FOUNDATIONONE

Patient Name	Report Date	Tumor Type
		Lung adenocarcinoma

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

ABOUT THE TEST:

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

PATIENT RESULTS

2 genomic findings

2 therapies associated with potential clinical benefit

0 therapies associated with lack of response

5 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alteration Identified†

ROS1 CD74-ROS1 fusion

Additional Findings†

Tumor Mutation Burden TMB-Low; 0.80 Muts/Mb

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

INFORMATION REGARDING PHARMACEUTICAL PRODUCTS AND CLINICAL TRIALS

Genomic Findings Detected	Therapies available in Germany (in patient's tumor type)	Therapies available in Germany (in another tumor type)	Potential Clinical Trials
ROS1 CD74-ROS1 fusion	Ceritinib Crizotinib	None	Yes, see clinical trials section
Tumor Mutation Burden TMB-Low; 0.80 Muts/Mb	None	None	None

IMPORTANT: Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities); 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. This report includes scientific information. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies and clinical trials contained in this report, should not be used as the single basis for the therapy decision. The report should only be regarded and used as a supplementing source of information: All treatment decisions remain the full and final responsibility of the respective treating physician. For various reasons further explained below, both the therapies and the clinical trials listed in this report may not be complete and exhaustive.

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
ROS1 CD74-ROS1 fusion	**Gene and Alteration:** The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[1]. ROS1 is commonly involved in chromosomal rearrangements that lead to the expression of strongly oncogenic chimeric fusion proteins, such as observed here[2,3,4]. CD74-ROS1 fusions are found in both lung adenocarcinoma and lung squamous cell carcinoma samples[3,4,5,6] and have been reported to be oncogenic[3,4,7]. **Frequency and Prognosis:** ROS1 rearrangements or fusions have been reported in 1-2% of non-small cell lung carcinoma (NSCLC) tumors[2,3,4,8], including in 1-3.4% of lung adenocarcinoma cases[4,5,9,10,11]. CD74-ROS1 fusions accounted for 23% (3/13) to 27% (5/18) of the ROS1 rearrangements identified in two studies of lung cancer[3,5]. In the Lung Adenocarcinoma TCGA dataset, ROS1 point mutations have been detected in 3.5% of cases, whereas ROS1 amplification was not identified[12]. Elevated ROS1 protein levels have been observed in 22% of NSCLC samples evaluated in one study[6]. A study of 1,137 patients with lung adenocarcinoma showed that Stage 4 patients with ROS1 rearrangement had significantly better overall survival (OS) compared to other genetically defined Stage 4 subgroups, with an estimated mean OS of 5.3 years for patients who were treated with chemotherapy and crizotinib[8]. Positive kinase fusion status (ALK, ROS1, or RET) was associated with improved prognosis in lung adenocarcinoma, independently of other prognostic factors[3], although never-smokers with surgically resected lung adenocarcinoma and ALK or ROS1 fusion had significantly shorter disease-free survival (hazard ratio, 2.11)[11]. A study of 208 never-smokers observed an improved objective response rate and longer median progression-free survival (PFS) for ROS-fusion-positive patients treated with pemetrexed but a reduced PFS for ROS1-positive patients treated with EGFR-targeted kinase inhibitors[10]. **Potential Treatment Strategies:** Patients with ROS1 activating rearrangements may benefit from treatment with tyrosine kinase inhibitors with activity against ROS1, such as the approved therapies crizotinib (Moro-Sibilot et al., 2015; ASCO Abstract 8065)[4,5,7,13,14,15,16] and ceritinib[17,18,19,20]. Crizotinib has shown clinical efficacy in ROS1-rearranged non-small cell lung cancer (NSCLC)[8,13,21]. Ceritinib achieved a partial response for a patient with ROS1-rearranged NSCLC[17]; preclinical data support the sensitivity of ROS1 fusion-positive tumors to certinib[18,19,20]. Crizotinib, ceritinib, and other ROS1-targeted therapies, including AZD3463, brigatinib, cabozantinib, DS-6051-b, entrectinib, foretinib, and PF-06463922, are being investigated in clinical trials[2].
Tumor Mutation Burden TMB-Low; 0.80 Muts/Mb	**Gene and Alteration:** Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[22,23] and cigarette smoke in lung cancer[24,25], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[26,27,28,29,30], and microsatellite instability (MSI)[26,29,30]. The tumor seen here harbors a low TMB. Compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[31], anti-PD-L1 therapy in urothelial carcinoma[32], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[25,33].

GENE ALTERATION	INTERPRETATION

Frequency and Prognosis: Low TMB is observed more commonly in non-small cell lung carcinomas (NSCLC) harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are observed in approximately half of intermediate-high TMB cases (Spigel et al., 2016; ASCO Abstract 9017). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC (Schwartz et al., 2016; ASCO Abstract 8533)[34,35], several other large studies did find a strong association with increased TMB[36,37,38,39]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median overall survival (OS) for tumors with a higher number of mutations in a limited gene set compared with lower mutation number (48.4 vs. 61.0 months)[34].

Potential Treatment Strategies: On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[31], anti-PD-L1[32], and anti-PD-1 therapies[25,33]; FDA-approved agents include ipilimumab, atezolizumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[25]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab[25,33]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[40] or nivolumab[41] and two patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[42]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[31,43] and anti-PD-1 treatment (Johnson et al., 2016; ASCO Abstract 105). For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (mut) per megabase (Mb)] compared to nonresponders (6.4 mut/Mb)[32].

THERAPIES

THERAPIES AVAILABLE IN GERMANY IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Ceritinib	**Approved Indications:** Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is available in Germany to treat advanced ALK-positive non-small cell lung carcinoma (NSCLC) after previous crizotinib therapy. **Gene Association:** Activation of ROS1 may predict sensitivity to ceritinib[17,18,19,20]. **Supporting Data:** A Phase 3 study of ceritinib in ALK inhibitor naïve-patients with ALK-rearranged NSCLC observed a whole-body (WB) objective response rate (ORR) of 63.7%, a WB disease control rate (DCR) of 89.5%, and progression-free survival (PFS) of 11.1 months (Felip et al., 2015; ASCO Abstract 8060). Following progression on prior chemotherapy and crizotinib, patients with ALK-rearranged NSCLC achieved a WB ORR of 38.6%, WB DCR of 77.1%, and PFS of 5.4 months on ceritinib (Mok et al., 2015; ASCO Abstract 8059). A Phase 1 study of ceritinib reported a 58% response rate in 114 patients with ALK-rearranged NSCLC and a response rate of 56% in 80 of these patients who had previously been treated with crizotinib[44]. In preclinical studies, crizotinib-resistant cell lines, with and without secondary ALK mutations, demonstrated sensitivity to ceritinib (Anjum et al., 2013; ANE Abstract A98)[45].
Crizotinib	**Approved Indications:** Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is available in Germany to treat ALK-positive advanced non-small cell lung cancer (NSCLC). **Gene Association:** Crizotinib has shown clinical and preclinical evidence of activity in ROS1-rearranged NSCLC (Ou et al., 2013; ASCO Abstract 8032, Mazieres et al. 2014; ASCO Abstract 11035)[4,5,13,14,15]. **Supporting Data:** Patients with ROS1-rearranged metastatic NSCLC treated with crizotinib achieved an objective response rate (ORR) of 72% (36/50), with 3 complete responses and 33 partial responses; the median progression-free survival (PFS) was 19.2 months, and the median response duration was 17.6 months[13]. Preliminary Phase 2 data confirm a high ORR to crizotinib in ROS1-rearranged NSCLC (Moro-Sibilot et al., 2015; ASCO Abstract 8065). In retrospective studies, crizotinib therapy was associated with an ORR of 80% (24/30) or higher (5/5) and a median PFS of 9.1 months for patients with ROS1-rearranged advanced lung adenocarcinoma[8](Mazieres et al. 2015; 25667280). Crizotinib has also demonstrated efficacy in patients with NSCLC and ALK rearrangements[46], an NTRK1 fusion[47], or MET activation[48,49,50,51,52,53].

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

IMPORTANT: Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities), however the agents listed in this report may have little or no evidence in the patient's tumor type. In addition, the above list is not meant to be a complete and exhaustive list of available therapies. The therapies listed in this report are limited to pharmaceutical drug products and the therapies listed may not be a complete and exhaustive list of available pharmaceutical drug products. This report does not include medical devices, which may be approved for treatment in the particular patient indication. In addition, there may be therapies available which are neither a pharmaceutical product nor a medical device, e.g. rather a treatment method, surgical procedure or a cell therapy and similar methods which may not be subject to approval by the applicable regulatory authorities. There may be pharmaceutical products available which are not authorized by certain applicable regulatory authorities. The therapies approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities) in other tumor types listed in this report may not be complete and exhaustive because these may not be linked to a specific gene defect or because they were only authorized for other indications. The basis for the search of approved drugs may not be up-to date or may not be accurate. In addition, search errors when searching the therapies

cannot be ruled out completely. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies contained in this report, should not be used as the single basis for the therapy decision. The description of the approved indication in this report is a summary and does not include the exact wording of the approved indication. It is the responsibility of the treating physicians to check the exact indication of any approved label/SmPC/prescribing information for any therapy available in the respective country.

CLINICAL TRIALS TO CONSIDER

IMPORTANT: The clinical trials to consider listed in this report may not be complete and exhaustive or may include trials in which the patient cannot participate. Please keep in mind that the information available in the public domain is continuously updated and should be investigated by the physician or research staff. There may also be compassionate use programs where patients could be included, and these programs are not listed in this report. The clinical trial information may not be up to date or may not be accurate. In addition, search errors when searching the clinical trials cannot be ruled out completely.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***ROS1*** CD74-ROS1 fusion	Activating ROS1 fusions may predict sensitivity to inhibitors of ROS1. 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 "ROS1", "crizotinib", "ceritinib", "cabozantinib", "AP26113", "LDK378", "PF-06463922", "LY2801653", "lung adenocarcinoma", and/or "solid tumor".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements	Phase 2	ALK, ROS1, TRKA, TRKB, TRKC	Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming, (Australia), (Belgium), (France), (Italy), (Korea, Republic of), (Singapore), (Taiwan), (United Kingdom)	NCT02568267
Crizotinib in Pretreated Metastatic Non-small-cell Lung Cancer With MET Amplification or ROS1 Translocation (METROS)	Phase 2	ALK, MET, ROS1, RON	(Italy)	NCT02499614
A Phase 1/2a, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations	Phase 1	ALK, ROS1, TRKA, TRKB, TRKC	California, Colorado, District of Columbia, Florida, Massachusetts, New York, Tennessee, Texas, (Korea, Republic of), (Spain)	NCT02097810
National Lung Matrix Trial: Multi-drug, Genetic Marker-directed, Non-comparative, Multi-	Phase 2	ALK, MET, ROS1, RON,	(United Kingdom)	NCT02664935

centre, Multi-arm Phase II Trial in Non-small Cell Lung Cancer		FGFR, FGFR2, FGFR3, FGFR4, CDK4, CDK6, ERK, MEK, mTOR, AKT, EGFR, PD-L1		
Phase 1/2 Study Of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) In Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations	Phase 1/Phase 2	ALK, ROS1	Arkansas, California, Colorado, Connecticut, District of Columbia, Florida, Massachusetts, Michigan, Missouri, New York, Ohio, Pennsylvania, Tennessee, (Australia), (Belgium), (Canada), (France), (Germany), (Hong Kong), (Italy), (Japan), (Korea, Republic of), (Singapore), (Spain), (Switzerland), (Taiwan)	NCT01970865

APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

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

CIC	***FANCA***	***Microsatellite status***
S1159Y	P1164S	MSI-Ambiguous

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.

DNA Gene List: Entire Coding Sequence for the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

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

DNA Gene List: For the Detection of Select Rearrangements

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

Additional Assays: For the Detection of Select Cancer Biomarkers

Microsatellite status

Tumor Mutation Burden

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	>99.0% (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)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Sensitivity: Microsatellite status	At ≥20% tumor nuclei	97.0% (CI* 89.6%-99.6%)
Specificity: all variant types	Positive Predictive Value (PPV)	>99.0%
Specificity: Microsatellite status	Positive Predictive Value (PPV)	>95.0%
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision 95.8% microsatellite status precision 96.4% tumor mutation burden 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 rearrangement 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 rearrangement 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).

Microsatellite status (a measure of microsatellite instability, or "MSI") is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne test. Microsatellite status is assayed for all FoundationOne samples. MSI-High results are reported in all tumor types. In select tumor types, other Microsatellite status results may be reported (MS-Stable, MSI-Ambiguous, MSI-Unknown) when relevant. Microsatellite status result may be reported as "Unknown" if the sample is not of sufficient quality to confidently determine Microsatellite status.

Tumor Mutation Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne and FoundationOne Heme tests and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne and FoundationOne Heme samples. TMB-High results are reported in all tumor types. In select tumor types, other TMB results may be reported (TMB-Intermediate, TMB-Low, TMB-Unknown) when relevant. TMB results are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to less than or equal to 5 Muts/Mb. Tumor Mutation Burden may be reported as "Unknown" if the sample is not of sufficient quality to confidently determine Tumor Mutation Burden.

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

APPENDIX

REFERENCES

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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: subclonal 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