Personalized Therapeutic Report

Test Description

It is an integrated report of multiplatform testing including comprehensive genomic profiling (170 gene panel) and tumor mutation burden (TMB) using next generation sequencing (NGS), microsatellite instability (MSI) using molecular beacon probe-based multiplex polymerase chain reaction (7 biomarkers) and PD-L1 expression using immunohistochemistry.

Patient Demographic

Name: Firas Tauma Abbas
Sex: Male
Date of Birth/Age: 34 years
Disease: Adenocarcinoma Stomach

Clinician

Clinician Name: Dr Vinay Samuel Gaikwad
Medical Facility: Onco Care Clinic
Pathologist: Not Provided

Specimen

Booking ID: 011911280275
Site: Peritoneal Nodule
Sample Type: FFPE block (1), S6069/19F
Date of Collection: 29-11-2019
Date of Booking: 28-11-2019

CLINICAL SYNOPSIS

Stomach adenocarcinoma: diffuse type, poorly cohesive carcinoma (including signet-ring cell carcinoma) [as per the histopathology report dated 21-11-2019]. The tumor was identifiable in the block [S6069/19F] and it was adequate for further analysis.

RECOMMENDATION & REPORT INTERPRETATION

Clinically relevant alterations were identified in *ARID1A* and *EP300* genes. *S*ensitivity to HDAC and PARP inhibitors may be predicted.

Disclaimer: *Report interpretation & recommendation(s) should not be considered as final; and should be used at the discretion of the treating Physician or the molecular tumor board. The report interpretation & recommendation(s) does not bear any medical, legal, ethical & moral responsibilities, and liabilities.*

BIOMARKERS

Targeted Therapy

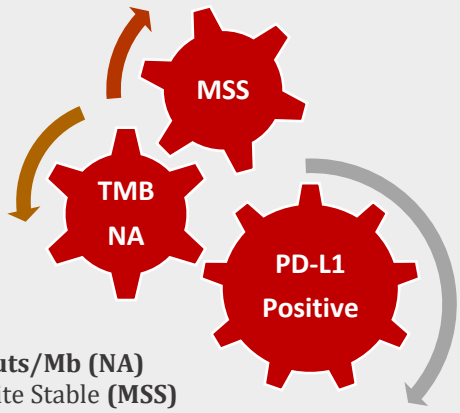
Genomic Findings

Clinically Significant

ARID1A ***p.Glu1444Ter,*** Exon 18
EP300 ***p.Ser941Ter,*** Intron 14

Variant of Unknown Significance
CDK12 ***p.Ser569del,*** Exon 2
KMT2A ***p.Ser2305_Ser2319del,*** Exon 27
NOTCH2 ***p.Asn1904_Ala1905del,*** Exon 31
CDK4 ***p.Gly247_Arg255del,*** Exon 7
MET ***p.Pro1323His,*** Exon 20
CSF1R ***p.Thr393Met,*** Exon 8

Immunotherapy



TMB NA **muts/Mb (NA)**
Microsatellite Stable **(MSS)**
PD-L1 **Positive**

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TABLE 1: GENOMIC ALTERATIONS THAT CAN BE TARGETED WITH APPROVED DRUGS IN THE SUBJECT'S TUMOR TYPE

Gene (Transcript) #	Location	Variant	Overall Depth	Mutant Allele Percentage	Function of the Gene in Cancer
		None			

TABLE 2: NON-DRUGGABLE/DRUGGABLE CLINICALLY SIGNIFICANT GENOMIC ALTERATIONS INDICATED IN OTHER TUMORS

Gene (Transcript) #	Location	Variant	Overall Depth	Mutant Allele Percentage	Function of the Gene in Cancer
ARID1A (ENST00000324856.7)	Exon 18	c.4330G>T (p.Glu1444Ter)	3601X	18.8%	Tumor Suppressor
EP300 (ENST00000263253.7)	Intron 14	c.2820_2832del (p.Ser941Ter)	366X	7.1%	Tumor Suppressor

TABLE 3: VARIANTS OF UNKNOWN SIGNIFICANCE

Gene (Transcript) #	Location	Variant	Overall Depth	Mutant Allele Percentage	Function of the Gene in Cancer
CDK12 (ENST00000447079.4)	Exon 2	c.1705_1707del (p.Ser569del)	5859X	35%	Tumor Suppressor
KMT2A (ENST00000534358.1)	Exon 27	c.6912_6956del (p.Ser2305_Ser2319del)	809X	5.4%	Oncogene
NOTCH2 (ENST00000256646.2)	Exon 31	c.5710_5715del (p.Asn1904_Ala1905del)	1425X	5.5%	Oncogene
CDK4 (ENST00000257904.6)	Exon 7	c.738_764del (p.Gly247_Arg255del)	2185X	6.4%	Oncogene
MET (ENST00000318493.6)	Exon 20	c.3968C>A (p.Pro1323His)	857X	8.9%	Oncogene
CSF1R (ENST00000286301.3)	Exon 8	c.1178C>T (p.Thr393Met)	2404X	43.4%	Oncogene

CLINICAL CORRELATION AND VARIANT INTERPRETATION

ARID1A **p.Glu1444Ter** **c.4330G>T** **Tumor Suppressor**
Overall depth: 3601X **Mutant Allele Percentage: 18.8%**

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AT rich interactive domain 1A (SWI-like) (*ARID1A*) is a gene that encodes a protein that is included in the SWI/SNF family and functions in the transcriptional activation of genes. It possesses at least two conserved domains that could be important for its function. First, it has a DNA-binding domain that can specifically bind an AT-rich DNA sequence known to be recognized by a SNF/SWI complex at the beta-globin locus. Second, the C-terminus of the protein can stimulate glucocorticoid receptor-dependent transcriptional activation. A nonsense variation (**chr1:g.27101048G>T: c.4330G>T**) that resulted in premature termination of the protein, at codon 1444 (**p.Glu1444Ter**) was detected in the *ARID1A* gene of this subject. This is a loss of function mutation in *ARID1A* gene. This variant has not been reported in the ExAC and 1000 genomes databases.

In a study on 55 gastrointestinal (GI) cancer samples with 28 metastatic and 27 primary samples, *ARID1A* alterations were noted in 20% (11/55) of GI cancers[1]. Tumor tissues harbouring *ARID1A* alterations included 2/8 gastro-esophageal cancers, 2/2 duodenal cancers, 3/29 colorectal (CRC) cancers, 2/2 small bowel cancers, and 2/7 bile duct cancers[1]. A study on cohort of 149 primary EACs, reported *ARID1A* gene mutations in 9% of cases, however, no prognostic relevance was reported[2].

Loss of ARID1A expression have shown prognostic relevance in other cancer types. From a recent meta-analysis investigation (six clinical studies on total 3019 CRC patients) on relationship between *ARID1A* mutation or loss of ARID1A protein expression and clinicopathological parameters of GC (gastric cancer) and CRC (colorectal cancer) patients, loss of ARID1A protein expression was significantly associated with poorly differentiated histologic grade CRC and advanced tumor infiltration depth[3]. The loss of ARID1A protein expression may be a marker of poor prognosis in individual GC and CRC patients[3]. In another study on 489 primary gastric adenocarcinomas, abnormal ARID1A expression (including loss of expression) was observed in 109 cases (22.3%) and was significantly correlated with lymphatic invasion (P = 0.022) and lymph node metastasis (P = 0.042)[4]. The tumors with abnormal ARID1A expression more frequently indicated mismatch repair deficiency (P < 0.001). The multivariate analysis identified abnormal ARID1A expression as an independent poor prognostic factor (HR = 1.36, 95%CI: 1.01-1.84; P = 0.040)[4].

Inactivating mutations in *ARID1A* sensitized ovarian tumors to PD-L1 blockade in preclinical mouse models. A proteomic screen revealed that ARID1A interacts with the MMR gene MSH2, and loss of ARID1A resulted in microsatellite instability. Loss of ARID1A was also associated with increased levels of PD-L1 expression[5]. Please correlate clinically.

EP300 **p.Ser941Ter**	**c.2820_2832del**	**Tumor Suppressor**
Overall depth: 366X	**Mutant Allele Percentage: 7.1%**	

EP300 gene encodes the adenovirus E1A-associated cellular p300 transcriptional co-activator protein, which functions as histone acetyltransferase that regulates transcription via chromatin remodeling and is important in the processes of cell proliferation and differentiation. EP300 mediates cAMP-gene regulation by binding specifically to phosphorylated CREB protein. Mutations in *EP300* gene leads to Rubinstein-Taybi syndrome and may also play a role in epithelial cancer. A frameshift deletion (**chr22:g.41547839_41547851del: c.2820_2832del**) that resulted in a stop codon and premature truncation of the protein, at codon 941 (**p.Ser941Ter**) was detected in the *EP300* gene of this subject and this is a loss of function mutation. This variant has not been reported in ExAC and 1000 genomes databases.

Somatic mutations in the *p300* gene are found in gastric cancer, colon cancer, glioblastoma, acute myeloid leukemia and small cell lung cancer. Dysfunction of CBP and/or p300 gene contributes to tumorigenesis in several human malignancies[6]. A clinical study on 101 CRCs and 91 gastric cancer patients with high microsatellite instability, the frequency of EP300 frameshift mutations was 4% and 3.3% in colorectal and gastric cancers respectively. From the same study, frameshift mutations of E1A-binding protein p300 and its expressional loss have been shown to be a feature of gastric and colorectal cancers with high microsatellite instability[7]. Clinical significance of this particular variant has not been very well documented in the medical literature for the tumor type of the subject under investigation. Please correlate clinically.

ADDITIONAL FINDINGS

Variants of unknown significance (VUS) in genes relevant in cancer

Table 3 provides a list of VUS in genes known to function as oncogene or tumor suppressor or relevant in epigenetic regulation in human cancers. These variants specifically detected in this tumor have not been characterized sufficiently in biochemical assays and therefore their impact in this cancer remains speculative.

Note:

- The *CDK12* gene variant p.Ser569del is reported in ExAC with MAF of 0.003% and it is not reported in 1000 genomes database. It is present in proline-rich domain of CDK12 protein.

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- The *KMT2A* gene variant p.Ser2305_Ser2319del is not reported in ExAC and 1000 genomes databases.
- The *NOTCH2* gene variant p.Asn1904_Ala1905del is not reported in ExAC and 1000 genomes databases.
- The *CDK4* gene variant p.Gly247_Arg255del is not reported in ExAC and 1000 genomes databases. This variant is present in the C-terminal of the CDK4 protein.
- The *MET* gene variant p.Pro1323His is not reported in ExAC and 1000 genomes databases. It is predicted to be damaging by SIFT, LRT and probably damaging by Polyphen2 functional prediction tools.
- The *CSF1R* gene variant p.Thr393Met is not reported in ExAC and 1000 genomes databases. It is predicted to be damaging by SIFT and probably damaging by Polyphen2 functional prediction tools.

RECOMMENDATIONS

Correlation of the genetic findings with the clinical condition of the patient is required to arrive at accurate diagnosis, prognosis or for therapeutic decisions.

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APPENDIX 1: TEST METHODOLOGY

Background

The next-generation sequencing based multi-gene analysis, allows us to sequence and identify variants associated with multiple genes with diagnostic, prognostic and therapeutic implications in different cancer types. This tumor somatic panel in investigation, has been designed to screen for somatic mutations in 170 cancer related genes associated with tumorigenesis, prognostication and predictive value for chemotherapy and targeted therapy drugs in different tumor types. Targeted sequencing represents a cost-effective approach with the ability to detect specific variants causing protein-coding changes in individual human genomes. These multi-gene, affordable tests will enable personalized treatment by matching the patient's tumor with the appropriate drug, based on the mutational findings.

Method

Tumor genomic DNA and RNA isolated from FFPE tissue was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced with a panel mean coverage depth of **4852X and 16229X** in DNA and RNA library respectively, on Illumina sequencing platform. The sequences obtained were aligned to human reference genome (GRCh37/hg19) using BWA program[1,2]. Somatic mutations were identified using LoFreq (version 2) variant caller[3,4]. Only non-synonymous and splice site variants found in the coding regions were used for clinical interpretation. The mutations were annotated using VariMAT annotation pipeline. Gene annotation of the variants was performed using VeP program[5] against the Ensembl release 90 human gene Model[6]. Clinically relevant mutations were annotated using published literature, databases and in-house propriety databases. The common variants were filtered for reporting based on the presence in various population databases (1000G, ExAC, EVS, 1000Japanese, dbSNP, UK10K[7-12]. Gene fusions at the RNA level were assessed using multiple fusion detection programs to arrive at the consensus on predicted fusions. The fusions are confirmed based on the number of spanning reads and/or split reads supporting the finding[13-17]. Reportable mutations are prioritized and prepared based AMP-ASCO-CAP guidelines[18] based on annotation metrics from OncoMD[19], reference lab's curated somatic database which includes somatic mutations from TCGA. Possibility of false negative or false positive below the limit of detection of this assay cannot be ruled out.

The transcript used for clinical reporting generally represents the canonical transcript (according to Ensembl release 90 human gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.

Variants annotated on incomplete and nonsense mediated decay transcripts will not be reported.

"This test was developed, and its performance characteristics determined by Reference lab".

DISCLAIMER

- The classification of variants of unknown significance can change over time. Please contact MolQ laboratory at a later date for any change.
- The scope of this assay limits to SNPs, Short Indels (in DNA) and gene fusions and splice variants (in RNA)
- Intronic variants are not assessed using this method.
- Large deletions of more than 20 bp or copy number variations / rearrangements cannot be assessed using this method.
- This panel is intended to screen for hotspot mutations only.
- The mutations have not been validated by Sanger sequencing.
- This NGS panel is not intended to report germline variants.
- This NGS test used does not allow definitive differentiation between germline and somatic variants
- TREATMENT DECISIONS BASED ON THESE MUTATIONS MAY BE TAKEN IN CORRELATION WITH OTHER CLINICAL AND PATHOLOGICAL INFORMATION.
- As per the reference lab inhouse validation of this assay, the limit of detection of the assay for SNVs and short Indels is 5% and for fusions is ≥10 spanning reads.
- Due to poor quality of FFPE DNA, possibility of assay failure/compromised results that include low gene/variant coverage and low depth, cannot be ruled out.

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APPENDIX 2: GENE LIST OF THE 170 GENES PANEL

SNVs and Short Indels (<25bp) (from DNA)									
AKT1	*BRIP1*	*CREBBP*	*FANCI*	*FGFR2*	*JAK3*	*MSH3*	*PALB2*	*RAD51D*	*TSC1*
AKT2	*BTK*	*CSF1R*	*FANCL*	*FGFR3*	*KDR*	*MSH6*	*PDGFRA*	*RAD54L*	*TSC2*
AKT3	*CARD11*	*CTNNB1*	*FBXW7*	*FGFR4*	*KIT*	*MTOR*	*PDGFRB*	*RB1*	*VHL*
ALK	*CCND1*	*DDR2*	*FGF1*	*FLT1*	*KMT2A(MLL)*	*MUTYH*	*PIK3CA*	*RET*	*XRCC2*
APC	*CCND2*	*DNMT3A*	*FGF2*	*FLT3*	*KRAS*	*MYC*	*PIK3CB*	*RICTOR*	
AR	*CCNE1*	*EGFR*	*FGF3*	*FOXL2*	*MAP2K1*	*MYCL1*	*PIK3CD*	*ROS1*	
ARID1A	*CD79A*	*EP300*	*FGF4*	*GEN1*	*MAP2K2*	*MYCN*	*PIK3CG*	*RPS6KB1*	
ATM	*CD79B*	*ERBB2*	*FGF5*	*GNA11*	*MCL1*	*MYD88*	*PIK3R1*	*SLX4*	
ATR	*CDH1*	*ERBB3*	*FGF6*	*GNAQ*	*MDM2*	*NBN*	*PMS2*	*SMAD4*	
BAP1	*CDK12*	*ERBB4*	*FGF7*	*GNAS*	*MDM4*	*NF1*	*PPP2R2A*	*SMARCB1*	
BARD1	*CDK4*	*ERCC1*	*FGF8*	*HNF1A*	*MET*	*NOTCH1*	*PTCH1*	*SMO*	
BCL2	*CDK6*	*ERCC2*	*FGF9*	*HRAS*	*MLH1*	*NOTCH2*	*PTEN*	*SRC*	
BCL6	*CDKN2A*	*ERG*	*FGF10*	*IDH1*	*MLLT3*	*NOTCH3*	*PTPN11*	*STK11*	
BRAF	*CEBPA*	*ESR1*	*FGF14*	*IDH2*	*MPL*	*NPM1*	*RAD51*	*TERT*	
BRCA1	*CHEK1*	*EZH2*	*FGF23*	*INPP4B*	*MRE11A*	*NRAS*	*RAD51B*	*TET2*	
BRCA2	*CHEK2*	*FAM175A*	*FGFR1*	*JAK2*	*MSH2*	*NRG1*	*RAD51C*	*TP53*	

Fusions and Splice Variants (from RNA)									
ABL1	*BRAF*	*EML4*	*ETV4*	*FGFR4*	*KIF5B*	*MYC*	*NTRK2*	*PIK3CA*	*TMPRSS2*
AKT3	*BRCA1*	*ERBB2*	*ETV5*	*FLI1*	*KIT*	*NOTCH1*	*NTRK3*	*PPARG*	
ALK	*BRCA2*	*ERG*	*EWSR1*	*FLT1*	*KMT2A(MLL)*	*NOTCH2*	*PAX3*	*RAF1*	
AR	*CDK4*	*ESR1*	*FGFR1*	*FLT3*	*MET*	*NOTCH3*	*PAX7*	*RET*	
AXL	*CSF1R*	*ETS1*	*FGFR2*	*JAK2*	*MLLT3*	*NRG1*	*PDGFRA*	*ROS1*	
BCL2	*EGFR*	*ETV1*	*FGFR3*	*KDR*	*MSH2*	*NTRK1*	*PDGFRB*	*RPS6KB1*	

iMSI Rapid™ Assay

MSI testing is used for Hereditary Cancer screening (Hereditary Non-Polyposis Colorectal Cancer -HNPCC or Lynch syndrome);
As a biomarker (Prognostic and predictive biomarker for the response of Immunotherapy)

Result — Microsatellite - Stable (MSS)

BIOMARKER FINDINGS

ACVR2A	No mutation detected
BTBD7	No mutation detected
DIDO1	No mutation detected
MRE11	No mutation detected
RYR3	No mutation detected
SEC13A	No mutation detected
SULF2	No mutation detected

INTERPRETATION

*MSS	<2 of the 7 markers demonstrate instability
#MSI-H	≥2 of the 7 markers demonstrate instability

*Microsatellite stable

Microsatellite Instability-High

For valid batch test results specific controls are being run with every batch.

METHODOLOGY

Multiplex detection of seven mononucleotide repeats using molecular beacon probe-based polymerase chain reaction followed by high resolution melt-curve analysis. The assay uses seven novel biomarkers *ACVR2A*, *BTBD7*, *DIDO1*, *MRE11*, *RYR3*, *SEC31A* and *SULF2* as this set of biomarkers is stable over different cancer types and ethnicities and show high performance than other known assays like *Bethesda Panel.* This test is carried out on Idylla platform using the MSI/1.0 Cartridge based kit which is CE IVD approved.

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APPENDIX 4

Programmed Death Ligand 1 (PD-L1) Immunohistochemistry

Test Description

This test is useful for identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP263). PD-L1 also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic Type equation here.marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Specimen

Sample Type: FFPE block S-6069/19D
Site: Stomach
Pathology ID: MOLQ/IHC-56112019
Disease: Diffused type Stomach Adenocarcinoma

Interpretation

The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, send request for Pathology Consultation.

Methodology

Immunostaining for PD-L1 protein was done using Dako Monoclonal Mouse Anti- PD-L1/22C3.
Positive PD-L1 staining/expression is defined as complete and/or partial, circumferential or linear plasma membrane or cytoplasmic staining at any intensity that can be differentiated from background.

Combined Positive Score $CPS = \left(\frac{No.of\ PDL{-}1\ Stained\ Cells\#}{(No.of\ Viable\ Tumor\ Cells)}\right) \times 100$

#Tumor cells and TILs

Note

Preclinical studies suggest that positive programmed cell death 1-ligand 1 (PD-L1) immunohistochemistry in tumor cells may predict tumor response to therapy with immune checkpoint inhibitors. This result should not be used as the sole factor in determining treatment, as other factors (eg, tumor mutation burden and microsatellite instability) have also been studied as predictive markers.

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Programmed Death Ligand 1 (PD-L1): Positive

Microscopy Evaluation

HE Staining
Tumor cells: 60%
Immune cells: 12%

Combined Positive Score (CPS): 28 %

PD-L1 IHC- Tumor Cells

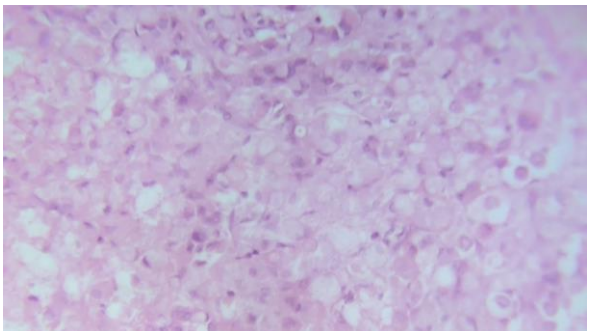

Figure 1

PD-L1 IHC- Tumor Cells

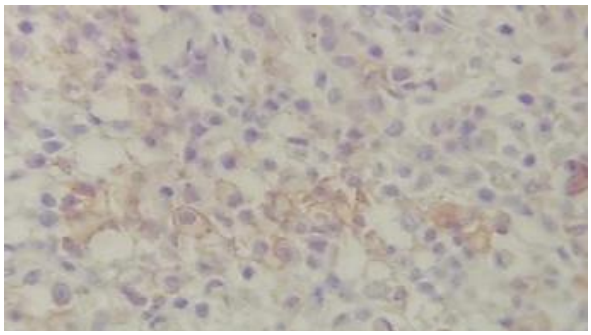

Figure 2

PD-L1 IHC- Immune Cells

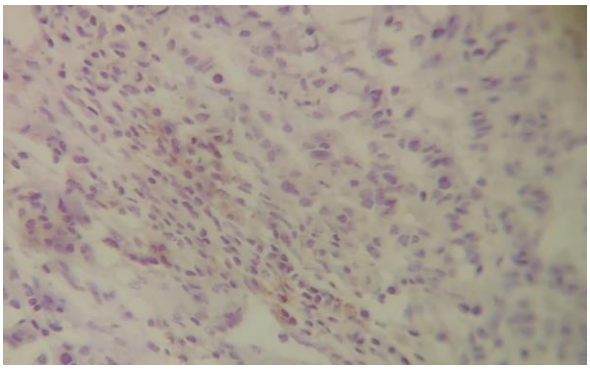

Figure 3