FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Sharma , Ashok	**25 December 2015**	**Small intestine adenocarcinoma**

Date of Birth	07 October 1961	**Medical Facility**	Max Healthcare	**Specimen Received**	14 December 2015
Sex	Male	**Ordering Physician**	Verma, Amit	**Specimen Site**	Soft Tissue
FMI Case #	TRF128487	**Additional Recipient**	Not Given	**Date of Collection**	12 November 2015
Medical Record #	Not Given	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	14254/15A	**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

6 genomic alterations

2 therapies associated with potential clinical benefit

0 therapies associated with lack of response

6 clinical trials

TUMOR TYPE: SMALL INTESTINE ADENOCARCINOMA

Genomic Alterations Identified†

KRAS G12V
APC L1342fs*73, S1545*
TERT promoter -124C>T
TP53 C135fs*35, E271K

†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
KRAS G12V	None	Cobimetinib Trametinib	Yes, see clinical trials section
APC L1342fs*73, S1545*	None	None	None
TERT promoter -124C>T	None	None	None
TP53 C135fs*35, E271K	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

KRAS
G12V

Gene and Alteration: KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[1,2]. The KRAS gene is one of the most commonly mutated genes in human malignancies[3,4,5]. KRAS alterations affecting amino acids G12, G13, Q22, A59, Q61, and A146, as well as mutations G10_A11insG, A18D, L19F, K117N have been characterized to be activating and oncogenic[1,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23].

Frequency and Prognosis: Mutations in KRAS have been reported in 23% of small intestine adenocarcinomas (COSMIC, Nov 2015). KRAS mutations are reportedly harbored in 55% of chromosome-unstable small bowel adenocarcinomas[24].

Potential Treatment Strategies: Constitutive activation of KRAS leads to activation of the RAF-MEK-ERK pathway, thereby leading to tumorigenesis[1,25], and may therefore predict sensitivity to inhibitors of this pathway. MEK inhibitors, alone or in combination with other targeted therapies, are in clinical trials in solid tumors, including tumors with KRAS mutations[26]. The MEK inhibitors trametinib and cobimetinib are FDA approved to treat melanoma with BRAF V600E or V600K mutations, and are being studied in clinical trials in solid tumors (Larkin et al., 2015; ASCO Abstract 9006)[27,28]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status (Juric et al., 2014; ASCO Abstract 9051). The reovirus Reolysin targets cells with activated RAS signaling[29,30,31] and is in clinical trials in some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer [32,33,34,35,36,37,38,39,40]. KRAS mutation status may predict lack of response to EGFR-targeted therapies, such as erlotinib and cetuximab, in non-small cell lung cancer (NSCLC) and colon cancer[41,42,43]. However, a retrospective analysis of a recent Phase 3 study examining patients with pancreatic cancer treated with erlotinib and chemotherapy found that KRAS mutation was not associated with objective response but was significantly associated with decreased overall survival[44].

APC
L1342fs*73, S1545*

Gene and Alteration: APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[45]. APC alterations that disrupt the beta-catenin binding domain (amino acids 1020-2035), such as observed here, are likely to disrupt APC binding to beta-catenin and may upregulate WNT signaling[46,47,48,49,50] and are therefore predicted to be inactivating. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[51,52,53]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[54], and in the appropriate clinical context germline testing of APC is recommended.

Frequency and Prognosis: APC mutations have been reported in 13.5% of small intestinal cancers analyzed (COSMIC, Jul 2015). In patients with familial adenomatous polyposis (FAP), there is an increased risk of duodenal cancer, which may develop from duodenal adenomas[54,55]. In one study, 5% (6/114) of FAP patients with diagnosed duodenal adenomas went on to develop duodenal

adenocarcinoma within 10 years[56]. The risk of developing duodenal adenomas in patients with FAP has been reported to be as high as 100%[54]. One study identified duodenal abnormalities in 100/102 patients with FAP[57].

Potential Treatment Strategies: There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors; however, several potential therapies, including WNT pathway inhibitors and TRAIL agonists, are in clinical trials. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[58]. In addition, the Cox-2 inhibitor celecoxib, which is FDA approved for arthritis, was shown to reduce WNT signaling in cancer cell lines[59,60]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[61].

TERT

promoter -124C>T

Gene and Alteration: Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[62]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells [63,64,65]. Mutations within the promoter region of TERT have been observed in melanoma, glioma, thyroid and bladder cancers[66]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[66,67,68], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[67].

Frequency and Prognosis: TERT promoter mutations have been observed in melanoma, glioma, thyroid and bladder cancers[66,68,69,70,71,72,73,74,75]. TERT promoter mutations have not been extensively studied in the context of small intestinal carcinoma (PubMed, Jul 2015). However, hTERT gene expression has been reported to be associated with decreased overall survival in patients with colorectal cancer or ampullary carcinoma[76,77,78].

Potential Treatment Strategies: Therapeutic options for targeting tumors with TERT mutations is currently limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

TP53

C135fs*35, E271K

Gene and Alteration: Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[79]. 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[80,81,82,83]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[84,85,86,87,88,89]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[90] to 1:20,000[89], and in the appropriate clinical context, germline testing of TP53 is recommended.

Frequency and Prognosis: TP53 mutation has been reported in 22% of small intestine adenocarcinoma samples analyzed (COSMIC, Nov 2015). Mutations in p53 have been reported in one of 10 duodenal carcinomas and three of 10 jejunal/ileal carcinomas in one study[91]. Loss of 17p heterozygosity, where the TP53 gene resides, has been observed in 20-67% of duodenal and 20% of ileal/jejunal carcinomas[91,92]. Expression of p53 has been observed in 24-53.3% of small intestine carcinomas[93,94,95]. In one study,

expression of p53 was more common in poorly differentiated tumors (71%) as compared with well-differentiated cases (30%)[95].

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 [96,97,98,99], therapies that reactivate mutant p53 such as APR-246[100], or p53 gene therapy and immunotherapeutics such as SGT-53[101,102,103,104] 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[105]. 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[106]. 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.

ADDITIONAL THERAPIES – FDA APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Cobimetinib	**Approved Indications:** Cobimetinib is a MEK inhibitor that is FDA approved in combination with vemurafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. **Gene Association:** Based on clinical studies (Bendell et al., 2014; AACR Abstract CT328) and preclinical studies[107], KRAS amplification or activating mutations may predict sensitivity to MEK inhibitors such as cobimetinib. **Supporting Data:** Cobimetinib has been investigated primarily in the context of BRAF V600-mutant melanoma. A Phase 3 study with 495 patients treated either with the BRAF inhibitor vemurafenib plus cobimetinib or vemurafenib alone reported a 68-70% overall response rate, 9.9-12.3 months progression-free survival, and a lower rate of cutaneous squamous cell carcinoma in the combination group; disease progression did not correlate with concurrent alterations in the RAS pathway (Larkin et al., 2015; ASCO Abstract 9006)[28]. In a Phase 1b study, vemurafenib combined with cobimetinib achieved an objective response rate of 87% for patients with BRAF V600-mutant melanoma who had not previously received a BRAF inhibitor[108]. One study reported near-complete response to vemurafenib in a patient with BRAF V600K-mutant melanoma who subsequently developed chronic myelomonocytic leukemia (CMML) with NRAS G12R mutation, and concurrent cobimetinib treatment led to suppression of CMML[109]. In a Phase 1b study, out of 47 patients treated with cobimetinib and the AKT inhibitor ipatasertib, 3 patients with KRAS-mutant ovarian, mesonephric cervical, or endometrial carcinoma had a partial response, with prolonged stable disease lasting for >6 months (Bendell et al., 2014; AACR Abstract CT328).
Trametinib	**Approved Indications:** Trametinib is a MEK inhibitor that is FDA approved as both a single agent and in combination with dabrafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. **Gene Association:** KRAS activating mutations may result in activation of the MAPK pathway and predict sensitivity to MEK inhibitors such as trametinib. **Supporting Data:** In a Phase 1 study of the combination of trametinib with the PI3K/mTOR inhibitor GSK2126458 (GSK458) in 69 patients with solid tumors, no responses were observed, but stable disease lasting longer than 22 weeks was reported in 7 patients, including 1 patient with KRAS-mutant small bowel cancer (Bedard et al., 2014; AACR Abstract CT205). A Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[110]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[111,112]. A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in patients with pancreatic or salivary gland cancer[113]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported disease control

(partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status (Juric et al., 2014; ASCO Abstract 9051). However, a Phase 1b trial of a combination of trametinib and the mTOR inhibitor everolimus in patients with solid tumors reported frequent adverse events and was unable to identify a recommended Phase 2 dose and schedule for the combination[114].

Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type

CLINICAL TRIALS TO CONSIDER

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continuously updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
KRAS G12V	KRAS activating mutations may result in activation of downstream pathways, including the MAPK pathway, and may predict sensitivity to inhibitors of this pathway. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "KRAS", "MEK", "reolysin", "trametinib", "MEK162", "PD-0325901", "small intestine adenocarcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase Ib Open-label, Multi-center, Dose Escalation and Expansion Study of Orally Administered MEK162 Plus BYL719 in Adult Patients With Selected Advanced Solid Tumors	Phase 1/Phase 2	MEK, PI3K-alpha	California, Illinois, Massachusetts, New York, Utah, multiple ex-US locations	NCT01449058
Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor PD-0325901 for Patients With KRAS Mutant Non-Small Cell Lung Cancer and Other Solid Tumors	Phase 1/Phase 2	MEK, CDK4, CDK6	Massachusetts	NCT02022982
A PHASE Ib, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MEHD7945A and GDC-0973 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS WITH MUTANT KRAS	Phase 1	EGFR, ERBB3, MEK	California, Colorado, Connecticut, Tennessee, Texas, multiple ex-US locations	NCT01986166
An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS Mutation-Positive Advanced Solid Tumors	Phase 1/Phase 2	MEK, BCL2	Massachusetts	NCT02079740
A Phase I Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients With Hepatic Dysfunction	Phase 1	MEK	California, Florida, Illinois, Massachusetts, Michigan, Missouri, Ohio, Pennsylvania, Texas, multiple ex-US locations	NCT02070549
A Dose-Escalation, Phase I/II, Open-Label, Three-Part Study of the MEK Inhibitor, Trametinib, Combined With the CDK4/6 Inhibitor, Palbociclib, To Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Anti-Cancer Activity in Subjects With Solid Tumors	Phase 1	CDK4, CDK6, MEK	Massachusetts, Tennessee, Texas	NCT02065063

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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.

ARID1A G87_A88insGG	***ARID1B*** Q129_Q130insQ	***CDKN2A*** Y129*	***ESR1*** R555C
FANCD2 R328Q	***FAT1*** H809Y,T746A	***JUN*** A187R	***KDR*** M627T
LRP1B S4147A	***MAP3K1*** S10L	***MLL*** S2319T	***MSH2*** S607G
NTRK3 R14Q			

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.

APPENDIX

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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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