FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Jain, Sunita	**12 January 2016**	**Lung adenocarcinoma**

Date of Birth	16 August 1956	**Medical Facility**	Max Healthcare	**Specimen Received**	14 December 2015
Sex	Female	**Ordering Physician**	Verma, Amit	**Specimen Site**	Lymph Node
FMI Case #	TRF128484	**Additional Recipient**	Not Given	**Date of Collection**	12 April 2015
Medical Record #	Not Given	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	H-1782/15 (15M-145) (1565807)	**Pathologist**	Not Provided		

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS[‖]

[‖]Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

1 genomic alteration

0 therapies associated with potential clinical benefit

0 therapies associated with lack of response

0 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alteration Identified[†]

TP53 Q331*

Additional Disease-relevant Genes with No Reportable Alterations Identified[†]

EGFR
KRAS
ALK
BRAF
MET
RET
ERBB2

[†]For a complete list of the genes assayed and performance specifications, please refer to the Appendix
[⌘]See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
TP53 Q331*	None	None	None

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

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GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION

TP53
Q331*

Gene and Alteration: Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[1]. Mutations affecting the DNA binding domain (aa 100-292), the tetramerization domain (aa 325-356), or the C-terminal regulatory domain (aa 356-393), such as observed here, are thought to disrupt the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[2,3,4,5]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[6,7,8,9,10,11]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[12] to 1:20,000[11], and in the appropriate clinical context, germline testing of TP53 is recommended.

Frequency and Prognosis: TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[13,14,15,16,17] and specifically in 45% of lung adenocarcinoma samples[18,19]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[20].

Potential Treatment Strategies: There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor AZD1775 [21,22,23,24], therapies that reactivate mutant p53 such as APR-246[25], or p53 gene therapy and immunotherapeutics such as SGT-53[26,27,28,29] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). In a Phase 1 clinical trial, 8 of 11 evaluable patients receiving SGT-53 as a single agent exhibited stable disease[30]. Clinical trials of SGT-53 in combination with chemotherapy are underway. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[31]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

THERAPIES

There are no therapies FDA approved in this patient's tumor type that are specific to the reported genomic alterations.

There are no therapies FDA approved in other tumor types that are specific to the reported genomic alterations.

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APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

Note: One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants have not yet been adequately characterized in the scientific literature at the time this report was issued and/or the genomic context of these alterations make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ALK P671S	***AXL*** K514M	***CHEK2*** E64K	***CSF1R*** T467A
INPP4B G25R	***JAK2*** M186V	***MLL3*** H502Q	***NOTCH3*** R1175W
NSD1 D1522N	***POLE*** R1519C	***RNF43*** R657P,V271L	

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APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 315 genes as well as introns of 28 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

ABL1	*BRAF*	*CHEK1*	*FANCC*	*GATA3*	*JAK2*	*MITF*	*PDCD1LG2*	*RBM10*	*STAT4*
ABL2	*BRCA1*	*CHEK2*	*FANCD2*	*GATA4*	*JAK3*	*MLH1*	*PDGFRA*	*RET*	*STK11*
ACVR1B	*BRCA2*	*CIC*	*FANCE*	*GATA6*	*JUN*	*MPL*	*PDGFRB*	*RICTOR*	*SUFU*
AKT1	*BRD4*	*CREBBP*	*FANCF*	*GID4 (C17orf39)*	*KAT6A (MYST3)*	*MRE11A*	*PDK1*	*RNF43*	*SYK*
AKT2	*BRIP1*	*CRKL*	*FANCG*	*GLI1*	*KDM5A*	*MSH2*	*PIK3C2B*	*ROS1*	*TAF1*
AKT3	*BTG1*	*CRLF2*	*FANCL*	*GNA11*	*KDM5C*	*MSH6*	*PIK3CA*	*RPTOR*	*TBX3*
ALK	*BTK*	*CSF1R*	*FAS*	*GNA13*	*KDM6A*	*MTOR*	*PIK3CB*	*RUNX1*	*TERC*
AMER1 (FAM123B)	*C11orf30 (EMSY)*	*CTCF*	*FAT1*	*GNAQ*	*KDR*	*MUTYH*	*PIK3CG*	*RUNX1T1*	*TERT (promoter only)*
APC	*CARD11*	*CTNNA1*	*FBXW7*	*GNAS*	*KEAP1*	*MYC*	*PIK3R1*	*SDHA*	*TET2*
AR	*CBFB*	*CTNNB1*	*FGF10*	*GPR124*	*KEL*	*MYCL (MYCL1)*	*PIK3R2*	*SDHB*	*TGFBR2*
ARAF	*CBL*	*CUL3*	*FGF14*	*GRIN2A*	*KIT*	*MYCN*	*PLCG2*	*SDHC*	*TNFAIP3*
ARFRP1	*CCND1*	*CYLD*	*FGF19*	*GRM3*	*KLHL6*	*MYD88*	*PMS2*	*SDHD*	*TNFRSF14*
ARID1A	*CCND2*	*DAXX*	*FGF23*	*GSK3B*	*KMT2A (MLL)*	*NF1*	*POLD1*	*SETD2*	*TOP1*
ARID1B	*CCND3*	*DDR2*	*FGF3*	*H3F3A*	*KMT2C (MLL3)*	*NF2*	*POLE*	*SF3B1*	*TOP2A*
ARID2	*CCNE1*	*DICER1*	*FGF4*	*HGF*	*KMT2D (MLL2)*	*NFE2L2*	*PPP2R1A*	*SLIT2*	*TP53*
ASXL1	*CD274*	*DNMT3A*	*FGF6*	*HNF1A*	*KRAS*	*NFKBIA*	*PRDM1*	*SMAD2*	*TSC1*
ATM	*CD79A*	*DOT1L*	*FGFR1*	*HRAS*	*LMO1*	*NKX2-1*	*PREX2*	*SMAD3*	*TSC2*
ATR	*CD79B*	*EGFR*	*FGFR2*	*HSD3B1*	*LRP1B*	*NOTCH1*	*PRKAR1A*	*SMAD4*	*TSHR*
ATRX	*CDC73*	*EP300*	*FGFR3*	*HSP90AA1*	*LYN*	*NOTCH2*	*PRKCI*	*SMARCA4*	*U2AF1*
AURKA	*CDH1*	*EPHA3*	*FGFR4*	*IDH1*	*LZTR1*	*NOTCH3*	*PRKDC*	*SMARCB1*	*VEGFA*
AURKB	*CDK12*	*EPHA5*	*FH*	*IDH2*	*MAGI2*	*NPM1*	*PRSS8*	*SMO*	*VHL*
AXIN1	*CDK4*	*EPHA7*	*FLCN*	*IGF1R*	*MAP2K1*	*NRAS*	*PTCH1*	*SNCAIP*	*WISP3*
AXL	*CDK6*	*EPHB1*	*FLT1*	*IGF2*	*MAP2K2*	*NSD1*	*PTEN*	*SOCS1*	*WT1*
BAP1	*CDK8*	*ERBB2*	*FLT3*	*IKBKE*	*MAP2K4*	*NTRK1*	*PTPN11*	*SOX10*	*XPO1*
BARD1	*CDKN1A*	*ERBB3*	*FLT4*	*IKZF1*	*MAP3K1*	*NTRK2*	*QKI*	*SOX2*	*ZBTB2*
BCL2	*CDKN1B*	*ERBB4*	*FOXL2*	*IL7R*	*MCL1*	*NTRK3*	*RAC1*	*SOX9*	*ZNF217*
BCL2L1	*CDKN2A*	*ERG*	*FOXP1*	*INHBA*	*MDM2*	*NUP93*	*RAD50*	*SPEN*	*ZNF703*
BCL2L2	*CDKN2B*	*ERRFI1*	*FRS2*	*INPP4B*	*MDM4*	*PAK3*	*RAD51*	*SPOP*	
BCL6	*CDKN2C*	*ESR1*	*FUBP1*	*IRF2*	*MED12*	*PALB2*	*RAF1*	*SPTA1*	
BCOR	*CEBPA*	*EZH2*	*GABRA6*	*IRF4*	*MEF2B*	*PARK2*	*RANBP2*	*SRC*	
BCORL1	*CHD2*	*FAM46C*	*GATA1*	*IRS2*	*MEN1*	*PAX5*	*RARA*	*STAG2*	
BLM	*CHD4*	*FANCA*	*GATA2*	*JAK1*	*MET*	*PBRM1*	*RB1*	*STAT3*	

Select Rearrangements									
ALK	*BRAF*	*BRD4*	*ETV4*	*FGFR1*	*KIT*	*MYC*	*NTRK2*	*RARA*	*TMPRSS2*
BCL2	*BRCA1*	*EGFR*	*ETV5*	*FGFR2*	*MSH2*	*NOTCH2*	*PDGFRA*	*RET*	
BCR	*BRCA2*	*ETV1*	*ETV6*	*FGFR3*	*MYB*	*NTRK1*	*RAF1*	*ROS1*	

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APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90%[1] >99% for ALK fusion[2] (CI* 89.1%-100%)
Specificity of all variant types	Positive Predictive Value (PPV)	>99%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision

*95% Confidence Interval
**Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.
[1]Based on analysis of coverage and re-arrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.
[2]Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. *et al.* Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

[‖]Reduced Sensitivity: Although we can definitively confirm the presence of the genomic alterations detailed in this report, the data obtained may have been insufficient for comprehensive detection of genomic alterations. Reduced sensitivity may be due to poor sample quality or, in rare cases, to patient transplant history.

APPENDIX

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APPENDIX

ABOUT FOUNDATIONONE™

FoundationOne™: FoundationOne was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal): An alteration denoted as "amplification – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne analytical methodology has identified as being present in <10% of the assayed tumor DNA.

The Report incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research.

NOTE: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

Level of Evidence Not Provided: Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

No Guarantee of Clinical Benefit: This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

No Guarantee of Reimbursement: Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne.

Treatment Decisions are Responsibility of Physician: Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report.

Certain sample or variant characteristics may result in reduced sensitivity. These include: sub clonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

FoundationOne complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

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