FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Not Given	**11 March 2015**	**Pancreas ductal adenocarcinoma**

Date of Birth	Not Given	**Medical Facility**	Not Given	**Specimen Received**	Not Given
Sex	Female	**Ordering Physician**	Not Given	**Specimen Site**	Lung
FMI Case #	SRF078789	**Additional Recipient**	Not Given	**Date of Collection**	Not Given
Medical Record #	0	**Medical Facility ID #**	-1	**Specimen Type**	Block
Specimen ID	Not Given	**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

4 genomic alterations

1 therapy associated with potential clinical benefit

0 therapies associated with lack of response

12 clinical trials

TUMOR TYPE: PANCREAS DUCTAL ADENOCARCINOMA

Genomic Alterations Identified†

KRAS G12R
NTRK1 A5T
TP53 R175H
SMAD4 G365fs*19

†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 G12R	None	Trametinib	Yes, see clinical trials section
NTRK1 A5T	None	None	Yes, see clinical trials section
TP53 R175H	None	None	Yes, see clinical trials section
SMAD4 G365fs*19	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 G12R	KRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling promotes cell growth, differentiation, and survival by activating the RAF/MEK/ERK, PI3K, and other pathways[1]. KRAS is one of the most commonly mutated genes in human malignancies, with particularly high incidences in pancreatic, colorectal, and lung cancers[2,3,4]. KRAS missense mutations affecting amino acids G12, G13, A59, Q61, and A146 of the KRAS protein have been characterized to be activating and oncogenic[1,5,6,7,8,9,10,11,12,13,14,15]. KRAS mutations have been reported in 70% of pancreatic ductal adenocarcinomas (COSMIC, Oct 2014). In the pancreatic adenocarcinoma TCGA dataset, KRAS mutations have been found in 63% of cases (cBioPortal, Oct 2014). In the literature, activating KRAS mutation has been reported in more than 80% of pancreatic adenocarcinomas, with the majority of mutations found at codon 12[3,16,17,18]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[16]. Constitutive activation of KRAS activates the RAF/MEK/ERK pathway, leading to tumorigenesis[1,19], 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[20]. The MEK inhibitor trametinib is FDA approved as both a single agent and in combination with dabrafenib for the treatment of melanoma and is being studied in clinical trials in solid tumors[21]. A preclinical study reported that pancreatic cancer cell lines with the KRAS G12V mutation specifically are much more resistant to MEK inhibitors than cells with wild type KRAS or other KRAS mutations[22]. Other preclinical studies have suggested that antitumorigenic effects of MEK inhibitors in models of pancreatic cancer are significantly improved by combination with PI3K-Akt pathway inhibitors, CDK4/6 inhibitors, or anti-EGFR and anti-HER2 antibodies; the synergistic effects were observed in both KRAS mutant and KRAS wild type tumors[23,24,25,26]. The reovirus Reolysin targets cells with activated RAS signaling[27,28,29] 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[30,31,32,33,34,35,36,37,38]. KRAS mutation status may predict lack of response to EGFR-targeted therapies such as erlotinib, gefitinib, cetuximab, and panitumumab in non-small-cell lung cancer (NSCLC) and colon cancer[39,40,41,42,43]. However, a retrospective analysis of a Phase 3 study examining pancreatic cancer patients treated with erlotinib and chemotherapy found that KRAS mutation was not associated with objective response but was significantly associated with decreased overall survival[44].
NTRK1 A5T	NTRK1 encodes the receptor tyrosine kinase TrkA, which plays a role in the development of the nervous system by regulating cell proliferation, differentiation, and survival of neurons. TrkA is activated upon binding of its ligand NGF to promote several downstream signaling pathways, including the GRB2-Ras-MAPK and NF-KappaB pathways[45,46,47,48]. The NTRK1 mutation observed here has not been characterized and its effect on TrkA function is unknown. However, this mutation has been observed in the context of cancer before, which may indicate biological relevance. NTRK1 mutations have been reported in 0.4-2% of pancreatic carcinomas (COSMIC, cBioPortal, Nov 2014). TrkA has been shown to be expressed in pancreatic carcinoma patients, and TrkA expression is correlated with aggressive disease, poor prognosis, pain, and perineural invasion[49,50]. TrkA expression and activity in pancreatic cancer cell lines was reported to be correlated with resistance to gemcitabine, and NTRK1 knockdown sensitized the cells to gemcitabine treatment[51]. NTRK1 expression was shown to promote the proliferation of pancreatic cancer cells, which could be reduced by ERK inhibitors and 2-deoxy-D-glucose[52]. There are currently no approved therapies targeting NTRK1. Pan-Trk inhibitors, including lestaurtinib (CEP-701) and AZD7451, have been evaluated in clinical trials in several tumor types, and additional studies are in progress in certain cancers[53,54,55]. Crizotinib, a TKI approved for NSCLC, has been reported to be effective in NSCLC cells with activating fusions in NTRK1[56]. However, as the mutation reported here has not been functionally characterized, it is not known whether this therapeutic approach would be relevant.
	Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[57]. TP53 missense mutations located within the DNA-binding domain (DBD;

TP53
R175H

aa 100-300) of the p53 protein, such as the mutation observed here, are thought to dysregulate the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[58,59]. TP53 mutations have been found in approximately 25-65% of pancreatic adenocarcinomas, including 48.6% of pancreas ductal carcinoma cases (COSMIC, cBioPortal, Feb 2015). TP53 mutations are common in pancreatic ductal adenocarcinoma and occur in the process of pancreatic carcinogenesis[60,61]. Studies have found inconsistent results regarding the prognostic significance of p53 expression in pancreatic ductal adenocarcinoma[62,63]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[64,65]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[66] to 1:20,000[67], and in the appropriate clinical context, germline testing of TP53 is recommended. There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the Wee-1 inhibitor MK-1775[68,69], therapies that reactivate mutant p53 such as APR-246[70], or p53 gene therapy and immunotherapeutics such as ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation. 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).

SMAD4
G365fs*19

SMAD4 encodes a transcription factor downstream of TGF-beta[71]. SMAD4, also known as DPC4 or MADH4, was first identified in a screen for tumor suppressors in pancreatic cancer[72]. SMAD4 alterations that result in loss of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320), such as observed here, are predicted to result in a loss of function[73]. SMAD4 mutations have been reported in 17% of pancreatic ductal carcinomas (COSMIC, Oct 2014). Homozygous loss of SMAD4 occurs in up to 55% of pancreatic tumors through a combination of loss of heterozygosity and gene mutation[74]. In one study, SMAD4 mutations were reported in 32% of pancreatic cancers and the presence of a mutation predicted poorer survival[75]. Loss of Smad4 protein expression has been reported in 32-60% of pancreatic ductal adenocarcinoma samples[63,76]. SMAD4 alteration, by mutation or homozygous deletion, as well as loss of Smad4 protein expression, has been found to be associated with poor prognosis in pancreatic ductal adenocarcinoma patients[63,75,77]. Germline mutations of SMAD4 are commonly seen in juvenile polyposis syndrome, which is associated with an increased risk of gastrointestinal cancers[78]. At present, there are no therapies available to address SMAD4 loss or mutation in cancer. Some studies suggest that pancreatic tumors with low Smad4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[79,80].

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
Trametinib	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. Activating KRAS mutations may activate the MAPK pathway and predict sensitivity to inhibitors such as trametinib. A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a breast cancer patient, as well as partial responses in pancreatic and salivary gland cancers. In particular, 3 of 10 patients with measurable pancreatic cancer exhibited partial responses[81]. However, in a Phase 2 study of 160 pancreatic cancer patients, the combination of trametinib with gemcitabine did not result in significant improvement in overall survival (OS), progression-free survival (PFS), or response rate (RR) compared with gemcitabine alone[82]; KRAS mutation status was not associated with overall survival in this study. Furthermore, a Phase 2 study of combination treatment with gemcitabine and refametinib (another MEK inhibitor) in pancreatic cancer reported a trend toward a higher RR (48% vs. 28%), longer PFS (9.0 months vs. 4.6 months) and longer OS (18.2 months vs. 6.6 months) in KRAS-wildtype patients compared to KRAS-mutant patients (Riess et al., 2014; ASCO Abstract 4129, Van Laethem et al., 2014; ASCO Abstract 4025). A Phase 2 trial of combination treatment with the MEK inhibitor selumetinib and the EGFR inhibitor erlotinib reported no responses in 41 pancreatic cancer patients but stable disease (SD) in 21/41 (51%) patients, with adverse events requiring dose reduction in 38% of patients; KRAS mutation status was not assessed (Ko et al., 2013; ASCO Abstract 4014). Similarly, a Phase 1b combination trial of trametinib and the pan-PI3K inhibitor BKM120 showed SD in 12/24 (50%) pancreatic cancer patients, but no responses; although the study recommended a Phase 2 dose, prevalent and often severe adverse effects were reported[83]. 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 the study was unable to identify a recommended Phase 2 dose and schedule for the combination[84].

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 G12R	KRAS-activating mutations may result in activation of downstream pathways, including the MAPK pathway. Therefore, MEK inhibitors may be relevant in a tumor with KRAS mutation. 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", "pancreatic carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Multi-Arm Phase 1 Dose Escalation Study Of The Safety, Pharmacokinetics, And Pharmacodynamics Of The Dual PI3K/mTOR Inhibitors PF-04691502 And PF-05212384 In Combination With Experimental Or Approved Anticancer Agents In Patients With Advanced Cancer	Phase 1	MEK, PI3K, mTOR, TOP1	California, Colorado, South Carolina, Barcelona (Spain), Milano (Italy), Ontario (Canada)	NCT01347866
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, Texas, 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	MEK, ERBB3, EGFR	California, Colorado, Tennessee, Texas, Barcelona (Spain), Madrid (Spain), Valencia (Spain)	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 1b Study of the Safety and Pharmacology of MPDL3280A Administered With Cobimetinib in Patients With Locally Advanced or Metastatic Solid Tumors	Phase 1	MEK, PD-L1	Colorado, Connecticut, Massachusetts, New York, North Carolina, Tennessee, Texas, Washington, multiple ex-US locations	NCT01988896

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CLINICAL TRIALS TO CONSIDER (CONT.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
NTRK1 A5T	Tumors with activating mutation in NTRK1 may be sensitive to Trk inhibitors, such as lestaurtinib (CEP-701), AZD7451, and crizotinib. However, as the mutation reported here has not been functionally characterized, it is not known whether this therapeutic approach would be relevant. 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 "Trk", "lestaurtinib", "AZD7451", "crizotinib", "pancreatic carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I/IIa Open-Label, Dose Escalation and Cohort Expansion Trial of Oral TSR-011 in Patients With Advanced Solid Tumors and Lymphomas	Phase 1/Phase 2	TrkA, TrkB, TrkC	Arizona, California, Tennessee, Washington, London (United Kingdom)	NCT02048488
A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX7486 as a Single Agent and in Combination With Gemcitabine and Nab-Paclitaxel in Patients With Advanced Solid Tumors	Phase 1	CSF1R, TrkA, TrkB, TrkC	Arizona, California, South Carolina	NCT01804530
A Phase I Trial of Dasatinib in Combination With Crizotinib in Patients With Advanced Malignancies	Phase 1	BCR-ABL, BTK, CSF1R, EphA2, KIT, PDGFRs, SRC, LYN, MET, ALK, ROS1, RON, NTRKs	Texas	NCT01744652
A Phase 1/1b Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies	Phase 1	MET, AXL, RET, TRK, DDR2, KDR, PDGFRA, KIT	Massachusetts, Missouri, New York, Tennessee	NCT02219711

CLINICAL TRIALS TO CONSIDER (CONT.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
TP53 R175H	Tumors with TP53 loss of function alterations may be sensitive to Wee-1 inhibitors, therapies that reactivate mutant p53, or p53 gene therapy and immunotherapeutics. 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 "p53", "AZD1775", "MK1775", "Wee1", "APR-246", "kevetrin", "ALT-801", "pancreatic carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1, Open-Label, Dose-Escalation, Safety, Pharmacokinetic and Pharmacodynamic Study of Kevetrin (Thioureidobutyronitrile) Administered Intravenously, in Patients With Advanced Solid Tumors	Phase 1	MDM2, p53	Massachusetts	NCT01664000
Phase 1 DOSE ESCALATION TRIAL OF THE Wee1 INHIBITOR MK1775, IN COMBINATION WITH GEMCITABINE (+RADIATION) FOR PATIENTS WITH UNRESECTABLE ADENOCARCINOMA OF THE PANCREAS	Phase 1/Phase 2	Wee-1	Michigan	NCT02037230

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.

AR	***ATR***	***JAK3***	***SPOP***
E238V	S1142G	A797V	N244S

STAG2
T601I

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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 236 genes as well as 47 introns of 19 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

ABL1	*BARD1*	*CD79A*	*CSF1R*	*EZH2*	*FGFR2*	*HRAS*	*KEAP1*	*MLL2*	*NRAS*	*PRKDC*	*SMARCB1*	*TSC2*
AKT1	*BCL2*	*CD79B*	*CTCF*	*FAM123B (WTX)*	*FGFR3*	*IDH1*	*KIT*	*MPL*	*NTRK1*	*PTCH1*	*SMO*	*TSHR*
AKT2	*BCL2L2*	*CDC73*	*CTNNA1*	*FAM46C*	*FGFR4*	*IDH2*	*KLHL6*	*MRE11A*	*NTRK2*	*PTEN*	*SOCS1*	*VHL*
AKT3	*BCL6*	*CDH1*	*CTNNB1*	*FANCA*	*FLT1*	*IGF1R*	*KRAS*	*MSH2*	*NTRK3*	*PTPN11*	*SOX10*	*WISP3*
ALK	*BCOR*	*CDK12*	*DAXX*	*FANCC*	*FLT3*	*IKBKE*	*LRP1B*	*MSH6*	*NUP93*	*RAD50*	*SOX2*	*WT1*
APC	*BCORL1*	*CDK4*	*DDR2*	*FANCD2*	*FLT4*	*IKZF1*	*MAP2K1*	*MTOR*	*PAK3*	*RAD51*	*SPEN*	*XPO1*
AR	*BLM*	*CDK6*	*DNMT3A*	*FANCE*	*FOXL2*	*IL7R*	*MAP2K2*	*MUTYH*	*PALB2*	*RAF1*	*SPOP*	*ZNF217*
ARAF	*BRAF*	*CDK8*	*DOT1L*	*FANCF*	*GATA1*	*INHBA*	*MAP2K4*	*MYC*	*PAX5*	*RARA*	*SRC*	*ZNF703*
ARFRP1	*BRCA1*	*CDKN1B*	*EGFR*	*FANCG*	*GATA2*	*IRF4*	*MAP3K1*	*MYCL1*	*PBRM1*	*RB1*	*STAG2*	
ARID1A	*BRCA2*	*CDKN2A*	*EMSY (C11orf30)*	*FANCL*	*GATA3*	*IRS2*	*MCL1*	*MYCN*	*PDGFRA*	*RET*	*STAT4*	
ARID2	*BRIP1*	*CDKN2B*	*EP300*	*FBXW7*	*GID4 (C17orf39)*	*JAK1*	*MDM2*	*MYD88*	*PDGFRB*	*RICTOR*	*STK11*	
ASXL1	*BTK*	*CDKN2C*	*EPHA3*	*FGF10*	*GNA11*	*JAK2*	*MDM4*	*NF1*	*PDK1*	*RNF43*	*SUFU*	
ATM	*CARD11*	*CEBPA*	*EPHA5*	*FGF14*	*GNA13*	*JAK3*	*MED12*	*NF2*	*PIK3CA*	*RPTOR*	*TET2*	
ATR	*CBFB*	*CHEK1*	*EPHB1*	*FGF19*	*GNAQ*	*JUN*	*MEF2B*	*NFE2L2*	*PIK3CG*	*RUNX1*	*TGFBR2*	
ATRX	*CBL*	*CHEK2*	*ERBB2*	*FGF23*	*GNAS*	*KAT6A (MYST3)*	*MEN1*	*NFKBIA*	*PIK3R1*	*SETD2*	*TNFAIP3*	
AURKA	*CCND1*	*CIC*	*ERBB3*	*FGF3*	*GPR124*	*KDM5A*	*MET*	*NKX2-1*	*PIK3R2*	*SF3B1*	*TNFRSF14*	
AURKB	*CCND2*	*CREBBP*	*ERBB4*	*FGF4*	*GRIN2A*	*KDM5C*	*MITF*	*NOTCH1*	*PPP2R1A*	*SMAD2*	*TOP1*	
AXL	*CCND3*	*CRKL*	*ERG*	*FGF6*	*GSK3B*	*KDM6A*	*MLH1*	*NOTCH2*	*PRDM1*	*SMAD4*	*TP53*	
BAP1	*CCNE1*	*CRLF2*	*ESR1*	*FGFR1*	*HGF*	*KDR*	*MLL*	*NPM1*	*PRKAR1A*	*SMARCA4*	*TSC1*	

Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*EGFR*	*ETV1*	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*MLL*	*MYC*	*NTRK1*
PDGFRA	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*							

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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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