FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Not Given	**20 August 2014**	**Lung adenocarcinoma**

Date of Birth	Not Given	**Medical Facility**	Not Given	**Specimen Received**	Not Given
Sex	Not Given	**Ordering Physician**	Not Given	**Specimen Site**	Not Given
FMI Case #	11	**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 Given		

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

All Report Updates

Amended Report 10/02/2015
This Amended Report has been issued to report the MET splice site variant, which was initially listed as a variant of unknown significance, and to list relevant therapies and clinical trials.

PATIENT RESULTS

4 genomic alterations

2 therapies associated with potential clinical benefit

0 therapies associated with lack of response

15 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†
MET exon 14 splice site (3028+2T>A)
CDKN2A/B loss
MDM2 amplification
MYST3 amplification

Additional Disease-relevant Genes with No Reportable Alterations Identified†
ALK
KRAS
EGFR
RET
ERBB2
BRAF

† 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
MET exon 14 splice site (3028+2T>A)	Crizotinib	Cabozantinib	Yes, see clinical trials section
CDKN2A/B loss	None	None	Yes, see clinical trials section
MDM2 amplification	None	None	Yes, see clinical trials section

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MYST3 amplification	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

MET
exon 14 splice site (3028+2T>A)

Gene and Alteration: MET, also known as hepatocyte growth factor receptor (HGFR) or c-MET, encodes a receptor tyrosine kinase that is activated by the ligand HGF; MET activation results in signaling mediated in part through the RAS-RAF-MEK and PI3K pathways to promote proliferation[1]. MET alterations predicted to affect exon 14 splicing, such as seen here, have been reported in 1-4% of lung tumors[2,3,4,5,6] and have been associated with skipping of exon 14[5,7,8,9]. Loss of exon 14 increases MET stability, leading to prolonged signaling upon HGF stimulation and increased oncogenic potential[7,10,11,12,13]. This mutation is therefore expected to be activating. Responses to various MET inhibitors have been reported for multiple patients with alterations in their tumors predicted to affect splicing of MET exon 14 [2,9,14,15,16].

Frequency and Prognosis: In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in ~3% of samples[2]. In the TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[3,17]. MET amplification has been reported at incidences of 14-48% in NSCLC and correlated with increased MET protein expression[18,19,20,21,22,23]. Studies into the effect of MET amplification on prognosis for patients with NSCLC have yielded conflicting results[18,22,24,25,26]. One study observed an association between MET amplification and increased long-term survival for patients with lung adenocarcinoma, although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[27,28].

Potential Treatment Strategies: MET amplification or activating mutations may predict sensitivity to targeted therapies[29] such as the kinase inhibitors crizotinib and cabozantinib. Crizotinib is FDA approved for the treatment of ALK-positive NSCLC[30]. Cabozantinib is FDA approved for the treatment of metastatic medullary thyroid cancer[31], and a patient with a MET amplification and a mutation associated with MET exon 14 skipping has achieved a complete response to cabozantinib[9]. Crizotinib has benefited patients with MET-amplified NSCLC[32], lung squamous cell carcinoma[33], lung adenocarcinoma[34], gastroesophageal cancer[35], glioblastoma[36], and carcinoma of unknown primary[37]. In one clinical trial, treatment with AMG 337 led to a response rate of 50% (5/10), including 1 complete response, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer (Kwak et al., 2015; ASCO GI Abstract 01). MET-targeting antibodies onartuzumab and MetMAb have elicited responses in patients with MET-amplified NSCLC[23] and gastric cancer[38]. In addition, high MET expression has been suggested to predict patient response to therapy regimens involving rilotumumab, a monoclonal HGF-targeting antibody (Oliner et al., 2012; ASCO Abstract 4005). Furthermore, MET inhibitors crizotinib, capmatinib, PF-04217903, and foretinib have provided benefit to patients with MET-mutated papillary renal cell carcinoma[39,40,41], histiocytic sarcoma[2], lung adenocarcinoma[9,14,15], lung large cell carcinoma[2], and lung squamous cell carcinoma[2,16].

CDKN2A/B
loss

Gene and Alteration: CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[42,43]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, maintaining the growth-suppressive activity of the RB tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin D-RB pathway and loss of cell cycle control[44,45]. The p14ARF tumor-suppressive

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functions involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[46,47]. This alteration is predicted to result in loss of function of p16INK4a[48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68] and p14ARF[52,69,70,71]. The CDKN2B alteration is predicted to inactivate p15INK4b.

Frequency and Prognosis: CDKN2A/B loss and mutation have been reported in 19% and 4% of lung adenocarcinomas, respectively[3]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-43% of NSCLC samples[44,72,73,74,75]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[72,76,77,78]. However, one study has reported that expression of p14ARF correlated with worse prognosis in patients with lung adenocarcinoma[79].

Potential Treatment Strategies: Preclinical data suggest that tumors with loss of p16INK4a or p15INK4b function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and the FDA-approved inhibitor palbociclib[80,81,82,83]. However, multiple clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents (Gopalan et al., 2014; ASCO Abstract 8077)[84,85,86], and it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[87,88], the clinical relevance of p14ARF as a predictive biomarker is not clear.

MDM2
amplification

Gene and Alteration: MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of Mdm2 may be oncogenic[89,90]. MDM2 has been reported to be amplified in cancer[91] and may be biologically relevant in this context[92,93].

Frequency and Prognosis: Amplification of MDM2 has been reported in 8% of cases in the Lung Adenocarcinoma TCGA dataset[3]. Separate studies have reported similar incidences of 6-7% in non-small cell lung cancer (NSCLC), mainly in patients with adenocarcinoma, but a higher incidence of 21% has also been observed, with amplification found in various NSCLC subtypes[94,95,96]. The role of MDM2 expression/amplification as a prognostic marker is complex, with some studies showing a negative and others a positive effect on survival in patients with NSCLC[94,96,97,98].

Potential Treatment Strategies: MDM2 antagonists disrupt the MDM2-p53 interaction, leading to the stabilization of p53[99]. Preclinical studies have suggested that amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[88,100]. Multiple MDM2 antagonists are under investigation in clinical trials (Beryozkina et al., 2011; ASCO Abstract 3039, Siu et al., 2014; ASCO Abstract 2535).

MYST3
amplification

Gene and Alteration: MYST3 (also referred to as KAT6A) encodes a histone lysine acetyltransferase protein known most commonly as MOZ[101]. MYST3 was identified as the chromosome 8 gene interrupted by the recurrent t(8;16)(p11;p13) rearrangement associated with the M4 and M5 subtypes of acute myeloid leukemia (AML). The MYST3/MOZ fusion partner on chromosome 16 is the CREB-binding protein locus CBP; the resulting fusion protein may exert its oncogenic effect by interfering with the normal function of transcription factors including nuclear receptors and Runx proteins[102]. Less frequently, AML may be characterized by chromosome 8 inversions (p11q13) that result in a fusion between MYST3/MOZ and NCOA2/TIF2, which encodes a nuclear receptor co-activator[103].

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Frequency and Prognosis: Somatic sequence alterations, primarily missense substitutions, in MYST3 have been observed at low frequency in a range of solid tumors (COSMIC, 2015), but the functional impact of these alterations remains uncharacterized.

Potential Treatment Strategies: There are no targeted therapies available to address genomic alterations in MYST3.

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THERAPIES

FDA APPROVED THERAPIES IN PATIENT TUMOR TYPE	
THERAPY	**SUMMARY OF DATA IN PATIENT TUMOR TYPE**
Crizotinib	**Approved Indications:** Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements as detected by an FDA-approved test. **Gene Association:** Activating MET alterations may confer sensitivity to crizotinib. Crizotinib has benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[2,9,14,15,16]. **Supporting Data:** Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[30], ROS1 rearrangements[104], or MET activation[2,9,14,15,16,32]. Crizotinib has benefited patients with METamplified NSCLC[32], lung squamous cell carcinoma[33], and lung adenocarcinoma[34] and achieved partial responses for three patients with lung adenocarcinomas and MET exon 14 splice site alterations[9].

ADDITIONAL THERAPIES – FDA APPROVED IN OTHER TUMOR TYPES	
THERAPY	**SUMMARY OF DATA IN OTHER TUMOR TYPE**
Cabozantinib	**Approved Indications:** Cabozantinib is a kinase inhibitor that targets MET, RET, VEGFRs, KIT, FLT-3, TIE-2, AXL, and TRKB. It is FDA approved for the treatment of medullary thyroid cancer. **Gene Association:** Alterations that are expected to increase signaling through these kinases, in particular MET, RET, and VEGFR-2, may predict sensitivity to treatment with cabozantinib. A patient with a MET amplification and a mutation associated with MET exon 14 skipping has achieved a complete response to cabozantinib[9]. **Supporting Data:** A preclinical study in mouse models of multiple tumor types, including lung cancer, reported that cabozantinib treatment resulted in decreased cell proliferation and tumor growth as well as increased apoptosis[105]. A Phase 2 randomized discontinuation trial of cabozantinib in metastatic nonsmall cell lung cancer (NSCLC) reported a 64% rate of tumor regression in heavily pretreated patients, with a safety profile similar to that of other tyrosine kinase inhibitors (Hellerstedt et al., 2012; ASCO Abstract 7514). Preclinical studies have shown that lung cancer cells with dual EGFR and MET activation respond to combination treatment with EGFR inhibitors and MET inhibitors[106,107], and clinical trials investigating this combination are under way in NSCLC. A Phase 2 randomized trial of cabozantinib, erlotinib, or a combination in patients with EGFR-wild-type NSCLC reported improved PFS (3.9 months vs. 1.9 months on erlotinib alone, HR 0.33, p = 0.0002) and OS (HR 0.50, p = 0.02) for cabozantinib treatment compared to erlotinib, although MET expression did not correlate with response (Neal et al., 2015; ASCO Abstract 8003). As part of an ongoing Phase 2 study of cabozantinib for the treatment of NSCLC, 3 partial responses and two instances of stable disease have been achieved by patients with RET rearrangements in their tumors[108,109].

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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
● ***MET*** exon 14 splice site (3028+2T>A)	MET amplification or activating mutations may confer sensitivity to therapies targeting this kinase. 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 "MET", "crizotinib", "cabozantinib", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of PF-02341066, A c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer	Phase 1	MET	California, Colorado, Illinois, Massachusetts, Michigan, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Seoul (Korea, Republic of), Victoria (Australia)	NCT00585195
Phase I Study of INC280 Plus Erlotinib in Patients With C-Met Expressing Non-Small Cell Lung Cancer	Phase 1	MET, EGFR	California	NCT01911507
A Phase I Open-label Dose Escalation Study With Expansion to Assess the Safety and Tolerability of INC280 in Patients With c-MET Dependent Advanced Solid Tumors	Phase 1	MET	Arkansas, Illinois, Maryland, Michigan, New York, Tennessee, Texas, Utah, multiple ex-US locations	NCT01324479
Open-Label Dose-Escalation Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Daily Oral MGCD265 Administered Without Interruption to Subjects With Advanced Malignancies	Phase 1	AXL, DDR2, EPH, FLT1, KDR, KIT, MET, PDGFRs, RET, TRK, VEGFRs	California, Illinois, Massachusetts, Missouri, New York, North Carolina, Pennsylvania, Texas, Utah, Washington, Alberta (Canada), British Columbia (Canada), Gyeonggi-do (Korea, Republic of), Quebec (Canada), Seoul (Korea, Republic of)	NCT00697632
A Phase II, Multicenter, Open-label Study of EGF816 in Combination With Nivolumab in Adult Patients With EGFR Mutated Non-small Cell Lung Cancer and of INC280 in Combination With Nivolumab in Adult Patients With cMet Positive Non-small Cell Lung Cancer	Phase 2	MET, EGFR, PD-1	Amsterdam (Netherlands), Chur (Switzerland), New South Wales (Australia), PG (Italy), PI (Italy), PN (Italy), Queensland (Australia), Singapore (Singapore), South Australia (Australia)	NCT02323126

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CLINICAL TRIALS TO CONSIDER (CONT.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
CDKN2A/B loss	Tumors with p16INK4a or p15INK4b inactivation and intact RB1 may be sensitive to CDK4/6 inhibitors. 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 "CDK4", "CDK6", "PD 0332991", "LEE011", "LY2835219", "palbociclib", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A phase1 Multi-center, Open Label, Dose-escalation Study of Oral LEE011 in Patients With Advanced Solid Tumors or Lymphoma	Phase 1	CDK4, CDK6	Massachusetts, Michigan, New York	NCT01237236
A Phase I Study of the CDK4/6 Inhibitor PD-0332991, 5-Fluorouracil, and Oxaliplatin in Patients With Advanced Solid Tumor Malignancies	Phase 1	CDK4, CDK6	District of Columbia	NCT01522989
A Phase 1b Study of LY2835219 in Combination With Multiple Single Agent Options for Patients With Stage IV NSCLC	Phase 1	CDK4, CDK6, MEK, KDR, mTOR, PI3K	Arkansas, California, Indiana, New Jersey, New Mexico, North Carolina, Tennessee, Madrid (Spain), Majadahonda (Spain), Sevilla (Spain)	NCT02079636
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
Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module 8 - LEE011 for Patients With CDK4/6 Pathway Activated Tumors	Phase 2	CDK4, CDK6	Alaska, Arizona, California, Colorado, Connecticut, Indiana, Maryland, Missouri, New Mexico, North Carolina, Ohio, Oregon, Rhode Island, South Dakota, Tennessee, Texas, Utah, Virginia, Washington, Wisconsin	NCT02187783
A Phase I Study of CDK4/6 Inhibitor LEE011 Combined With Gemcitabine in Patients With Advanced Solid Tumors or Lymphoma	Phase 1	CDK4, CDK6	New York	NCT02414724

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CLINICAL TRIALS TO CONSIDER (CONT.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
MDM2 amplification	MDM2 overexpression or amplification in the context of wild-type p53 may increase sensitivity to inhibitors of the MDM2-p53 interaction. 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 "MDM2", "CGM097", "DS-3032b", "RO5503781", "RO6839921", "nutlin", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I, Open-label, Multi-center, Dose Escalation Study of Oral CGM097, a p53/HDM2-interaction Inhibitor, in Adult Patients With Selected Advanced Solid Tumors	Phase 1	MDM2	Massachusetts, Essen (Germany), Köln (Germany), Lyon Cedex (France), Singapore (Singapore), Zürich (Switzerland)	NCT01760525
A Phase 1 Multiple Ascending Dose Study of DS-3032b, an Oral MDM2 Inhibitor, in Subjects With Advanced Solid Tumors or Lymphomas	Phase 1	MDM2	Michigan, New York, Tennessee, Texas	NCT01877382
A Multi-Center, Open-Label, First-in-Human, Phase I Dose-Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO6839921, An MDM2 Antagonist, Following Intravenous Administration in Patients With Advanced Malignancies, Including Acute Myeloid Leukemia (AML)	Phase 1	MDM2	Colorado, Missouri, South Carolina, Ontario (Canada), Quebec (Canada)	NCT02098967
A Phase I, Open Label, Multicenter, Dose-escalation Study of HDM201 in Adult Patients With Advanced Solid and Hematological Tumors Characterized by Wild-type TP53	Phase 1	MDM2	New York, Amsterdam (Netherlands), Catalunya (Spain), Essen (Germany), Lyon Cedex (France), Singapore (Singapore), Taiwan ROC (Taiwan), Tokyo (Japan), Utrecht (Netherlands), Würzburg (Germany)	NCT02143635

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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.

ATM D1099N	***CDH1*** D433G	***FANCA*** S1061G	***FLT3*** A80D
FLT4 E1336K	***KDM5C*** S741C	***MYST3*** K656E	***PRKDC*** Q3148E
TET2 G1160E			

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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).

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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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