

Test Description

The MolQ Liquid Precision Panel includes 50 genes, involving hotspot regions and 3159 unique variants, applicable to a wide range of tumor types for detection of SNV (single and multiple nucleotide variation), Insertion-Deletion, Copy Number Variation (CNV), and gene Fusions. Fusion and splice variants are detected in RNA.

Patient Demographic

Name: Mr. Jagat S Rawat
Sex: Male
Date of Birth/Age: 78 years
Disease: Metastatic Carcinoma of unknown primary

Clinician

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

Specimen

Booking ID: 012411140086
Sample Type: Blood
Tumor Content Percentage: NA
Date of Collection: 14-11-2024
Date of Booking: 14-11-2024

CLINICAL SYNOPSIS

Jagat S Rawat, is a known case of metastatic carcinoma of unknown primary.

OTHER VARIANTS

TP53 (p.Gly266Glu, VAF = 1.72%) mutation is detected in the given specimen.

The sequencing was performed on 26.6 in the given specimen. Average Base Coverage Depth achieved was 55498 (X) in this sample.

RESULTS

No clinically relevant mutations causative of the reported phenotype was detected.

RELEVANT BIOMARKERS

No biomarkers associated with relevant evidence.

PREVALENT CANCER BIOMARKERS WITHOUT RELEVANT EVIDENCE BASED ON INCLUDED DATA SOURCES

Gene	Variant ID	Variant	Coverage	Allele Frequency	Variant Effect	ClinVar#
<i>TP53</i> NM_000546.5	COSM10867	c.797G>A (p.Gly266Glu)	1219	1.72%	Missense	Conflicting interpretations of pathogenicity

*Based on Clinvar version 20200329

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

None.

CLINICAL CORRELATION AND VARIANT INTERPRETATION

***TP53* p.Gly266Glu Coverage Frequency 1219**

Gene description: The *TP53* gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept

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inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in *TP53* is required for oncogenesis as they result in loss of protein function and gain of transforming potential¹. Germline mutations in *TP53* are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{2,3}.

Alterations and prevalence: *TP53* is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing *TP53* mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high *TP53* mutation rates (60-90%)⁴⁻⁹. Approximately two-thirds of *TP53* mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R2824,5. Invariably, recurrent missense mutations in *TP53* inactivate its ability to bind DNA and activate transcription of target genes¹⁰⁻¹³.

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a *TP53* Y220C mutation¹⁴. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,¹⁵ and breakthrough designation¹⁶ (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a *TP53* mutation, respectively. In addition to investigational therapies aimed at restoring wild-type *TP53* activity, compounds that induce synthetic lethality are also under clinical evaluation^{17,18}. *TP53* mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)¹⁹⁻²⁴. In mantle cell lymphoma, *TP53* mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant²⁵. Mono- and bi-allelic mutations in *TP53* confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system²⁶.

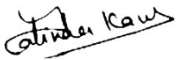
REFERENCES

1. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell*. 2014 Mar 17;25(3):304-17. PMID: 24651012
2. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol*. 2010 Jan;2(1):a001008. PMID: 20182602
3. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med*. 2017 Apr 3;7(4). PMID: 28270529
4. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov*. 2012 May;2(5):401-4. PMID: 22588877
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet*. 2013 Oct;45(10):1113-20. PMID: 24071849
6. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012 Sep 27;489(7417):519-25. PMID: 22960745
7. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015 Jan 29;517(7536):576-82. PMID: 25631445
8. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet*. 2016 Jun;48(6):607-16. PMID: 27158780
9. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
10. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum. Mutat*. 2002 Jun;19(6):607-14. PMID: 12007217
11. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes Cancer*. 2011 Apr;2(4):466-74. PMID: 21779514
12. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*. 2007 Apr 2;26(15):2157-65. PMID: 17401424
13. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. *Hum. Mutat*. 2014 Jun;35(6):766-78. PMID: 24729566
14. <https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html>
15. <https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation>
16. <http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fdabreakthrough-therapy-designation-1769167>
17. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. *Front Oncol*. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
18. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci*. 2017 Nov;74(22):4171-4187. PMID: 28643165
19. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]
20. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
21. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

22. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2023]
23. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2023]
24. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2023]
25. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 5.2023]
26. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829

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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APPENDIX 1: TEST METHODOLOGY

Method

Circulating cell-free total nucleic acid (cfTNA) were isolated from samples using the MagMAX Cell-Free Total Nucleic Acid Isolation Kit. Quantity and quality is checked by Qubit assay and Tape station, respectively. After quality check the isolated and purified sample was directly loaded on Ion Torrent Genexus Next Generation Sequencer and subjected to automated library preparation and template preparation followed by in-depth sequencing.

It utilizes unique molecular tags to enable high sensitivity detection of variants. Analysis is done using Ion Torrent Reporter Software, the data is visualized on Integrative Genomics Viewer (IGV) and analyzed. The final report is generated using OncoPrint curated knowledgebase reporter and includes clinical trials information continuously being updated for the best of the patient management as per clinical guidelines.

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).
- 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

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- misleading or even wrong result of any testing if such could not be recognized by MolQ Laboratory in advance.
- A negative value in liquid biopsy does not mean true absence of mutation. It may not be detectable in the blood sample but may still be positive in tissue biopsy.
 - 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.

APPENDIX 2: GENE LIST WITH COVERAGE

DNA Hotspots					
<i>AKT1</i>	<i>AKT2</i>	<i>AKT3</i>	<i>ALK</i>	<i>AR</i>	<i>ARAF</i>
<i>BRAF</i>	<i>CDK4</i>	<i>CDKN2A</i>	<i>CHEK2</i>	<i>CTNNB1</i>	<i>EGFR</i>
<i>ERBB2</i>	<i>ERBB3</i>	<i>ERBB4</i>	<i>ESR1</i>	<i>FGFR1</i>	<i>FGFR2</i>
<i>FGFR3</i>	<i>FGFR4</i>	<i>FLT3</i>	<i>GNA11</i>	<i>GNAQ</i>	<i>GNAS</i>
<i>HRAS</i>	<i>IDH1</i>	<i>IDH2</i>	<i>KIT</i>	<i>KRAS</i>	<i>MAPK1</i>
<i>MAPK2</i>	<i>MET</i>	<i>MTOR</i>	<i>NRAS</i>	<i>NTRK1</i>	<i>NTRK2</i>
<i>NTRK3</i>	<i>PDGFRA</i>	<i>PIK3CA</i>	<i>PTEN</i>	<i>RAF1</i>	<i>RET</i>
<i>ROS1</i>	<i>SMO</i>	<i>TP53</i>			
CNVs					
<i>ALK</i>	<i>AR</i>	<i>CD274</i>	<i>CDKN2A</i>	<i>EGFR</i>	<i>ERBB2</i>
<i>ERBB3</i>	<i>FGFR1</i>	<i>FGFR2</i>	<i>FGFR3</i>	<i>KRAS</i>	<i>MET</i>
<i>PIK3CA</i>	<i>PTEN</i>				
Inter-genetic Fusions					
<i>ALK</i>	<i>BRAF</i>	<i>ESR1</i>	<i>FGFR1</i>	<i>FGFR2</i>	<i>FGFR3</i>
<i>MET</i>	<i>NRG1</i>	<i>NTRK1</i>	<i>NTRK2</i>	<i>NTRK3</i>	<i>NUTM1</i>
<i>RET</i>	<i>ROS1</i>	<i>RSPO2</i>	<i>RSPO3</i>		
Intra-genetic Fusions					
<i>AR</i>	<i>EGFR</i>	<i>MET</i>			