ABOUT THE TEST FoundationOne®Liquid is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating tumor DNA.

PATIENT

DISEASE Lung cancer (NOS)
NAME
DATE OF BIRTH
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID
SPECIMEN TYPE Blood
DATE OF COLLECTION
SPECIMEN RECEIVED
MEDIAN EXON COVERAGE

Biomarker Findings

MSI Status Undetermined.

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ATM I1469M
STK11 G276fs*11

5 Therapies with Clinical Benefit
0 Therapies with Lack of Response

19 Clinical Trials

BIOMARKER FINDINGS

ACTIONABILITY

MSI Status Undetermined

GENOMIC FINDINGS	MAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ATM - I1469M	0.26%	None	[redacted]
10 Trials see p. 7			
STK11 - G276fs*11	0.35%	None	[redacted]
10 Trials see p. 9			

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. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PALB2*, *RB1*, *RET*, *STK11*, and *TP53* is recommended.

Mutant Allele Frequency is not applicable for copy number amplifications or rearrangements.

GENE
ATM

ALTERATION
I1469M

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair, and may predict sensitivity to [redacted] It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 8-11% of lung adenocarcinomas [13-15] and 5% of lung squamous cell carcinomas (SCCs)[16]. Expression of ATM protein has been reported to be significantly higher in non-small cell lung carcinoma samples than in normal tissues [17]. In one study, higher ATM protein levels in lung SCC, but not in lung adenocarcinoma, significantly correlated with shorter disease-free and overall survival of patients treated with cisplatin [18].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response [19]. Loss of functional ATM promotes tumorigenesis [20] and mutations in ATM underlie the rare autosomal recessive inherited disorder ataxia-telangiectasia that is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer [19]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
STK11

ALTERATION
G276fs*11

POTENTIAL TREATMENT STRATEGIES

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors [redacted]

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%) [15-16,22,32-35]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases [13] and was not observed in any of 178 lung squamous cell carcinoma cases [16]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab [36]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations [34-35]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas [22].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels [21]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis [31,37]. Functional disruption of the STK11 kinase domain (amino acids 49-309) or STRAD binding domain (amino acids 320-343) through mutation or loss, such as observed here, is predicted to be inactivating [38-49]. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation [50]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers [50-52], and individuals with this syndrome have a 30-50% risk of developing breast cancer [50,52]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

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.

ATM	*CHEK2*
Y1470C	R346C

APPENDIX Genes assayed in FoundationOne®Liquid

FoundationOne Liquid interrogates the complete exonic sequence of 35 genes, introns of 7 genes involved in rearrangements, and select exons of an additional 35 genes. 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

APC	*AR*	*ATM*	*BRCA1*	*BRCA2*	*CCND1*	*CD274 (PD-I1)*	*CDH1*	*CDK4*
CDK6	*CDK12*	*CDKN2A*	*CHEK2*	*CRKL*	*EGFR*	*ERBB2*	*ERRFI1*	*FGFR1*
FGFR2	*FOXL2*	*KRAS*	*MDM2*	*MET*	*MYC*	*MYCN*	*NF1*	*PALB2*
PDCD1LG2 (PD-L2)	*PTEN*	*PTPN11*	*RB1*	*SMO*	*STK11*	*TP53*	*VEGFA*	

DNA GENE LIST: SELECT EXONIC SEQUENCE OF THE DETECTION OF BASE SUBSTITUTIONS, INSERTIONS/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1 *Exons 4-9*	*AKT1* *Exon 3*	*ALK* *Exons 20-29*	*ARAF* *Exons 4, 5, 7, 11, 13, 15, 16*	*BRAF* *Exons 11-18*	*BTK* *Exons 2, 15*	*CTNNB1* *Exon 3*	*DDR2* *Exons 5, 17, 18*	*ESR1* *Exons 4-8*
EZH2 *Exons 4, 16, 18*	*FGFR3* *Exons 7, 9, 14*	*FLT3* *Exons 14, 15, 20*	*GNA11* *Exons 4, 5*	*GNAQ* *Exons 4, 5*	*GNAS* *Exons 1, 8*	*HRAS* *Exons 2, 3*	*IDH1* *Exon 4*	*IDH2* *Exon 4*
JAK2 *Exon 14*	*JAK3* *Exons 5, 11-13, 15, 16*	*KIT* *Exons 8, 9, 11-13, 17*	*MAP2K1 (MEK1)* *Exons 2, 3*	*MAP2K2 (MEK2)* *Exons 2-4, 6, 7*	*MPL* *Exon 10*	*MTOR* *Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56*	*MYD88* *Exon 4*	*NPM1* *Exons 4-6, 8, 10*
NRAS *Exons 2, 3*	*PDGFRA* *Exons 12, 18*	*PDGFRB* *Exons 12-21, 23*	*PIK3CA* *Exons 2, 3, 5-8, 10, 14, 19, 21*	*RAF1* *Exons 3-7, 10, 14, 15, 17*	*RET* *Exons 11, 13-16*	*ROS1* *Exons 36-38, 40*	*TERT* *(Promoter only)*	

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*EGFR*	*FGFR2*	*FGFR3*	*PDGFRA*	*RET*	*ROS1*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)

The median exon coverage for this sample is 5,176x

PERFORMANCE SPECIFICATIONS

	Mutant Allelle Frequency (MAF) / Tumor Fraction‡	Sensitivity*	Positive Predictive Value (PPV)*
Base Substitutions	>0.5%	99.9% (99.7%-99.9%)	100% (99.9%-100%)
	0.25%-0.5%	95.8% (94.5%-96.9%)	99.8% (99.3%-99.9%)
	<0.25%	68.4% (65.7%-70.9%)	96.1% (94.8%-97.1%)
Insertions/Deletions†	>0.5%	99.7% (98.7%-99.9%)	100% (99.3%-100%)
	0.25%–0.5%	87.7% (81.1%-92.2%)	98.8% (95.4%-99.8%)
	<0.25%	60.5% (52.7%-67.7%)	96.8% (92.3%-98.8%)
Rearrangements**	>0.5%	100% (85.9%-100%)	100% (85.9%-100%)
	0.25%–0.5%	89.4% (65.5%-98.2%)	100% (77.1%-100%)
	<0.25%	68.4% (43.5%-86.4%)	100% (71.7%-100%)
Copy Number Amplifications§	≥20%	95.3% (82.9%-99.2%)	97.6% (85.9%-99.9%)
	<20%	Varies depending on amplitude of CNA and ctDNA fraction	
MSI¶	>2.0%	92.0% (72.5%-98.6%)	100% (82.2%-100%)
Reproducibility (average concordance between replicates)			
97.7% inter-batch precision		95.9% intra-batch precision	

*95% confidence intervals. Sensitivity assessment for <0.25% bin restricted to alterations in the 0.125%-0.25% expected allele frequency range.

†Deletions up to 2kb and insertions up to 40bp are detected. Sensitivity is lower for indels in repetitive regions.

**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.

‡Sensitivity for MSI and copy number amplifications was determined using contrived samples with tumor fraction >20%. Most clinical samples will have less than 20% tumor fraction.

§Copy-number ≥8.

¶Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at a subset of homopolymer repeat loci covered by the assay. Microsatellite status is assayed for all FoundationOne®Liquid samples and will only be reported if MSI-High is determined.

Assay specifications are based on samples meeting a minimum coverage threshold (>85% of targeted regions must have >2500× redundant coverage). Specimens with higher input mass typically obtain higher coverage and have higher sensitivity for low-frequency alterations.

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

ABOUT FOUNDATIONONE®LIQUID

FoundationOne Liquid was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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 Liquid 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 Liquid identifies alterations to select cancer-associated genes or portions of genes (biomarkers).

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls. The threshold used in FoundationOne Liquid for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. For copy number amplifications, the equivocal status may be applied to calls in samples with calculated tumor fraction <30% but above the noise threshold. In addition, copy number amplifications in genes with three (3) baited exons are also marked as equivocal.

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.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker Findings

Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings

Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies

Sensitizing therapies → Resistant Therapies. (If multiple therapies exist within any of these categories, they are listed in alphabetical order.)

Clinical Trials

Pediatric trial qualification → Geographical Proximity → Later trial phase.

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 Liquid.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid is performed using cell-free DNA, and as such germline events may not be reported. The following target typically has low coverage resulting in a reduction in sensitivity: *TP53* exon 1 and *PDGFRA* exon 12.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

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