MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS® LIFE SCIENCES

FINAL REPORT

PATIENT

Name: Patient, Test
Date of Birth: XX-Mon-19XX
Sex: Male
Case Number: TN16-XXXXXX
Diagnosis: Squamous cell carcinoma, metastatic, NOS

SPECIMEN INFORMATION

Primary Tumor Site: Nasopharynx, NOS
Specimen Site: Head, face or neck, NOS
Specimen ID: ABC-1234
Specimen Collected: XX-Mon-2016
Testing Completed: XX-Mon-2016

ORDERED BY

Ordering Physician, MD
Cancer Center
123 Main Street
Springfield, XY 12345
USA
1 (123) 456-7890

Bold Therapies = On NCCN Compendium® Therapies

✔ THERAPIES WITH **POTENTIAL BENEFIT** (PAGE 4)

docetaxel, **paclitaxel**	TUBB3★	**gemcitabine**	RRM1★	nab-paclitaxel	TUBB3★
fluorouracil	TS★	capecitabine, pemetrexed	TS★		

★ **Indicates Clinical Trial Opportunity • 265 Chemotherapy Trials • 126 Targeted Therapy Trials** *(See Clinical Trials Connector™ on page 7 for details.)*

✘ THERAPIES WITH **POTENTIAL LACK OF BENEFIT** (PAGE 5)

carboplatin, **cisplatin**	ERCC1, BRCA2, BRCA1, ATM	dabrafenib, vemurafenib	BRAF	oxaliplatin	ERCC1, BRCA2, BRCA1, ATM

? THERAPIES WITH **INDETERMINATE BENEFIT** (PAGE 6)

everolimus, temsirolimus	imatinib	vandetanib

Therapies associated with potential benefit or lack of benefit, as indicated above, are based on biomarker results provided in this report and are based on published medical evidence. This evidence may have been obtained from studies performed in the cancer type present in the tested patient's sample or derived from another tumor type. The selection of any, all, or none of the matched therapies resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information in addition to this report concerning the patient's condition in accordance with the applicable standard of care.

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CE

SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

Assay	Result
Total Mutational Load	Low | 9 Mutations / Megabase

Biomarker	Method	Result
AKT2	NGS	Amplification Not Detected
ALK	NGS	Amplification Not Detected
ARID1A	NGS	Amplification Not Detected
ATM	NGS	Mutation Not Detected
AURKB	NGS	Amplification Not Detected
BRAF	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected
BRCA2	NGS	Mutation Not Detected
c-KIT	NGS	Mutation Not Detected
CCND1	NGS	Amplification Not Detected
CCND3	NGS	Amplification Not Detected
CCNE1	NGS	Amplification Not Detected
CDK4	NGS	Amplification Not Detected
CDK6	NGS	Amplification Not Detected
CDK8	NGS	Amplification Not Detected
CDKN2A	NGS	Amplification Not Detected
cMET	NGS	Amplification Not Detected
	NGS	Mutation Not Detected
CREBBP	NGS	Amplification Not Detected
CRKL	NGS	Amplification Not Detected
EGFR	NGS	Amplification Not Detected
	NGS	Mutation Not Detected
EP300	NGS	Amplification Not Detected
ERCC1	IHC	Positive | 2+, 60%
EZH2	NGS	Amplification Not Detected
FGF10	NGS	Amplification Not Detected
FGF3	NGS	Amplification Not Detected
FGF4	NGS	Amplification Not Detected
FGFR1	NGS	Amplification Not Detected
FGFR2	NGS	Amplification Not Detected

Biomarker	Method	Result
FGFR3	NGS	Amplification Not Detected
GATA3	NGS	Amplification Not Detected
Her2/Neu	NGS	Amplification Not Detected
Her2/Neu (ERBB2)	NGS	Mutation Not Detected
IDH1	NGS	Mutation Not Detected
KDR (VEGFR2)	NGS	Amplification Not Detected
KRAS	NGS	Mutation Not Detected
MCL1	NGS	Amplification Not Detected
MDM2	NGS	Amplification Not Detected
MEK1	NGS	Amplification Not Detected
MYC	NGS	Amplification Not Detected
NF2	NGS	Amplification Not Detected
NFKBIA	NGS	Amplification Not Detected
NRAS	NGS	Mutation Not Detected
NTRK1	NGS	Amplification Not Detected
PD-L1	IHC	Positive | 2+, 80%
PDGFRA	NGS	Mutation Not Detected
PIK3CA	NGS	Mutation Not Detected
RB1	NGS	Amplification Not Detected
RET	NGS	Mutated, Presumed Benign
		Exon 20 | M1064T
RICTOR	NGS	Amplification Not Detected
ROS1	NGS	Amplification Not Detected
RRM1	IHC	Negative | 2+, 5%
TOP1	NGS	Amplification Not Detected
TP53	NGS	Mutation Not Detected
TrkA/B/C	IHC	Negative | 0, 100%
TS	IHC	Negative | 0, 100%
TUBB3	IHC	Negative | 0, 100%
WT1	NGS	Amplification Not Detected

IHC: Immunohistochemistry **NGS:** Next-Generation Sequencing

Biomarker Results continued on the next page. >

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SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

The Next-Generation Sequencing results above include only the genes most commonly associated with cancer. See summary below and for full Next-Generation Sequencing results, see Appendix page 1.
Genes tested: 592 | Genes with actionable mutations: 1 | Genes with unclassified mutations: 28 | Genes with no mutations detected: 543

See the Appendix section for a detailed overview of the biomarker test results for each technology.

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✔ THERAPIES WITH **POTENTIAL BENEFIT**

Therapies	Test	Method	Result	Value†	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
capecitabine, fluorouracil, pemetrexed	TS	IHC	Negative	0+ 100%	✔			I / Good	1, 2, 3
docetaxel, nab-paclitaxel, paclitaxel	TUBB3	IHC	Negative	0+ 100%	✔			I / Good	20, 21, 22, 23
gemcitabine	RRM1	IHC	Negative	2+ 5%	✔			I / Good	27

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

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✘ THERAPIES WITH **POTENTIAL LACK OF BENEFIT**

Therapies	Test	Method	Result	Value†	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
carboplatin, cisplatin, oxaliplatin	ATM	NGS	Mutation Not Detected				✔	II-2 / Good	13, 14, 15
	BRCA1	NGS	Mutation Not Detected				✔	II-2 / Good	9, 10, 11, 12
	BRCA2	NGS	Mutation Not Detected				✔	II-2 / Good	9, 10, 11
	ERCC1	IHC	Positive	2+ 60%			✔	II-2 / Good	4, 5, 6, 7, 8
dabrafenib, vemurafenib	BRAF	NGS	Mutation Not Detected				✔	I / Good	16, 17, 18, 19

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

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? THERAPIES WITH **INDETERMINATE BENEFIT**

(Biomarker results do not impact potential benefit or lack of potential benefit)

Therapies	Test	Method	Result	Value†	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
everolimus, temsirolimus	PIK3CA	NGS	Mutation Not Detected			✔		II-2 / Good	24, 25#, 26
imatinib	c-KIT	NGS	Mutation Not Detected				✔	II-2 / Good	28, 29
	PDGFRA	NGS	Mutation Not Detected				✔	II-3 / Good	30, 31, 32
vandetanib	RET	NGS	Mutated, Presumed Benign	M1064T					

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

Evidence reference includes data from the same lineage as the tested specimen.

†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

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CLINICAL TRIALS CONNECTOR™

For a complete list of open, enrolling clinical trials visit MI Portal to access the **Clinical Trials Connector** . This personalized, real-time web-based service provides additional clinical trial information and enhanced searching capabilities, including, but not limited to:

- Location: filter by geographic area
- Biomarker(s): identify specific biomarkers associated with open clinical trials to choose from
- Drug(s): search for specific therapies
- Trial Sponsor: locate trials based on the organization supporting the trial(s)

Visit www.CarisMolecularIntelligence.com to view all matched trials.

CHEMOTHERAPY CLINICAL TRIALS (265)			
Drug Class	**Biomarker**	**Method**	**Investigational Agent(s)**
Antifolates (12)	TS	IHC	methotrexate, pemetrexed
Nucleoside analog (36)	RRM1	IHC	gemcitabine
Pyrimidine analog (89)	TS	IHC	capecitabine, fluorouracil, tegafur-uracil
Taxanes (128)	TUBB3	IHC	docetaxel, paclitaxel

TARGETED THERAPY CLINICAL TRIALS (126)			
Drug Class	**Biomarker**	**Method**	**Investigational Agent(s)**
Cell cycle inhibitors (10)	RB1	NGS	LEE011, palbociclib
Immunomodulatory agents (114)	PD-L1	IHC	MK-3475, MPDL3280A, atezolizumab, avelumab, nivolumab, pembrolizumab
MDM2 inhibitors (2)	TP53	NGS	DS-3032, RO5503781

( ) = represents the total number of clinical trials identified by the Clinical Trials Connector for the provided drug class or table.

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
1. Chen, C.-Y., P.-C. Yang, et al. (2011). "Thymidylate synthase and dihydrofolate reductase expression in non-small cell lung carcinoma: The association with treatment efficacy of pemetrexed." Lung Cancer 74(1): 132-138. View Citation Online	II-1 / Good
2. Qiu, L.X., M.H. Zheng, et. al. (2008). "Predictive value of thymidylate synthase expression in advanced colorectal cancer patients receiving fluoropyrimidine-based chemotherapy: Evidence from 24 studies." Int. J. Cancer: 123, 2384-2389. View Citation Online	I / Good
3. Lee, S.J., Y.H. Im, et. al. (2010). "Thymidylate synthase and thymidine phosphorylase as predictive markers of capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer." Cancer Chemother. Pharmacol. DOI 10.1007/s00280-010-1545-0. View Citation Online	II-3 / Good
4. Scheil-Bertram, S., A. Fisseler-Eckhoff, et. al. (2010). "Excision repair cross-complementation group 1 protein overexpression as a predictor of poor survival for high-grade serous ovarian adenocarcinoma." Gynecologic Oncology. 119, 325-331. View Citation Online	II-3 / Good
5. De Dosso, S., E. Zanellato, et al.(2013). "ERCC1 predicts outcome in patients with gastric cancer treated with adjuvant cisplatin-based chemotherapy". Cancer Chemotherapy and Pharmacology. 72:159-165. View Citation Online	II-3 / Good
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7. Steffensen, K.D., A. Jakobsen, et al. (2009). "The Relationship of Platinum Resistance and ERCC1 Protein Expression in Epithelial Ovarian Cancer." Int. J. Gynecol. Cancer 19: 820-825. View Citation Online	II-3 / Good
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11. Lowery, M.A., E.M. O'Reilly, et.al. (2011) "An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions." Oncologist. 16(10):1397-402. View Citation Online	II-3 / Fair
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14. Pennington, K.P., E.M. Swisher, et al. (2014). "Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas". Clin Cancer Res. 20(3):764-775.	II-3 / Good
15. Plimack, E.R., E.A. Ross, et al. (2015). "Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer". Eur Urol. 68:959-967.	II-2 / Good
16. Flaherty, K.T., P.B. Chapman, et al. (2010). "Inhibition of Mutated, Activated BRAF in Metastatic Melanoma." N Engl J Med 363:809-819. View Citation Online	II-2 / Good
17. Hauschild, A., P.B. Chapman, et al. (2012). "Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial." Lancet 358-365. View Citation Online	I / Good
18. Chapman, P.B., G.A. McArthur, et. al. (2011). "Improved survival with vemurafenib in melanoma with BRAF V600E mutation." N. Engl. J. Med. This article (10.1056/NEJMoa1103782) was published on June 5, 2011, at nejm.org. View Citation Online	I / Good

** See Appendix page 5 for Level of Evidence description.*

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
19. Falchook, G.S., R. F. Kefford, et al. (2012). "Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase I dose-escalation trial." Lancet 379:1893-901. View Citation Online	II-2 / Good
20. Ploussard, G., A. de la Taille, et al. (2010). "Class III β-Tubulin Expression Predicts Prostate Tumor Aggressiveness and Patient Response to Docetaxel-Based Chemotherapy." Clin Cancer Res 70(22): 9253-9264. View Citation Online	II-3 / Good
21. Gao, S., J. Gao, et al. (2012). "Clinical implications of REST and TUBB3 in ovarian cancer and its relationship to paclitaxel resistance." Tumor Biol 33:1759-1765. View Citation Online	II-3 / Good
22. Zhang, H.-L., X.-W. Zhou, et al. (2012). "Association between class III β-tubulin expression and response to paclitaxel/vinorelbine-based chemotherapy for non-small cell lung cancer: A meta-analysis." Lung Cancer 77: 9-15. View Citation Online	I / Good
23. Seve, P., C. Dumontet, et al. (2005). "Class III β-tubulin expression in tumor cells predicts response and outcome in patients with non-small cell lung cancer receiving paclitaxel." Mol Cancer Ther 4(12): 2001-2007. View Citation Online	II-3 / Good
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26. Janku, F., R. Kurzrock, et. al. (2012). "PI3K/Akt/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations." Journal of Clinical Oncology. DOI: 10.1200/JCO.2011.36.1196. View Citation Online	II-3 / Good
27. Gong, W., J. Dong, et. al. (2012). "RRM1 expression and clinical outcome of gemcitabine-containing chemotherapy for advanced non-small-cell lung cancer: A meta-analysis." Lung Cancer. 75:374-380. View Citation Online	I / Good
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34. Ledermann, J., U. Matulonis, et.al. (2014). "Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial." Lancet Oncol. 15(8):852-61. View Citation Online	I / Good
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** See Appendix page 5 for Level of Evidence description.*

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
37. Bang, Y-J., Y-K. Kang, et. al. (2010). "Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial." Lancet. 376:687-97. View Citation Online	I / Good
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45. Amir, E. et. al. (2010). "Lapatinib and HER2 status: results of a meta-analysis of randomized phase III trials in metastatic breast cancer." Cancer Treatment Reviews. 36:410-415. View Citation Online	I / Good
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** See Appendix page 5 for Level of Evidence description.*

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SPECIMEN INFORMATION

Specimen ID: ABC-123

Specimen Collected: XX-Mon-2016

Specimen Received: XX-Mon-2016

Testing Initiated: XX-Mon-2016

Gross description: 1 (A) Paraffin Block - Client ID(ABC-123) with the corresponding surgical pathology report labeled "ABC-1234-XYZ".

Pathologic Diagnosis: Right neck mass, US-guided FNA and needle core biopsy: Malignant cells present. Consistent with metastatic nonkeratinizing squamous cell carcinoma.

Disclaimer

All of the individual assays that are available through Caris Molecular Intelligence™ were developed and validated by Caris MPI, Inc. d/b/a Caris Life Sciences® and their test performance characteristics were determined and validated by Caris Life Sciences pursuant to the Clinical Laboratory Improvements Amendments and accompanying regulations ("CLIA"). Some of the assays that are part of Caris Molecular Intelligence have been approved by the U.S. Food and Drug Administration (FDA). For any remaining assays, Caris MPI, Inc. is certified under CLIA to perform high complexity testing, including all of the assays that comprise the Caris Molecular Intelligence.

The CLIA certification number of Caris MPI, Inc. laboratory performing testing in connection with Caris Molecular Intelligence can be found at the bottom of each page. This report includes information about therapies that appear to be associated with clinical benefit based on NCCN Compendium® guidelines, relevance of tumor lineage, level of published evidence and strength of biomarker results. This report, neither ranks biomarkers listed nor therapies associated with such biomarkers, in order of potential or predicted efficacy, and such therapies may or may not be suitable for administration to a particular patient. A determination of biomarker results do not necessarily indicate pharmacologic effectiveness or lack thereof. This report does not guarantee or suggest that any particular agent will be effective with the treatment of any particular condition. Caris Life Sciences expressly disclaims and makes no representation or warranty whatsoever relating, directly or indirectly, to review of identified scientific literature, the conclusions drawn from such review or any of the information set forth in this report that is derived from such review, including information and conclusions relating to therapies that are included or omitted from this report.

Decisions regarding care and treatment should not be based on a single test such as this test or the information contained in this report. The decision to select any, all or none of the listed therapies resides solely within the discretion of the treating physician. 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, including but not limited to, patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the applicable standard of care.

The information presented in the Clinical Trials Connector™ section of this report (if applicable) is compiled from sources believed to be reliable and current. We have used our best efforts to make this information as accurate as possible. However, the accuracy and completeness of this information cannot be guaranteed. The contents are to be used for clinical trial guidance and may not include all relevant trials. Current enrollment status for these trials is unknown. The clinical trials information present in the biomarker description was compiled from www.clinicaltrials.gov. The contents are to be used only as a guide, and health care providers should employ their judgment in interpreting this information for a particular patient. Specific eligibility criteria for each clinical trial should be reviewed as additional inclusion criteria may apply. Caris Life Sciences makes no promises or guarantees that a healthcare provider, insurer or other third party private or government payor, will provide reimbursement for any of the tests performed.

The next-generation sequencing assay performed by Caris Life Sciences examines nucleic acids obtained from tumor tissue only and does not examine normal tissue such as tumor adjacent tissue or whole or peripheral blood. As such, the origin of any mutation detected may be a somatic mutation (not inherited) or a germline mutation (inherited) and will not be distinguishable by this assay. It is recommended that results be considered within the patient's clinical and health history. If a germline inheritance pattern is suspected then counseling by a board certified genetic counselor is recommended.

Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique. Candidate slides were examined under a microscope and areas containing tumor cells (and separately normal cells, when necessary for testing) were circled. A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope. The areas marked and extracted were microscopically reexamined on post-microdissected slides and adequacy of microdissection was verified by a board certified Pathologist.

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MUTATIONAL ANALYSIS BY **NEXT-GENERATION SEQUENCING (NGS)**

TOTAL MUTATIONAL LOAD

Result	Mutations / Megabase (Mb)	Threshold
Low	9	≥ 17 Mutations per Mb

Interpretation: Total Mutational Load is calculated using only missense mutations that have not previously been reported as germline alterations. In colorectal cancer, all samples tested by our laboratory that exhibited microsatellite instability (MSI-H) had a Total Mutational Load of ≥ 17 mutations per megabase sequenced. Samples with 17 or more mutations may be hypermutated, which is a potential indicator of immunotherapy response. (Le et al., NEJM, 2015; Rizvi et al., Science, 2015; Rosenberg et al., Lancet, 2016; Snyder et al., NEJM, 2014)

GENES TESTED WITH ALTERATIONS

Gene	Alteration	Frequency (%)	Exon	Result
RET	M1064T	48	20	Mutated, Presumed Benign

Interpretation: This rare variant has been reported in population genetic database ExAC for three carriers. In addition, this variant has been reported as germline in patients affected by Hirschsprung Disease (PMID: 7581377; 22174939) in which RET is known to have reduced or loss of function. Cell culture experiments have shown that this mutation does not change the transforming ability of RET (PMID: 9502784). However, in a report by Lorenzo et al (PMID: 9047383) it was shown that this variant decreases the Shc's binding to phosphorylated RET supporting that this variant may result in reduced RET signaling. Although the evidence for causality for Hirschsprung Disease is mixed, it is clear from experimental evidence that this variant is very likely not activating.

RET or rearranged during transfection gene, located on chromosome 10, activates cell signaling pathways involved in proliferation and cell survival. RET mutations are found in 23-69% of sporadic medullary thyroid cancers (MTC), but RET fusions are common in papillary thyroid cancer, and more recently have been found in 1-2% of lung adenocarcinoma. Germline activating mutations of RET are associated with multiple endocrine neoplasia type 2 (MEN2), which is characterized by the presence of medullary thyroid carcinoma, bilateral pheochromocytoma, and primary hyperparathyroidism. Germline inactivating mutations of RET are associated with Hirschsprung's disease.

GENES TESTED WITH NO MUTATIONS DETECTED

ATM	BRCA2	EGFR	KRAS	PIK3CA
BRAF	c-KIT	Her2/Neu (ERBB2)	NRAS	TP53
BRCA1	cMET	IDH1	PDGFRA	

The mutations reported in the section below have not been analyzed to determine clinical significance and are being reported for informational purposes. In addition, the origin of the reported mutations (germline or somatic) has not been determined. All variants listed in the dbSNP 137 common list have been excluded from this table, as well as non-coding variants that are not part of the conserved splice sequence (+/- 1 or 2 bases). All excluded variants and regions are available upon request. Certain gene regions were also excluded due to high homology with other loci in the genome.

Additional Next-Generation Sequencing results continued on the next page. >

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MUTATIONAL ANALYSIS BY **NEXT-GENERATION SEQUENCING (NGS)**

GENES TESTED WITH UNCLASSIFIED MUTATIONS

Gene	Alteration	Gene	Alteration	Gene	Alteration	Gene	Alteration
AFF3	H914Q	FANCA	P1220A	NOTCH1	L819P	TCF3	G431S
ATRX	P609A	FCRL4	R78Q	PCM1	N159S	TRAF7	V602M
BRIP1	A144T	IRS2	G855R	PDE4DIP	A1688V	TRRAP	E2732D
CLTCL1	G375R	KMT2D	R5432Q	PMS1	R919C	TSC1	V175A
CSF3R	P760T	LRP1B	I761V	PRDM1	E80V	USP6	I67 _R68 delinsMW
EPS15	N845S	MEK2	c.-18 _-16delCCG	SS18L1	P87S	WRN	P1300L
ERCC4	V81F	NFKBIA	E85fs	SUFU	P24A	ZNF217	F269fs

GENES TESTED WITH INDETERMINATE RESULTS

AFF4	COPB1	LIFR	NOTCH2	STAT5B
ARID1A	ELL	MED12	NUTM2B	SUZ12
BIRC3	KDM5C	MLLT10	PCSK7	TSHR
CASC5	KMT2C	MNX1	PMS2	VEGFB

For Next-Generation Sequencing, a total of 592 genes were analyzed. The results above include genes most commonly associated with cancer and any additional mutations identified. No alterations were identified in 543 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

NGS Methods

Next Generation Sequencing: Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina NextSeq platform. An Agilent custom-designed SureSelect XT assay was used to enrich 592 whole-gene targets. The genes and amino acids evaluated in this report can be found at www.carislifesciences.com. All variants reported by this assay are detected with > 99 % confidence based on the frequency of the mutation present and the amplicon coverage. This test is not designed to distinguish between germ line inheritance of a variant or acquired somatic mutation. This test has a sensitivity to detect as low as approximately 10 % population of cells containing a mutation. This test has not been cleared or approved by the United States Food and Drug Administration (FDA) as such approval is not necessary. All performance characteristics were determined by Caris Life Sciences. Benign and non-coding variants are not included in this report but are available upon request.

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COPY NUMBER VARIATIONS BY **NEXT-GENERATION SEQUENCING (NGS)**

GENES TESTED WITH NO AMPLIFICATION DETECTED					
AKT2	CDK4	EGFR	FGFR2	MEK1	ROS1
ALK	CDK6	EP300	FGFR3	MYC	TOP1
ARID1A	CDK8	EZH2	GATA3	NF2	WT1
AURKB	CDKN2A	FGF10	Her2/Neu	NFKBIA	
CCND1	cMET	FGF3	KDR	NTRK1	
CCND3	CREBBP	FGF4	MCL1	RB1	
CCNE1	CRKL	FGFR1	MDM2	RICTOR	

CNV Methods

Copy number variation was determined by comparing the depth of sequencing of genomic loci to a diploid control as well as the known performance of these genomic loci. Copy number gains ≥8 copies can be detected by this assay with >95% sensitivity. Please note: high levels of polyploidy or scant tumor cells may prevent the detection of copy number changes.

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PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

Biomarker	Patient Tumor			Thresholds*
	Staining Intensity (0, 1+, 2+, 3+)	Percent of cells	Result	Conditions for a Positive Result:
ERCC1	2 +	60	Positive	Intensity of ≥3+ with ≥10% or ≥2+ with ≥50% of cells stained
PD-L1	2 +	80	Positive	Intensity ≥2+ and ≥5% of cells stained
RRM1	2 +	5	Negative	Intensity ≥2+ and ≥50% of cells stained
TrkA/B/C	0	100	Negative	Intensity ≥1+ and ≥1% of cells stained
TS	0	100	Negative	Intensity ≥1+ and ≥10% of cells stained
TUBB3	0	100	Negative	Intensity ≥2+ and ≥30% of cells stained

IHC Methods

These tests were developed and their performance characteristics determined by Caris MPI, Inc. d/b/a Caris Life Sciences®

* Caris Life Sciences has defined threshold levels of reactivity of IHC to establish cutoff points based on published evidence. Polymer detection systems are used for each IHC.

* HER2 results and interpretation follow the ASCO/CAP scoring criteria. See reference section for more information.

* Please note that PD-L1 staining is read from the membrane staining of cancer cells.

Clones used: TUBB3(Polyclonal), ERCC1(8F1), PD-L1(SP142), TrkA/B/C(EPR17341), RRM1(Polyclonal), TS(TS106/4H4B1).

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LITERATURE LEVEL OF EVIDENCE ASSESSMENT FRAMEWORK*

STUDY DESIGN	
Hierarchy of Design	**Criteria**
I	Evidence obtained from at least one properly designed **randomized controlled trial**.
II-1	Evidence obtained from well-designed controlled trials **without randomization**.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
III	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

STUDY VALIDITY	
Grade	**Criteria**
Good	The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions and shows no significant flaws.
Fair	The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions, but contains at least one significant but not fatal flaw.
Poor	The study is judged to have a fatal flaw such that the conclusions are not valid for the purposes of this test.

* Adapted from Harris, T., D. Atkins, et al. (2001). "Current Methods of the U.S. Preventive Services Task Force." Am J Prev Med 20(3S)

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