SAMPLE REPORT

Admera Health, LLC
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PATIENT INFORMATION		SAMPLE INFORMATION		REFERING PHYSICIAN		COPY TO (if different from ordering)	
Name:	Someone, Smith	Date Collected:	01/20/2019	Name:	Oncologist, M.D.	Name:	Pathologist, M.D.
DOB:	09/04/1959	Date Received:	01/22/2019	Institution:	Oncology Practice	Institution:	Pathology Practice
Age:	59	Date of Report:	01/25/2019	Address:	12 Any Street Anytown, NJ, 07080	Address:	321 Any Street Anytown, NJ, 07080
Sex:	Male	lab ID:	TGZY1603173				
Address:	South Plainfield, NJ, 07080	Testing Method:	Plasma Biopsy (NGS)	Contact:	123-456-7890	Contact:	103-546-7990

Tumor Profile for Someone, Smith

ICD-10: C34.9: Malignant neoplasm of unspecified part of unspecified bronchus or lung

LiquidGx™

Result: **POSITIVE**

Mutations Detected: EGFR-G719A, MET-Amplification

MSI status: STABLE

Clinical Trial Available: Yes

Medically Actionable Alterations

THERAPIES LINKED TO VARIANTS OF KNOWN CLINICAL SIGNIFICANCE

Gene	Molecular Abnormality	Therapies	Approved For	Allele Freq	LOE
EGFR	G719A	Afatinib	NSCLC	0.35	A
EGFR	G719A	Osimertinb, Erlotinib, Gefitnib	EGFR-mutant NSCLC	0.35	B
MET	Amplification	Crizotinib	ALK- and ROS1-rearranged NSCLC	NA	B/C

RESISTANCE OR INTERACTION VARIANTS OF KNOWN CLINICAL SIGNIFICANCE

Gene	Molecular Abnormality	Therapies	Resistance/Interaction	Allele Freq	LOE
MET	Amplification	Erlotinib, Gefitinib	Interaction	NA	A

LOE: Therapeutic-level-of-evidence, definition of LOE shown in Table 1.

MICROSATELLITE INSTABILITY (MSI)

BAT-25	BAT-26	NR-21	NR-24	NR-27	Therapies	Tumor Type
Negative	Negative	Negative	Negative	Negative	NA	NSCLC

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THERAPIES LINKED TO VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Gene	Molecular Abnormality	Therapies	Approved For	Allele Freq	LOE
EGFR	G719A	Neratinib	Breast carcinoma	0.35	C
MET	Amplification	Cabozantinib	Hepatocellular carcinoma, Renal cell carcinoma, Thyroid medullary carcinoma	NA	C

Table 1: Definitions of Variant Tiers and Levels of Evidence

Strong Clinical Significance	**Level A**	Therapy is FDA-approved in this disease/biomarker, or, included in professional guidelines as providing resistance to therapy.
	Level B	Strong evidence resulting from well-powered studies with expert consensus that biomarker predicts sensitivity to therapy. Evidence for resistance may be from well-powered studies with expert consensus or smaller studies repeatedly confirmed or reproduced by different groups.
	Level B/C	Consensus from experts, but lacking well-powered studies that biomarker predicts sensitivity to therapy.
Potential Clinical Significance	**Level C**	Therapy is FDA-approved for this biomarker but for a different disease, or, is criteria for a clinical trial. Preclinical data strongly suggests resistance.

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CLINICAL TRIALS TO CONSIDER

1. EGFR Associated Clinical Trials

Therapies	NCT ID	Title	Phase	Locations#
AC0010MA	NCT02448251	Safety, Pharmacokinetic and Preliminary Efficacy Study of AC0010MA in Advanced Non-Small Cell Lung Cancer	1	CA, GA, TX,
Navitoclax Osimertinib	NCT02520778	Osimertinib and Navitoclax inTreating Patients With EGFRPositive Previously Treated Advanced or Metastatic Nonsmall Cell Lung Cancer	1	CA, FL, GA, MA, MD, NC, NJ, OH, PA, VA
Itacitinib Osimertinib	NCT02917993	An Open-Label Phase 1/2 Study of Itacitinib in Combination With Osimertinib in Subjects With Non-Small Cell Lung Cancer	1/2	CA, CO, DC, FL, MA, MI, NJ, NY, OH, OR, TX, UT, VA, WV,
Osimertinib AZD4635	NCT03381274	Oleclumab (MEDI9447) EGFRm NSCLC Novel Combination Study	1/2	CA, CO, CT, FL, GA, IL, MD, NY, TX

2. MET Associated Clinical Trials

Therapies	NCT ID	Title	Phase	Locations#
INC280 erlotinib hydrochloride	NCT01911507	INC280 and Erlotinib Hydrochloride in Treating Patients With Non-small Cell Lung Cancer	1	CA

 # The locations closest to the patient's address based on zip code are shown (for US locations, otherwise show all locations).
Note: Select clinical trials are shown. For a full list of clinical trials, please search the ClinicalTrials.gov website.

ABOUT GENES

EGFR

EGFR encodes the Epidermal growth factor receptor (Egfr), a receptor tyrosine kinase that passes biochemical messages to the cell that stimulate it to grow and divide. Amplification, mutation, and overexpression of EGFR may cause excessive proliferation and tumor formation.

Mutation location in gene and/or protein

EGFR G719A is a missense mutation within the protein kinase domain of the Egfr protein (UniProt). This exon 18 mutation has been reported to result in ligand-independent activation of the Egfr protein (Bivona et al., 2013; ASCO 2013, Abstract 11067, Kobayashi et al., 2015; 26206867, Furuyama et al., 2013; 23387505). Mutations at G719 have been frequently reported in combination with other EGFR alterations and shown to confer sensitivity to the Egfr tyrosine kinase inhibitors erlotinib and gefitinib, both as single and complex mutations (Kobayashi et al., 2013; 23242437, Kancha et al., 2011; 21252719, Chen et al., 2006; 16205628, Bivona et al., 2013; ASCO 2013, Abstract 11067, van Noesel et al., 2013; 23358982, Wu et al., 2011; 21531810, Lynch et al., 2004; 15118073, Han et al., 2005; 15710947, Takano et al., 2005; 15998907). Indeed, EGFR G719A specifically has been shown to be sensitive to erlotinib, gefitinib, and afatinib in several studies of non-small cell lung carcinoma (NSCLC) patients, as well as to neratinib, dacomitinib, osimertinib, and rociletinib in preclinical studies (Bivona et al., 2013; ASCO 2013, Abstract 11067, Kobayashi et al., 2015; 26206867, van Noesel et al., 2013; 23358982, Beau-Faller et al., 2014;

24285021, Furuyama et al., 2013; 23387505, Han et al., 2005; 15710947, Yamaguchi et al., 2015; Yamaguchi 2015). In addition, clinical responses have been observed in NSCLC patients treated with neratinib who harbor mutations at G719 (Sequist et al., 2010; 20479403).

Mutation prevalence

EGFR mutations have been reported in 27% (25179/93101) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (Jan 2019). EGFR mutations have been reported in 10-29% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, Jan 2019). EGFR mutations have been reported in 14-36% of NSCLC cases and are found more commonly in East Asian patients as compared with other ethnicities (Zhang et al., 2018; 29543321, Riess et al., 2018; 29981927, Zhang et al., 2016; 27738317, Imyanitov et al., 2016; 27259329, Giannini et al., 2016; 27373829, Lee et al., 2016; 26992209, Han et al., 2017; 29110846).

Effect of mutation

EGFR-G719A is an activating mutation. EGFR activating mutations or amplification may predict sensitivity to Egfr targeted therapies, including inhibitors of multiple ErbB family members, and several have received FDA approva in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883). However, activation of Met, through METamplification or high Met protein expression, has been implicated in resistance to Egfr tyrosine kinase inhibitors (Engelman et al., 2007; 17463250, La et al., 2013; 24167634, Benedettini et al., 2010; 20489150).

MET

MET encodes the Met protein, also known as c-Met or hepatocyte growth factor receptor (HGFR), which is a receptor tyrosine kinase that is activated by the ligand HGF; Met activation results in signaling mediated partly through the Ras/Raf/MAPK and PI3K pathways to promote proliferation.

Mutation location in gene and/or protein

Numerous studies have reported significant correlations between increased copy number of MET and increased Met expression (Bubendorf et al., 2017; 28838386, Ha et al., 2013; 23807774, Lee et al., 2013; 24222167, Sun et al., 2013; 23720678, Lee et al., 2012; 22644302, Dziadziuszko et al., 2012; 22237262, Tsuta et al., 2012; 22198430). Reports in multiple tumor types suggest that MET amplification may predict sensitivity to crizotinib (Lennerz et al., 2011; 22042947, Chi et al., 2012; 22162573, Ou et al., 2011; 21623265).

Mutation prevalence

Putative high-level amplification of MET has been reported in 1.7% of Non-small cell lung carcinoma (NSCLC) cases (cBioPortal for Cancer Genomics, Jan 2019). In the literature, MET amplification has been reported in approximately 1-9% of non-small cell lung carcinoma (NSCLC) specimens (Xu et al., 2017; 28590585, Albitar et al., 2018; 29568386, Bubendorf et al., 2017; 28838386, Tong et al., 2016; 26847053, Cappuzzo et al., 2009; 19255323, Park et al., 2012; 22207554). Met expression has been reported in 17-44% of non-small cell lung carcinoma (NSCLC) samples; Met expression in NSCLC has also been reported to correlate with MET copy number alterations (Pyo et al., 2016; 27465837, Sterlacci et al., 2017; 28528511, Tong et al., 2016; 26847053, Jurmeister et al., 2015; 25534130, Bubendorf et al., 2017; 28838386).

Effect of mutation

MET-amplification is an activating alteration. Aberrant activation of Met in cancer can occur through MET gene mutation or amplification, or excessive/inappropriate signaling via the Met receptor's ligand, HGF (Lennerz et al., 2011; 22042947). Cabozantinib, which targets Met and other kinases, has been FDA approved for certain indications (Hart and De Boer, 2013; 23319867, Choueiri et al., 2015; 26406150). Crizotinib, a kinase inhibitor that has been FDA approved for treatment of ALK- and ROS1-rearranged non-small cell lung cancer, also targets Met (Shaw et al., 2013; 23724913, Mazières et al., 2015; 25667280, Solomon et al., 2014; 25470694).

CANCER DRUG INFORMATION

MEKINIST® (Trametinib)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204114s001lbl.pdf

COTELLIC® (Cobimetinib)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206192s000lbl.pdf

OPDIVO® (Nivolumab)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf

KEYTRUDA® (Pembrolizumab)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf

References:

- NCCN Biomarkers Compendium at: http://www.nccn.org/professionals/biomarkers/content/
- U.S. Food and Drug Administration, Table of Pharmacogenomic Biomarkers in Drug Labeling. Available online at: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
- My Cancer Genome at: http://www.mycancergenome.org/
- Knowledge Base of Precision Oncology at: https://pct.mdanderson.org/
- Catalogue Of Somatic Mutations In Cancer (COSMIC) at: cancer.sanger.ac.uk
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Test Methodology and Limitations for LiquidGx™:

Target regions of interest were sequenced using tagging of individual molecules followed by amplicon library generation and massive parallel sequencing (Illumina platform). The detected mutations are annotated based on hg19 reference genome assembly. The LiquidGx™ test was developed by Admera Health, including determination and validation of performance characteristics. The sensitivity and specificity of this test is greater than 94.5% and 99%, respectively. The limit of detection is 0.1% for single nucleotide variants, insertion/deletions, and fusions. Greater than 2% fraction of microsatellite instability can be detected. For copy number variation, LiquidGx™ can detect as low as an extra 0.5 copies of a gene (equivalent to 2.5 total copies). This test has not been approved by the U.S. Food and Drug Administration (FDA) and is for research purposes only. The Admera Health clinical laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), accredited by the College of American Pathologists, and is qualified to perform high complexity clinical laboratory testing.

The panel includes 17 genes, 5 repeat regions, and approximately 170 variants in alignment with National Comprehensive Cancer Network (NCCN) guidelines. The following genetic variants may be detected in the assay: BRAF D594G/V, L597R/Q/S/V, V600D/E/G/K/M/R, K601E; EGFR G719A/C/S, K745_A750del, E746_A750del, E746_A750delELREA, E746_S752delinsA, L747_S752del, L747_P753delinsS, A763_Y764insFQEA, D770_N771insSVD, T790M, C797S, L858R, L861Q/R, Exon19_del, Exon19_ins, Exon20_ins, Amplification; ERBB2 G776L, A775_G776insYVMA, G776_777insVC, Amplification; KRAS G12A/C/D/R/S/V, G13A/C/D/R/S/V, Q61H/K/L/P/R, K117N, A146P/T/V; AKT1 E17K; ALK T1151_L1152insT, F1174L, L1196M, G1202R, S1206Y, G1269A, EML4-ALK, KIF5B-ALK, TFG-ALK, STRN_ALK; MET Exon14_skipping, Amplification; PIK3CA E542K, E545K/G, H1047R; RET M918T, C634R/Y/W, CCDC6-RET, NCOA4-RET, KIF5B-RET; LRIG3-ROS1, TPM3-ROS1, EZR-ROS1, SDC4-ROS1, GOPC-ROS1, SLC34A2-ROS1, CD74-ROS1; NRAS G12C/S/A/D/V/R, G13R/C/A/D/V, Q61K/R/L/H/E/P; KIT W557R, L559A/D, L576P, K642E, W557-L576_indel; MAP2K1 I111S, C121S, P124S/L; PDGFRA D842V; HRAS G12R/V, G13C/R, Q61R; TP53 R175H, G245S, R248Q/W, R249S, R273H/C, R282W; PTEN R130G//Q, R159S, R233*, P248fs, K267fs, T319fs, N323fs. A normal (wild type) genotype signifies the absence of the targeted alleles and does not indicate the absence of other mutations not covered by the assay. The possibility cannot be ruled out that the indicated variants may be present but below the limits of detection for this assay. Microsatellite instability (MSI) is determined by detecting the length of mononucleotide repeats at five genomic sites (BAT-25, BAT-26, NR-21, NR-24, and NR-27) indicating a defect in DNA repair. Anti-PD-1 therapy has been FDA approved for patients classified as MSI-UNSTABLE. A positive call at ≥ 2 sites is required for a patient to be classified as MSI-UNSTABLE.*

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The information contained in this report is provided as a service and does not constitute medical advice. At the time of report generation this information is believed to be current and is based upon published research; however, research data evolves and amendments to the prescribing information of the drugs listed and knowledge of gene variants will change over time. While this report is believed to be accurate and complete as of the date issued, THE DATA IS PROVIDED "AS IS", WITHOUT WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. As medical advice must be tailored to the specific circumstances of each case, the treating health care professional has ultimate responsibility for all treatment decisions made with regard to a patient including any made on the basis of a patient's genotype.

N-of-One, Inc. has provided to Admera Health research, analysis and interpretation, on a patient specific basis, of peer-reviewed studies and publicly available databases. This information may include the association between a specific molecular alteration and clinical benefit, of lack thereof, from FDA-approved therapies and therapies under clinical investigation. Additional information from N-of-One is available on its website at www.n-of-one.com.

I certify that these lab results are accurate.

Signatures:

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