Comprehensive Panel- 500 Genes

Test Description

The MolQ Comprehensive Panel includes 500+ key solid tumor genes (for SNV, CNV, TMB, MSI and fusions) 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.

Patient Demographic

Name: Ms. Farida
Sex: Female
Date of Birth/Age: 38 years
Disease: Breast carcinoma metastasis to lung

Clinician

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

Specimen

Booking ID: 012402060076
Sample Type: FFPE Block No. B-314/24 (Lung Biopsy)
Tumor Content Percentage: 30%
Date of Collection: 06-02-2024
Date of Booking: 06-02-2024

CLINICAL SYNOPSIS

Farida, is a known case of breast carcinoma with metastasis to lung. Lung biopsy has been evaluated for pathogenic variations in the genes listed in Appendix 2.

RESULT SUMMARY

Variants detected as per NCCN Guidelines: No clinically relevant alteration detected.

Other variants detected: *ESR1* (p.Asp538Gly, VAF= 22.46%) mutation is present.

Note: The average Base Coverage Depth achieved was 3487X in this sample.

RESULTS

Variant in *ESR1* gene was detected.

Tumor Mutation Burden is 5.54 Mut/Mb.

Microsatellite Instability (MSI) is stable.

RELEVANT BIOMARKERS

Gene/ Transcript (Locus)	Variant ID	Variant	Exon	Coverage	Allele Frequency	Variant Effect	*Relevant Therapies (In this cancer type)	*Relevant Therapies (In other cancer type)	Tier[2]
ESR1 (chr6:152419926)	COSM94250	c.1613A>G (p.Asp538Gly)	9	2863	22.46%	Missense	Elacestrant[i,ii]	None	Ia

* Public data sources included in relevant therapies: FDA[i], NCCN, EMA[ii], ESMO

[2] Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

RELEVANT BREAST CANCER FINDINGS

Gene	Findings	Gene	Findings
AKT1	None detected	*NTRK3*	None detected

ERBB2	None detected	*PIK3CA*	None detected
ESR1	p.Asp538Gly; c.1613A>G	*PTEN*	None detected
NTRK1	None detected	*RET*	None detected
NTRK2	None detected		

VARIANT OF UNKNOWN SIGNIFICANCE (VUS)

Not identified.

CLINICAL CORRELATION AND VARIANT INTERPRETATION

ESR1 **p.Asp538Gly** **Coverage Frequency 2863**

Gene description: The *ESR1* gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses. A related gene, *ESR2*, encodes the cognate ERβ protein. ERα is a ligand activated transcription factor regulated by the hormone estrogen[1,2]. Estrogen binding to ERα results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[3].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[4-7]. *ESR1* gene fusions and *ESR1* copy number gains have also been observed and are associated with advanced endocrine resistant disease[8-12].

Potential relevance: The FDA has approved elacestrant[13] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, *ESR1*-mutated advanced or metastatic breast cancer[14]. The FDA has also granted fast track designations to three therapies: seviteronel[15] (2016) for ER-positive breast cancer, lasofoxifene[16] (2019) for *ESR1* mutated, ER-positive/ERBB2 negative metastatic breast cancer, and camizaestrant[17] for *ESR1* mutated, HR-positive/ERBB2 negative metastatic breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[18] (1977), fulvestrant[19] (2002), letrozole[20] (1995), and exemestane[21] (2005) are FDA approved for ER-positive metastatic breast cancers[22,23]. Although ERα and ERβ positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[24-26].

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RECOMMENDATIONS

- Validation of the variant(s) by Sanger sequencing is recommended to rule out false positives.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.

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Dr. Gulshan Yadav, MD
Head, Pathology

APPENDIX 1: TEST METHODOLOGY

METHOD

Pathology Assessment

The FFPE block is reviewed for presence of tumor cells and tumor percentage by histopathologists through screening of H & E staining slides.

Assay Methods

The test was performed using the Oncomine Comprehensive Assay Plus targeted, amplicon based next-generation sequencing assay that analyses 500+ unique genes for SNV, CNV, TMB, MSI and fusions. The minimum of 20ng of DNA isolated by Qiagen nucleic acid isolation kit is amplified using Oncomine Comprehensive assay plus as per the instruction manual. The amplicon libraries are prepared from 4 pools of primer which includes 2 pools of DNA based targets. The amplified primer pools are enzyme fragmented and Ion adapter barcodes are added. Amplified library is purified followed by quantitation using Ion Library TaqManTM Quantitation Kit. The quality of amplified libraries having 150-200bp sizes are confirmed by Agilent TapeStation. The quantified pooled library is loaded on Ion 550 Chip using Ion Chef and sequencing is performed on the Ion GeneStudio S5 prime system. For the current report RNA was not included.

Secondary Analysis Methods

The sequence data is processed using Ion Torrent server and the Ion reporter software 5.20.2.0. TMB is reported as High (>10 mutations/Mb), Intermediate (>3 to 10 mutations/Mb) and Low (<3 mutations/Mb). All the reported alterations are manually curated using Integrative Genomics Viewer (IGV). The Final report is generated using oncomine knowledgebase which includes contextual investigations of sample-specific variants with respect to labels, guidelines (AMP, ASCO, CAP), current clinical trials and peer-reviewed literature which is frequently updated.

Genes Assayed

The panel covers 1.50M bases of DNA region, including 1.06M bases of exonic regions. It includes a total of 500+ genes covering 165 hotspot genes, 333 genes with focal CNV gains and loss, 227 genes with full coding sequence (CDS), >1 Mb exonic regions for TMB evaluation and 76 MSI markers for Microsatellite Instability (MSI) and Microsatellite stable (MSS). It also covers 46 genes (SNVs, Indels, CNVs) for homologous recombination deficiency (HRD) including *BRCA1* and *BRCA2*. A subset of these (20 genes) were assessed for determining Loss of Heterozygosity (LOH) at gene level. Details available on request.

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.

DISCLAIMER

- This report was generated using the materials and methods as recommended which required the use of quality reagents, protocols, instruments, software, databases and other items, some of which were provided or made accessible by third

parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases and/or other items may compromise the quality or accuracy of the report.

- The report has been created based on, or incorporated inferences to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the Report may be adversely impacted. MolQ Laboratory is not obligated to notify you of any of the impact that future scientific or medical findings may have on the report.
- The report must always be interpreted and considered within the clinical context, and a physician should always consider the report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis or developing and implementing a plan of care for the patient. The report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestations of many diseases are caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the report. This report is based on a Next Generation Assay which does not distinguish between a somatic and a germline variant. If germline variant is in question, further testing is recommended. The report provided by MolQ Laboratory is on a "as is" basis. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the report. In no event will MolQ Laboratory be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the report, your reliance on the report, or any defect or inaccurate information included within the report.
- Medical knowledge and annotation are constantly updated and reflects the current knowledge at the time.
- 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.
- 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).
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- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory as required by the CLIA 1988 regulations. The report, and the tests used to generate the Report have not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The test results have scientifically shown to be clinically useful.

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.
- 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).

APPENDIX 2: GENE LIST

Gene	Gene	Gene	Gene	Gene	Gene	Gene
ABL1	*CDKN2A*	*FANCF*	*HIST3H3*	*MEN1*	*PIK3R3*	*SMAD3*
ABL2	*CDKN2B*	*FANCG*	*HLA-A*	*MET*	*PIM1*	*SMAD4*
ACVR1	*CDKN2C*	*FANCI*	*HLA-B*	*MGA*	*PLCG2*	*SMARCA4*
ACVR1B	*CEBPA*	*FANCL*	*HLA-C*	*MITF*	*PLK2*	*SMARCB1*
AKT1	*CENPA*	*FAS*	*HNF1A*	*MLH1*	*PMAIP1*	*SMARCD1*
AKT2	*CHD2*	*FAT1*	*HNRNPK*	*MLL*	*PMS1*	*SMC1A*
AKT3	*CHD4*	*FBXW7*	*HOXB13*	*MLLT3*	*PMS2*	*SMC3*
ALK	*CHEK1*	*FGF1*	*HRAS*	*MPL*	*PNRC1*	*SMO*
ALOX12B	*CHEK2*	*FGF10*	*HSD3B1*	*MRE11A*	*POLD1*	*SNCAIP*
ANKRD11	*CIC*	*FGF14*	*HSP90AA1*	*MSH2*	*POLE*	*SOCS1*
ANKRD26	*CREBBP*	*FGF19*	*ICOSLG*	*MSH3*	*PPARG*	*SOX10*
APC	*CRKL*	*FGF2*	*ID3*	*MSH6*	*PPM1D*	*SOX17*
AR	*CRLF2*	*FGF23*	*IDH1*	*MST1*	*PPP2R1A*	*SOX2*
ARAF	*CSF1R*	*FGF3*	*IDH2*	*MST1R*	*PPP2R2A*	*SOX9*
ARFRP1	*CSF3R*	*FGF4*	*IFNGR1*	*MTOR*	*PPP6C*	*SPEN*
ARID1A	*CSNK1A1*	*FGF5*	*IGF1*	*MUTYH*	*PRDM1*	*SPOP*
ARID1B	*CTCF*	*FGF6*	*IGF1R*	*MYB*	*PREX2*	*SPTA1*
ARID2	*CTLA4*	*FGF7*	*IGF2*	*MYC*	*PRKAR1A*	*SRC*
ARID5B	*CTNNA1*	*FGF8*	*IKBKE*	*MYCL1*	*PRKCI*	*SRSF2*
ASXL1	*CTNNB1*	*FGF9*	*IKZF1*	*MYCN*	*PRKDC*	*STAG1*
ASXL2	*CUL3*	*FGFR1*	*IL10*	*MYD88*	*PRSS8*	*STAG2*
ATM	*CUX1*	*FGFR2*	*IL7R*	*MYOD1*	*PTCH1*	*STAT3*
ATR	*CXCR4*	*FGFR3*	*INHA*	*NAB2*	*PTEN*	*STAT4*
ATRX	*CYLD*	*FGFR4*	*INHBA*	*NBN*	*PTPN11*	*STAT5A*
AURKA	*DAXX*	*FH*	*INPP4A*	*NCOA3*	*PTPRD*	*STAT5B*
AURKB	*DCUN1D1*	*FLCN*	*INPP4B*	*NCOR1*	*PTPRS*	*STK11*
AXIN1	*DDR2*	*FLI1*	*INSR*	*NEGR1*	*PTPRT*	*STK40*
AXIN2	*DDX41*	*FLT1*	*IRF2*	*NF1*	*QKI*	*SUFU*
AXL	*DHX15*	*FLT3*	*IRF4*	*NF2*	*RAB35*	*SUZ12*
B2M	*DICER1*	*FLT4*	*IRS1*	*NFE2L2*	*RAC1*	*SYK*
BAP1	*DIS3*	*FOXA1*	*IRS2*	*NFKBIA*	*RAD21*	*TAF1*
BARD1	*DNAJB1*	*FOXL2*	*JAK1*	*NKX2-1*	*RAD50*	*TBX3*
BBC3	*DNMT1*	*FOXO1*	*JAK2*	*NKX3-1*	*RAD51*	*TCEB1*
BCL10	*DNMT3A*	*FOXP1*	*JAK3*	*NOTCH1*	*RAD51B*	*TCF3*
BCL2	*DNMT3B*	*FRS2*	*JUN*	*NOTCH2*	*RAD51C*	*TCF7L2*
BCL2L1	*DOT1L*	*FUBP1*	*KAT6A*	*NOTCH3*	*RAD51D*	*TERC*
BCL2L11	*E2F3*	*FYN*	*KDM5A*	*NOTCH4*	*RAD52*	*TERT*
BCL2L2	*EED*	*GABRA6*	*KDM5C*	*NPM1*	*RAD54L*	*TET1*
BCL6	*EGFL7*	*GATA1*	*KDM6A*	*NRAS*	*RAF1*	*TET2*
BCOR	*EGFR*	*GATA2*	*KDR*	*NRG1*	*RANBP2*	*TFE3*
BCORL1	*EIF1AX*	*GATA3*	*KEAP1*	*NSD1*	*RARA*	*TFRC*
BCR	*EIF4A2*	*GATA4*	*KEL*	*NTRK1*	*RASA1*	*TGFBR1*
BIRC3	*EIF4E*	*GATA6*	*KIF5B*	*NTRK2*	*RB1*	*TGFBR2*
BLM	*EML4*	*GEN1*	*KIT*	*NTRK3*	*RBM10*	*TMEM127*
BMPR1A	*EP300*	*GID4*	*KLF4*	*NUP93*	*RECQL4*	*TMPRSS2*
BRAF	*EPCAM*	*GLI1*	*KLHL6*	*NUTM1*	*REL*	*TNFAIP3*

Comprehensive Panel- 500 Genes

BRCA1	*EPHA3*	*GNA11*	*KMT2B*	*PAK1*	*RET*	*TNFRSF14*
BRCA2	*EPHA5*	*GNA13*	*KMT2C*	*PAK3*	*RFWD2*	*TOP1*
BRD4	*EPHA7*	*GNAQ*	*KMT2D*	*PAK7*	*RHEB*	*TOP2A*
BRIP1	*EPHB1*	*GNAS*	*KRAS*	*PALB2*	*RHOA*	*TP53*
BTG1	*ERBB2*	*GPR124*	*LAMP1*	*PARK2*	*RICTOR*	*TP63*
BTK	*ERBB3*	*GPS2*	*LATS1*	*PARP1*	*RIT1*	*TRAF2*
C11orf30	*ERBB4*	*GREM1*	*LATS2*	*PAX3*	*RNF43*	*TRAF7*
CALR	*ERCC1*	*GRIN2A*	*LMO1*	*PAX5*	*ROS1*	*TSC1*
CARD11	*ERCC2*	*GRM3*	*LRP1B*	*PAX7*	*RPS6KA4*	*TSC2*
CASP8	*ERCC3*	*GSK3B*	*LYN*	*PAX8*	*RPS6KB1*	*TSHR*
CBFB	*ERCC4*	*H3F3A*	*LZTR1*	*PBRM1*	*RPS6KB2*	*U2AF1*
CBL	*ERCC5*	*H3F3B*	*MAGI2*	*PDCD1*	*RPTOR*	*VEGFA*
CCND1	*ERG*	*H3F3C*	*MALT1*	*PDCD1LG2*	*RUNX1*	*VHL*
CCND2	*ERRFI1*	*HGF*	*MAP2K1*	*PDGFRA*	*RUNX1T1*	*VTCN1*
CCND3	*ESR1*	*HIST1H1C*	*MAP2K2*	*PDGFRB*	*RYBP*	*WISP3*
CCNE1	*ETS1*	*HIST1H2BD*	*MAP2K4*	*PDK1*	*SDHA*	*WT1*
CD274	*ETV1*	*HIST1H3A*	*MAP3K1*	*PDPK1*	*SDHAF2*	*XIAP*
CD276	*ETV4*	*HIST1H3B*	*MAP3K13*	*PGR*	*SDHB*	*XPO1*
CD74	*ETV5*	*HIST1H3C*	*MAP3K14*	*PHF6*	*SDHC*	*XRCC2*
CD79A	*ETV6*	*HIST1H3D*	*MAP3K4*	*PHOX2B*	*SDHD*	*YAP1*
CD79B	*EWSR1*	*HIST1H3E*	*MAPK1*	*PIK3C2B*	*SETBP1*	*YES1*
CDC73	*EZH2*	*HIST1H3F*	*MAPK3*	*PIK3C2G*	*SETD2*	*ZBTB2*
CDH1	*FAM123B*	*HIST1H3G*	*MAX*	*PIK3C3*	*SF3B1*	*ZBTB7A*
CDK12	*FAM175A*	*HIST1H3H*	*MCL1*	*PIK3CA*	*SH2B3*	*ZFHX3*
CDK4	*FAM46C*	*HIST1H3I*	*MDC1*	*PIK3CB*	*SH2D1A*	*ZNF217*
CDK6	*FANCA*	*HIST1H3J*	*MDM2*	*PIK3CD*	*SHQ1*	*ZNF703*
CDK8	*FANCC*	*HIST2H3A*	*MDM4*	*PIK3CG*	*SLIT2*	*ZRSR2*
CDKN1A	*FANCD2*	*HIST2H3C*	*MED12*	*PIK3R1*	*SLX4*	
CDKN1B	*FANCE*	*HIST2H3D*	*MEF2B*	*PIK3R2*	*SMAD2*	