Comprehensive Panel- 590 Genes

Test Description

The MolQ Comprehensive Panel includes 590 key solid tumor genes that are well characterized in the published literature and associated with oncology drugs that are FDA approved, part of NCCN guidelines, or in clinical trials. The assay allows concurrent analysis of DNA and RNA in a single workflow involving detection of multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs and gene fusions.

Patient Demographic

Name: Ms. Sadhvi Bansal
Sex: Female
Date of Birth/Age: 38 years
Disease: Metastatic adenosquamous carcinoma of uterine cervix

Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Dr AV Institute of Personalized Therapy and Cancer Research (IPTCR)
Pathologist: Not Provided

Specimen

Booking ID: 012308250261
Sample Type: FFPE Block ID- 1309/23 9 (1)
Tumor Content Percentage: 90%
Date of Collection: 21-08-2023
Date of Booking: 21-08-2023

CLINICAL SYNOPSIS

Sadhvi Bansal, is a known case of metastatic adenosquamous carcinoma of uterine cervix. She has been evaluated for pathogenic variations in the genes listed in Appendix 2.

RESULTS

Pathogenic variants were detected in *STK11* and *RB1* genes.

Tumor Mutation Burden is 14 Mut/Mb (TMB-Intermediate).

Microsatellite Instability (MSI) is stable.

Gene	Variant Nomenclature	Variant Allele Frequency	Location	Tier
STK11 (NM_000455.5)	c.290+1G>A	87.44%	Intron 1	2D
RB1 (NM_000321.3)	c.610G>T p.Glu204Ter	57.61%	Exon 7	2D

RELEVANT CANCER SPECIFIC FINDINGS

Gene	Findings (At DNA Level)	Gene	Findings (At RNA Level)
PTEN	None detected	*FGFR*	None detected
TP53	None detected	*RET*	None detected
BRAF	None detected	*ALK*	None detected
ADRID1A	None detected	*NTRK*	None detected
CTNNB1	None detected		
KRAS	None detected		

CLINICAL CORRELATION AND VARIANT INTERPRETATION

STK11 **c.290+1G>A**

Variant description: *STK11*, a tumor suppressor and intracellular kinase, is frequently mutated in various solid neoplasms. The *STK11* c.290+1G>A mutation is likely pathogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with *STK11* c.290+1G>A mutant cervical adenosquamous carcinoma. Cervical adenosquamous carcinomas most frequently harbor alterations in *STK11*, *PTEN*, *PIK3CA*, *PIK3R1* and *KRAS*. Mutations in the *STK11* gene have been identified as being responsible for Peutz–Jeghers syndrome (PJS). Large genomic deletion in exon 1 of *STK11* gene has been associated with lobular endocervical gland hyperplasia (LEGH), minimal deviation adenocarcinoma (MDA) and mucinous adenocarcinoma of cervix. Inactivation of *STK11* may occur during progression from MDA to mucinous adenocarcinoma.

RB1 **p.Glu204Ter**

Variant description: *RB1*, a regulator of the cell cycle, is inactivated by mutation, deletion or allelic loss in various cancer types, including retinoblastoma and lung cancer. *RB1* E204* is a truncating mutation in a tumor suppressor gene, and therefore is likely oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with *RB1* E204* mutant cervical adenosquamous carcinoma.

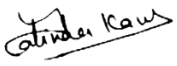
RB1 mutation was an independent survival predictor in stage IIB-IV Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC), and CESC patients with *RB1* mutation may be more sensitive to cisplatin.

RECOMMENDATIONS

- In view of the above observation and the high VAF of 87% in this case, the patient may be evaluated for germline *STK11* testing.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).

REFERENCES

1. P Luo et al. Journal of Clinical Oncology 2019
2. The AACR Project GENIE Consortium. Cancer Discovery, 2017.



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APPENDIX 1: TEST METHODOLOGY

Method

Massively Parallel Sequencing (Next Generation Sequencing): Tumor Nucleic acid from the submitted specimen was enriched for the coding regions of genes in the panel and splice site junctions of genes. DNA and RNA were extracted from samples using the Qiagen FFPE DNA and RNAeasy FFPE kit. Paired end sequencing was performed on Illumina platform (NovaSeq 6000/NextSeq2000) with a minimum depth of 500X. The assay allows concurrent analysis of DNA and RNA. Assay detect multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs, and gene fusions, in a single workflow**.** All positive variants are visualized on Integrative Genomics Viewer (IGV) and reported. MSI analysis was performed by Next Generation Sequencing.

AMP/ASCO/CAP Classification

Tier I: Variants of Strong Clinical Significance	1A	Biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in **professional guidelines** as **therapeutic, diagnostic, and/or prognostic biomarkers** for specific types of tumors.
	1B	Biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on **well- powered studies with expert consensus**.
Tier II: Variants of Potential Clinical Significance	2C	Biomarkers that predict response or resistance to therapies approved by FDA or professional **societies for a different tumor type (ie, off-label use of a drug)**, serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies.
	2D	Biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on **small studies or multiple case reports** with no consensus.
Tier III: Variants of Unknown Clinical Significance		Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases No convincing published evidence of cancer association.
Tier IV: Benign or Likely Benign Variants		Observed at significant allele frequency in the general or specific subpopulation databases.

Tumor Mutational Burden (TMB) analysis was performed based on Next Generation Sequencing analysis from genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina platform. TMB is calculated using nonsynonymous, in-frame indel, and frameshift indel mutations. The assay detects and annotates low frequency somatic variants (SNPs) from 590 genes related to cancer biology with a size of 1.8Mb.

TMB Interpretation: The TMB status is considered low if the TMB score is lower than 10; intermediate if the TMB score is between 10 and 15; and high if the TMB score is larger than 15.

TMB Clinical interpretation: Association of high TMB with improved response to immune checkpoint inhibitors such as nivolumab, ipilimumab, pembrolizumab, and atezolizumab in cancer types including non-small cell lung cancer, melanoma, and urothelial carcinoma are noted.
TMB could be a useful predictive biomarker for response to pembrolizumab therapy in patients with previously treated recurrent or metastatic advanced solid tumors[1-3].
The FDA has approved pembrolizumab in all cancers with TMB > 10Mut/Mb based on the findings from the phase 2 KEYNOTE-158 study.

References

1. Chan TA et al. Ann Oncol. 2019
2. Goodman AM et al. Mol Cancer Ther. 2017
3. Van Allen EM et al. Science.2016
4. Denis LJ et al. Cancer Cell 2021

DISCLAIMER

- Interpretation of variants in this report is performed to the best knowledge of the laboratory based on the information available at the time of reporting. The classification of variants can change over time and MolQ cannot be held responsible for this. Please feel free to contact MolQ Laboratory (contact@molq.in) in the future to determine if there have been any changes in the classification of any variations. Re-analysis of variants in previously issued reports in light of new evidence is not routinely performed, but may be considered upon request, provided the variant is covered in the current panel.
- Due to inherent technology limitations of the assay, not all bases of the exome can be covered by this test. Accordingly, variants in regions of insufficient coverage may not be identified and/or interpreted. Therefore, it is possible that certain variants are present in one or more of the genes analyzed, but have not been detected. The variants not detected by the assay that was performed may/ may not impact the phenotype.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- Genes with pseudogenes, paralog genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions.
- The mutations have not been validated/confirmed by Sanger sequencing.
- Incidental or secondary findings (if any) that meet the ACMG guidelines can be given upon request.
- The report shall be generated within turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MolQ Laboratory under no circumstances will be liable for any delay beyond afore mentioned TAT.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MolQ Laboratory hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MolQ Laboratory hereby disclaims all liability arising in connection with the report(s).
- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MolQ Laboratory. In case where any test provided by MolQ Laboratory fails for unforeseeable or unknown reasons that cannot be influenced by MolQ Laboratory in advance, MolQ Laboratory shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognized by MolQ Laboratory in advance.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory.

LIMITATIONS

- Testing has been performed assuming that the sample received belongs to the above-named individual(s) and any stated relationships between individuals are accepted as true.
- Negative (wild type) result does not rule out the presence of a mutation that may be present but below the limits of detection of this assay. The analytical sensitivity of this assay is 5%. Sequencing is performed at a depth of 500x
- This test does not differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.
- Due to inherent technology limitations, coverage is not uniform across all regions. Hence pathogenic variants present in areas of insufficient coverage may not be analyzed/ reported.
- The classification and interpretation of all the variants in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information comes to light.
- Test results should be interpreted in context of clinical findings, tumor sampling, histopathology, and other laboratory data.
- If results obtained do not match other clinical laboratory findings, please contact the laboratory for possible. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.
- Genetic testing is highly accurate. Rarely, inaccurate results may occur for various reasons. These reasons include, but are not limited to mislabelled samples, inaccurate reporting of clinical/medical information, rare technical errors or unusual circumstances such as bone marrow transplantation, blood transfusion; or the presence of change(s) in such a small percentage of cells that may not be detectable by the test (mosaicism).
- The TMB cutoff of 10 mutations/megabase was established in NSCLC and its applicability towards other tumor types has not been established at this time.
- Optimal thresholds for classification of TMB values into high, intermediate, and low categories are not yet standardized across different methods and panels.

- A TMB cutoff is a function of the gene panel (genomic footprint and bioinformatics platform) that is used in a given study. Since data obtained from a given gene panel cannot be directly applied to another panel without a conversion algorithm, direct comparisons of results between panels can be very problematic. Certain cancer types, such as uterine, bladder and colon cancers exhibited greater variability in panel TMB values, compared with lung and head and neck cancers.
- The Cancer Genome Atlas compares TMB values derived using WES, which is currently considered as the gold standard for calculating TMB.

APPENDIX 2: GENE LIST

Gene	Gene	Gene	Gene	Gene	Gene	Gene
ASPSCR1	*CD99*	*ERCC3*	*IGF1*	*MYBL1*	*PPM1D*	*SPEN*
ABCB1	*CDC42*	*ERCC4*	*IGF1R*	*MYC*	*PPP2R1A*	*SPINK1*
ABCC2	*CDC73*	*ERCC5*	*IGF2*	*MYCL*	*PPP2R2A*	*SPOP*
ABL1	*CDH1*	*ERF*	*IKBKE*	*MYCN*	*PPP6C*	*SPRED1*
ACVR1	*CDK1*	*ERG*	*IKZF1*	*MYD88*	*PRDM1*	*SQSTM1*
ACVRL1	*CDK12*	*ERRFI1*	*IL10*	*MYOD1*	*PREX2*	*SRC*
ADCY9	*CDK4*	*ESR1*	*IL7R*	*NAB2*	*PRKACA*	*SRP19*
AFAP1	*CDK6*	*ETV1*	*INHA*	*NACC2*	*PRKAR1A*	*SRSF2*
AGBL4	*CDK8*	*ETV4*	*INPP4A*	*NBN*	*PRKCI*	*SS18*
AGO2	*CDKN1A*	*ETV6*	*INPP4B*	*NCOA1*	*PRKD1*	*SSX1*
AHCYL1	*CDKN1B*	*EWSR1*	*INPPL1*	*NCOA2*	*PRSS1*	*SSX2*
AIP	*CDKN2A*	*EZH1*	*INSR*	*NCOA3*	*PTCH1*	*SSX4*
AKAP9	*CDKN2B*	*EZH2*	*IRF4*	*NCOA4*	*PTEN*	*STAG2*
AKT1	*CDKN2C*	*FAM175A*	*IRS1*	*NCOR1*	*PTPN11*	*STAT3*
AKT2	*CEBPA*	*FAM46C*	*IRS2*	*NDUFA13*	*PTPRD*	*STAT5A*
AKT3	*CFTR*	*FANCA*	*JAK1*	*NF1*	*PTPRS*	*STAT5B*
ALK	*CHD4*	*FANCC*	*JAK2*	*NF2*	*PTPRT*	*STAT6*
ALOX12B	*CHEK1*	*FANCD2*	*JAK3*	*NFASC*	*QKI*	*STK11*
AMELY	*CHEK2*	*FANCE*	*JAZF1*	*NFE2L2*	*RAC1*	*STK19*
AMER1	*CHN1*	*FANCF*	*JUN*	*NFKBIA*	*RAC2*	*SUFU*
ANKRD11	*CHTOP*	*FANCG*	*KDM5A*	*NKX2-1*	*RAD21*	*SUZ12*
ANO1	*CIC*	*FANCI*	*KDM5C*	*NOTCH1*	*RAD50*	*SYK*
ANTXR1	*CLTC*	*FANCL*	*KDM5C*	*NOTCH2*	*RAD51*	*TACC1*
APC	*COL1A1*	*FANCM*	*KDM6A*	*NOTCH3*	*RAD51B*	*TACC3*
AR	*COL2A1*	*FAT1*	*KDR*	*NOTCH4*	*RAD51C*	*TAF15*
ARAF	*CREB1*	*FBXW7*	*KEAP1*	*NPM1*	*RAD51D*	*TAP1*
ARHGEF2	*CREB3L1*	*FEV*	*KIF1B*	*NR4A3*	*RAD52*	*TAP2*
ARID1A	*CREB3L2*	*FGF19*	*KIF5B*	*NRAS*	*RAD54L*	*TBX3*
ARID1B	*CREBBP*	*FGF23*	*KIT*	*NRG1*	*RAF1*	*TCF12*
ARID2	*CRKL*	*FGF3*	*KLF5*	*NSD1*	*RANBP2*	*TCF3*
ARID5B	*CRLF2*	*FGF4*	*KMT2A*	*NSD2*	*RARA*	*TEK*
ASCC1	*CSDE1*	*FGFR1*	*KMT2B*	*NTHL1*	*RASA1*	*TERT*
ASXL1	*CSF1R*	*FGFR2*	*KMT2C*	*NTM*	*RASAL2*	*TET2*
ASXL2	*CSF3R*	*FGFR3*	*KMT2D*	*NTRK1*	*RB1*	*TFE3*
ATF1	*CTCF*	*FGFR4*	*KMT5A*	*NTRK2*	*RBM10*	*TFG*
ATIC	*CTLA4*	*FH*	*KNSTRN*	*NTRK3*	*RECQL*	*TGFBR1*
ATM	*CTNNA1*	*FLCN*	*KRAS*	*NUF2*	*RECQL4*	*TGFBR2*
ATR	*CTNNB1*	*FLI1*	*LATS1*	*NUP93*	*REL*	*TMC6*
ATRX	*CUL3*	*FLT1*	*LATS2*	*NUTM2A*	*RET*	*TMC8*
AURKA	*CXCR4*	*FLT3*	*LMO1*	*NUTM2B*	*RHBDF2*	*TMEM127*
AURKB	*CXORF67*	*FLT4*	*LYN*	*PAK1*	*RHEB*	*TMPRSS2*
AXIN1	*CYLD*	*FOXA1*	*MALT1*	*PALB2*	*RHOA*	*TNFAIP3*
AXIN2	*CYP19A1*	*FOXL2*	*MAP2K1*	*PALLD*	*RICTOR*	*TNFRSF14*
AXL	*CYP1B1*	*FOXO1*	*MAP2K2*	*PARK2*	*RIT1*	*TOE1*

Comprehensive Panel- 590 Genes

B2M	*CYP21A2*	*FOXO4*	*MAP2K4*	*PARP1*	*RNASEL*	*TOP1*
BAG4	*CYP2B6*	*FOXP1*	*MAP3K1*	*PATZ1*	*RNF43*	*TP53*
BAIAP2L1	*CYP2D6*	*FUBP1*	*MAP3K13*	*PAX2*	*ROS1*	*TP53BP1*
BAP1	*CYP3A4*	*FUS*	*MAP3K14*	*PAX3*	*RPA1*	*TP63*
BARD1	*CYP3A5*	*FYN*	*MAPK1*	*PAX5*	*RPS20*	*TPM3*
BCAN	*CYSLTR2*	*GALNT12*	*MAX*	*PAX7*	*RPTOR*	*TPM4*
BCL10	*DAXX*	*GATA1*	*MBTD1*	*PAX8*	*RRAS*	*TPMT*
BCL2	*DDIT3*	*GATA2*	*MC1R*	*PBRM1*	*RRAS2*	*TPR*
BCL2L1	*DDR2*	*GATA3*	*MCL1*	*PDCD1*	*RTEL1*	*TRAF7*
BCL6	*DDX3X*	*GEN1*	*MDH2*	*PDCD1LG2*	*RUNX1*	*TRIM24*
BCR	*DICER1*	*GLI1*	*MDM2*	*PDE11A*	*RXRA*	*TSC1*
BICC1	*DIS3*	*GLIS3*	*MDM4*	*PDGFB*	*SCRIB*	*TSC2*
BLM	*DNAJB1*	*GNA11*	*MEAF6*	*PDGFRA*	*SDHA*	*TSHR*
BMPR1A	*DNMT1*	*GNAQ*	*MECOM*	*PDGFRB*	*SDHAF2*	*TSPAN31*
BRAF	*DNMT3A*	*GNAS*	*MED12*	*PGR*	*SDHB*	*TYMS*
BRCA1	*DNMT3B*	*GOPC*	*MEF2B*	*PHF1*	*SDHC*	*U2AF1*
BRCA2	*DOT1L*	*GREM1*	*MEN1*	*PHF6*	*SDHD*	*UGT1A1*
BRD4	*DPYD*	*GRIN2A*	*MET*	*PHOX2B*	*SESN3*	*UGT1A8*
BRD8	*DROSHA*	*GSK3B*	*MGA*	*PIK3C2B*	*SETD2*	*UPF1*
BRIP1	*DUX4*	*GSTP1*	*MGMT*	*PIK3C2G*	*SF3B1*	*VCL*
BTK	*EED*	*H3-3B*	*MIR143*	*PIK3CA*	*SH2B3*	*VEGFA*
CALR	*EGFR*	*H3C1*	*MITF*	*PIK3CB*	*SH2D1A*	*VHL*
CAMTA1	*EHBP1*	*H3C11*	*MLH1*	*PIK3CD*	*SHOC2*	*WRN*
CARD11	*EIF1AX*	*H3C8*	*MLH3*	*PIK3CG*	*SHTN1*	*WT1*
CARM1	*ELF3*	*H3F3A*	*MPL*	*PIK3R1*	*SLC29A1*	*XIAP*
CARS	*ELOC*	*HDAC2*	*MPRIP*	*PIK3R2*	*SLC34A2*	*XPC*
CASP8	*EML4*	*HEY1*	*MRE11*	*PIK3R3*	*SLC4A4*	*XPO1*
CBFB	*EMSY*	*HFE*	*MRE11A*	*PIM1*	*SLX4*	*XRCC1*
CBL	*ENG*	*HGF*	*MSH2*	*PLAG1*	*SMAD2*	*XRCC2*
CCDC6	*EP300*	*HIST1H3B*	*MSH3*	*PLCG1*	*SMAD3*	*XRCC3*
CCNB3	*EPC1*	*HLA-A*	*MSH6*	*PLCG2*	*SMAD4*	*YAP1*
CCND1	*EPC2*	*HMGA2*	*MSI*	*PLK2*	*SMARCA4*	*YWHAE*
CCND2	*EPCAM*	*HNF1A*	*MSMB*	*PMS1*	*SMARCB1*	*ZC3H7B*
CCND3	*EPHA3*	*HOOK3*	*MSR1*	*PMS2*	*SMARCD1*	*ZFHX3*
CCNE1	*EPHA5*	*HOXB13*	*MST1*	*POLD1*	*SMO*	*ZMYM3*
CCNQ	*EPHB1*	*HRAS*	*MST1R*	*POLE*	*SMYD3*	*ZNF217*
CD274	*ERBB2*	*ICOSLG*	*MTAP*	*POU6F2*	*SOCS1*	*ZNF703*
CD34	*ERBB3*	*ID3*	*MTHFD1*	*PPARA*	*SOS1*	*ZRSR2*
CD74	*ERBB4*	*IDH1*	*MTHFR*	*PPARG*	*SOX17*	
CD79A	*ERCC1*	*IDH2*	*MTOR*	*PPHLN1*	*SOX2*	
CD79B	*ERCC2*	*IFNGR1*	*MUTYH*	*PPL*	*SOX9*	