19883730, 26784937) and colorectal cancer (PMID: 24962792).

Mutation Effect on Gene #3	SEE BELOW			

MUTATION EFFECT
copy number alteration (amplification).

The NTRK1
amplification is known to be oncogenic (PMID: 26496938). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the NTRK1 amplification. Pre-clinical and clinical evidence are not available for this indication.

NCCN
GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

FDA Tumor Drugs #3	SEE BELOW			
	None			
FDA Non-Tumor Drugs #3	SEE BELOW			
	None			
Clinical Trials #3	SEE BELOW			
	None			
Companion Diagnostics #3	SEE BELOW			
	None			

PATIENT INFORMATION
KAYEMBE,KABEDI

REPORT STATUS **Final**

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Test Name	In Range	Out of Range	Reference Range	Lab
Gene Regions Passing QC				EZ
Gene Regions Passing QC	SEE BELOW			

In this specimen, 894 of 900 regions (>99%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 6 of 900 regions (<1%) 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% 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

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Test Name	In Range	Out of Range	Reference Range	Lab

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

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

Quest Diagnostics | With Watson

Report Status: Final

KAYEMBE, KABEDI

Patient Information	Specimen Information	Client Information
KAYEMBE, KABEDI **DOB: 05/15/1981 AGE: 37** Gender: F Phone: NG Patient ID: 83173411	Specimen: 83173411 Requisition: Lab Ref #: 2270146 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 19:27 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: Breast Invasive Ductal Carcinoma

The following clinically significant alterations were found in this specimen:

1- TP53 I195fs 2- DDR2 amplification 3- NTRK1 amplification

** no other significant alteration was found in the genes tested

TP53 SUMMARY

The TP53 I195fs mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring TP53 pathogenic mutation. There is clinical evidence that such mutations confer sensitivity to AZD1775.

DDR2 SUMMARY

The DDR2 Amplification is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the DDR2 amplification. There is clinical evidence that the DDR2 amplification confers sensitivity to Nilotinib.

NTRK1 SUMMARY

The NTRK1 Amplification is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the NTRK1 amplification. Pre-clinical and clinical evidence are not available for this indication.

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 Ductal Breast 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:	INVASIVE DUCTAL CARCINOMA				
Tumor-Tissue Type:	DUCTAL CARCINOMA	**Specimen Source**	BREAST		
Block/Specimen ID	S/2971/17	**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
TP53	I195fs	FRAMESHIFT	52 % Frequency	NO	NO	YES

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Report Status: Final

KAYEMBE, KABEDI

Patient Information	Specimen Information	Client Information
KAYEMBE, KABEDI **DOB: 05/15/1981 AGE: 37** Gender: F Patient ID: 83173411	Specimen: 83173411 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 19:27 PDT	Client #: 55001 A VORA/A VERMA

RESULT SUMMARY **Lab: EZ**

Gene Name	Mutation	Alteration Type	Mutation Frequency	Tumor Type Drugs	Non-Tumor Type Drugs	Clinical Trials
DDR2	Amplification	CNV	Ratio 2.5X % Frequency	NO	YES	YES
NTRK1	Amplification	CNV	Ratio 2X % Frequency	NO	NO	NO

ADDITIONAL MUTATIONS **Lab: EZ**

None

INTERACTING MUTATIONS **Lab: EZ**

None

TP53 I195fs 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 I195fs mutation is known to be oncogenic. Truncating mutations, which disrupt the DNA-binding domain or oligodimerization domain of the protein are predicted to be inactivating (PMID: 11900253, 11753428, 16007150). Inactivation of TP53 can confer cells additive growth and survival advantages, such as increased proliferation, evasion of apoptosis, and chemoresistance (PMID: 11156366, 19691397). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring TP53 pathogenic mutation. There is clinical evidence that such mutations confer sensitivity to AZD1775. **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

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TP53 I195fs CLINICAL IMPLICATIONS **Lab: EZ**

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

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 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).

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

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TP53 I195fs CLINICAL IMPLICATIONS **Lab: EZ**

	predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN
Companion Diagnostics	None

DDR2 Amplification CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** DDR2 is a widely expressed tyrosine kinase and the cell surface receptor for fibrillar collagen that regulates cell differentiation, remodeling of the extracellular matrix, cell migration and cell proliferation. It is required for normal bone development and regulates osteoblast differentiation and chondrocyte maturation via a signaling pathway that involves MAP kinases and leads to the activation of the transcription factor RUNX2. In addition, DDR2 is also involved in cutaneous wound healing promoting fibroblast migration and proliferation. DDR2 plays a key role in cancer progression by regulating the interactions of tumor cells with their surrounding collagen matrix (PMID: 22366781). DDR2 is amplified in a wide variety of cancer types and activating mutations have been reported in NSCLC cancer that are associated with sensitivity to dasatinib (PMID: 22328973, 23932362, 26206333).
Mutation Effect on Gene	**MUTATION EFFECT** copy number alteration (amplification) The DDR2 amplification is known to be oncogenic. DDR2 amplification is observed at low frequency in multiple tumor types, including bladder cancer, nerve sheath tumors, adrenocortical and ampullary carcinomas and uterine sarcomas (cBioPortal, Zehir, A et al. Nature Medicine, 2017). The amplification of DDR2 has also been detected in liposarcomas (PMID: 24505276, 28099935). Elevated expression levels of DDR2 have been detected in hepatocellular carcinoma cell lines and clinical specimens. In vitro studies have shown that DDR2 regulates the epithelial-to-mesenchymal process (PMID: 26362312) indicating a possible oncogenic role for DDR2 amplification. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the DDR2 amplification. There is clinical evidence that the DDR2 amplification confers sensitivity to Nilotinib. NCCN GUIDELINES none **STANDARD THERAPEUTIC IMPLICATIONS** none
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	DASATINIB Acute Lymphoblastic Leukemia, Chronic Myeloid Leukemia IMATINIB Acute Lymphoblastic Leukemia, Chronic Eosinophilic Leukemia, Not Otherwise Specified, Chronic Myeloid Leukemia, Dermatofibrosarcoma Protuberans, Gastrointestinal Stromal

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DDR2 Amplification CLINICAL IMPLICATIONS **Lab: EZ**

	Tumor, Mastocytosis/Hypereosinophilic Syndrome, Myelodysplastic Syndromes, Myeloproliferative Neoplasm, Systemic Mastocytosis NILOTINIB Chronic Myeloid Leukemia
Clinical Trials	CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE NCT01471106, Phase 2 TITLE: Phase II Short-term Adjuvant Therapy and Biomarker Studies With Targeted Agents in Women With Estrogen Receptor Negative Breast Cancer NCT01738139, Phase 1 TITLE: A Phase I Trial of Ipilimumab (Immunotherapy) and Imatinib Mesylate (c-Kit Inhibitor) in Patients With Advanced Malignancies NCT02379416, Phase 1 TITLE: Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults With Refractory Solid Tumors NCT02791334, Phase 1 TITLE: A Phase 1a/1b Study of a Novel Anti-PD-L1 Checkpoint Antibody (LY3300054) Administered Alone or in Combination With Other Agents in Advanced Refractory Solid Tumors (Phase 1a/1b Anti-PD-L1 Combinations in Tumors-PACT) NCT03292536, Phase 1 TITLE: An Exploratory Phase 1B Study to Assess the Effects of Merestinib on Bone Metastases in Subjects With Breast Cancer **INVESTIGATIONAL THERAPEUTIC IMPLICATIONS** NILOTINIB Highest level of evidence: 3B An orally bioavailable aminopyrimidine-derivative Bcr-Abl tyrosine kinase inhibitor with antineoplastic activity. Designed to overcome Imatinib resistance, Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of the Abl protein of the Bcr-Abl fusion protein, resulting in the inhibition of the Bcr-Abl-mediated proliferation of Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukemia (CML) cells. This agent also inhibits the receptor tyrosine kinases platelet-derived growth factor receptor (PDGF-R) and c-kit, a receptor tyrosine kinase mutated and constitutively activated in most Gastrointestinal Stromal Tumors (GISTs). With a binding mode that is energetically more favorable than that of Imatinib, Nilotinib has been shown to have an approximately 20-fold increased potency in kinase and proliferation assays compared to Imatinib. IMATINIB Highest level of evidence: 4 An antineoplastic agent that inhibits the Bcr-Abl fusion protein tyrosine kinase, an abnormal enzyme produced by Chronic Myeloid Leukemia cells that contain the Philadelphia chromosome. Imatinib also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF)/c-kit, the SCF/c-kit receptor tyrosine kinase is activated in Gastrointestinal Stromal Tumor (GIST). This agent inhibits proliferation and induces apoptosis in cells that overexpress these oncoproteins. MERESTINIB Highest level of evidence: 4 Inhibition of DDR2 by Merestinib has been demonstrated in biochemical assays resulting in inhibition of kinase activity (PMID: 23275061). DASATINIB

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DDR2 Amplification CLINICAL IMPLICATIONS **Lab: EZ**

	Highest level of evidence: 4 Preclinical studies in vitro have shown that Dasatinib binds to DDR2 blocks its activity and inhibits cell proliferation and tumor growth in cell and animal models of DDR2-driven cancer (PMID: 27434411, 26206333, 18938156). In addition, a patient with Lung Squamous Cell Carcinoma harboring a DDR2 had a positive response to the treatment with Dasatinib (PMID: 23932362). 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

NTRK1 Amplification CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** NTRK1 is a neurotrophic transmembrane receptor that is present on neural cells. It is the high affinity receptor for nerve growth factor (NGF) and ligand binding results in autophosphorylation and activation of the MAPK pathway. NTRK1 is involved in differentiation and survival of neurons as well as the control of gene expression of enzymes that play a role in neurotransmitter synthesis. MPRIP-NTRK1 and CD74-NTRK1 fusions have been identified in NSCLC (PMID: 24162815). Somatic rearrangements of the gene are also observed in a fraction of papillary thyroid cancer cases (PMID: 19883730, 26784937) and colorectal cancer (PMID: 24962792).
Mutation Effect on Gene	**MUTATION EFFECT** copy number alteration (amplification). The NTRK1 amplification is known to be oncogenic (PMID: 26496938). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Ductal Breast Carcinoma harboring the NTRK1 amplification. Pre-clinical and clinical evidence are not available for this indication. NCCN GUIDELINES none **STANDARD THERAPEUTIC IMPLICATIONS**

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NTRK1 Amplification CLINICAL IMPLICATIONS **Lab: EZ**

	none
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	None
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

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, 894 of 900 regions (>99%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 6 of 900 regions (<1%) 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:

EZ QUEST DIAGNOSTICS/NICHOLS SJC, 33608 ORTEGA HWY, SAN JUAN CAPISTRANO, CA 92675-2042 Laboratory Director: IRINA MARAMICA, MD PHD, CLIA: 05D063352

This is supplemental to your standard report.