MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS® LIFE SCIENCES

FINAL REPORT

PATIENT

Name: Patient, Test
Date of Birth: XX-Mon-19XX
Sex: Female
Case Number: TN16-XXXXXX
Diagnosis: Olfactory neuroblastoma

SPECIMEN INFORMATION

Primary Tumor Site: Nasal cavity
Specimen Site: Submandibular lymph node
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
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✔ THERAPIES WITH **POTENTIAL BENEFIT** (PAGE 4)

carboplatin, cisplatin, oxaliplatin	ERCC1	gemcitabine	RRM1★		

★ **Indicates Clinical Trial Opportunity • 23 Chemotherapy Trials • 130 Targeted Therapy Trials** *(See Clinical Trials Connector™ on page 7 for details.)*

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

ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab	Her2/Neu	dabrafenib, vemurafenib	BRAF	lapatinib	Her2/Neu
capecitabine, fluorouracil, pemetrexed	TS	docetaxel, nab-paclitaxel, paclitaxel	TUBB3		

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

everolimus, temsirolimus		imatinib			

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.

CE

SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

Assay	Result
Total Mutational Load	Low | 3 Mutations / Megabase

Biomarker	Method	Result
AKT2	NGS	Amplification Not Detected
ALK	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
ARID1A	NGS	Amplification Not Detected
ATM	NGS	Mutation Not Detected
AURKB	NGS	Amplification Not Detected
BRAF	RNA-Seq	Fusion Not Detected
	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
cMET - exon 14	RNA-Seq	Variant Transcript Not Detected
CREBBP	NGS	Amplification Not Detected
CRKL	NGS	Amplification Not Detected
EGFR	NGS	Amplification Not Detected
	NGS	Mutation Not Detected
EGFRvIII	RNA-Seq	Variant Transcript Not Detected
EP300	NGS	Amplification Not Detected
ERCC1	IHC	Negative | 2+, 5%
EZH2	NGS	Amplification Not Detected
FGF10	NGS	Amplification Not Detected
FGF3	NGS	Amplification Not Detected

Biomarker	Method	Result
FGF4	NGS	Amplification Not Detected
FGFR1	NGS	Amplification Not Detected
FGFR2	NGS	Amplification Not Detected
FGFR3	NGS	Amplification Not Detected
GATA3	NGS	Amplification Not Detected
Her2/Neu	IHC	Negative | 0, 100%
	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
NF1	NGS	Mutated, Pathogenic
		Exon 30 | R1362X
NF2	NGS	Amplification Not Detected
NFKBIA	NGS	Amplification Not Detected
NRAS	NGS	Mutation Not Detected
NTRK1	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
NTRK2	RNA-Seq	Fusion Not Detected
NTRK3	RNA-Seq	Fusion Not Detected
PD-1	IHC	Positive | 1/HPF
PD-L1	IHC	Negative | 0, 100%
PDGFRA	NGS	Mutation Not Detected
PIK3CA	NGS	Mutation Not Detected
RB1	NGS	Amplification Not Detected
RET	RNA-Seq	Fusion Not Detected
	NGS	Mutation Not Detected

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

Biomarker Results continued on the next page. >

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SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

Biomarker	Method	Result
RICTOR	NGS	Amplification Not Detected
ROS1	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
RRM1	IHC	Negative | 2+, 20%
RSPO3	RNA-Seq	Fusion Not Detected
TOP1	NGS	Amplification Not Detected
TOP2A	IHC	Negative | 2+, 7%

Biomarker	Method	Result
TP53	NGS	Mutated, Variant of Unknown Significance
		Exon 7 | T231S
TrkA/B/C	IHC	Positive | 1+, 2%
TS	IHC	Positive | 1+, 10%
TUBB3	IHC	Positive | 3+, 100%
WT1	NGS	Amplification Not Detected

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

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: 2 | Genes with unclassified mutations: 9 | Genes with no mutations detected: 530

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
carboplatin, cisplatin, oxaliplatin	ATM	NGS	Mutation Not Detected					II-2 / Good	21, 22, 23
	BRCA1	NGS	Mutation Not Detected					II-2 / Good	17, 18, 19, 20
	BRCA2	NGS	Mutation Not Detected					II-2 / Good	17, 18, 19
	ERCC1	IHC	Negative	2+ 5%	✔			II-2 / Good	12, 13, 14, 15, 16
gemcitabine	RRM1	IHC	Negative	2+ 20%	✔			I / Good	35

* 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
ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab	Her2/Neu	IHC	Negative	0+ 100%			✔	I / Good	1, 2, 3, 4, 5, 7, 8
	Her2/Neu	NGS	Amplification Not Detected				✔	I / Good	1, 2, 3, 4, 5, 6, 7, 8
capecitabine, fluorouracil, pemetrexed	TS	IHC	Positive	1+ 10%			✔	I / Good	9, 10, 11
dabrafenib, vemurafenib	BRAF	NGS	Mutation Not Detected				✔	I / Good	24, 25, 26, 27
docetaxel, nab-paclitaxel, paclitaxel	TUBB3	IHC	Positive	3+ 100%			✔	I / Good	28, 29, 30, 31
lapatinib	Her2/Neu	IHC	Negative	0+ 100%			✔	I / Good	41, 42, 43
	Her2/Neu	NGS	Amplification Not Detected				✔	I / Good	6, 41, 42, 43

* 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	32, 33, 34
imatinib	c-KIT	NGS	Mutation Not Detected				✔	II-2 / Good	39, 40
	PDGFRA	NGS	Mutation Not Detected				✔	II-3 / Good	36, 37, 38

* 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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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 (23)

Drug Class	Biomarker	Method	Investigational Agent(s)
Nucleoside analog (23)	RRM1	IHC	gemcitabine

TARGETED THERAPY CLINICAL TRIALS (130)

Drug Class	Biomarker	Method	Investigational Agent(s)
Cell cycle inhibitors (10)	RB1	NGS	LEE011, LY2606368, MK-1775, palbociclib
	TP53	NGS	
ERK inhibitors (1)	NF1	NGS	BVD-523
Immunomodulatory agents (75)	PD-1	IHC	MK-3475, MPDL3280A, atezolizumab, avelumab, nivolumab, pembrolizumab
MEK inhibitors (20)	NF1	NGS	GDC-0973, PD0325901, XL518, selumetinib, trametinib
Multikinase inhibitors (17)	NF1	NGS	GSK2118436 (dabrafenib), sorafenib
NTRK inhibitors (6)	TrkA/B/C	IHC	LOXO-101, MGCD516, PLX7486, entrectinib (RXDX-101)
p53-targeted biological agents (1)	TP53	NGS	modified vaccinia virus ankara vaccine expressing p53

( ) = 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*
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10. 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
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** See Appendix page 6 for Level of Evidence description.*

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	SOURCE	LEVEL OF EVIDENCE*
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20.	Byrski, T., S. Narod, et. Al. (2009) "Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy." J Clin Oncol. 28(3):275-9. View Citation Online	II-3 / Good
21.	Bambury, R.M., J.E. Rosenberg, et al. (2015). "Association of somatic mutations in DNA damage repair (DDR) genes with efficacy of platinum-based chemotherapy in advanced urothelial carcinoma". J Clin Oncol. 33, (suppl; abstr 4532).	III / Good
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23.	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
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35.	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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** See Appendix page 6 for Level of Evidence description.*

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SOURCE	LEVEL OF EVIDENCE*
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38. Heinrich, M.C., J.A. Fletcher, et. al. (2008). "Correlation of kinase genotype and clinical outcome in North American Intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 study by Cancer and Leukemia Group B and Southwest Oncology Group." J Clin Oncol 26(33):5360-5367. View Citation Online	II-3 / Good
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53. Mateo, J., J.S. de Bono, et al. (2015). "DNA-repair defects and olaparib in metastatic prostate cancer". N Engl J Med. 373(18): 1697-1708. View Citation Online	II-1 / Good

** See Appendix page 6 for Level of Evidence description.*

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
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** See Appendix page 6 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 submandibular lymph nodes, lymph node dissection: Metastatic olfactory neuroblastoma involving one of three lymph nodes (1/3).

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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MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS LIFE SCIENCES

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

TOTAL MUTATIONAL LOAD

Result	Mutations / Megabase (Mb)	Threshold
Low	3	≥ 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
NF1	R1362X	68	30	Mutated, Pathogenic

Interpretation: A nonsense pathogenic mutation was identified, this mutation has been detected in the germline of patients with Neurofibromatosis 1 (Upadhyaya (1997) Hum Genet 99: 88).

The NF1 gene encodes neurofibromin, a protein that activates RAS GTP-ase, causing inactivation of RAS and serving as a negative regulator of the RAS pathway. Preclinical studies suggest that mutations in NF1 are associated with a decreased sensitivity to EGFR inhibitory drugs in lung cancer, perhaps due to an increased level of RAS activity that allows the tumor to escape the negative regulation of EGFR. Further preclinical studies have shown that NF1 mutations/deletions cause sensitivity to MEK inhibitors in sarcoma cell lines and resistance to RAF inhibition in melanoma cell lines. NF1 mutations have been observed in urothelial, ovarian, lung and triple negative breast cancer.

TP53	T231S	76	7	Mutated, Variant of Unknown Significance

Interpretation: A variant of unknown clinical significance in the TP53 gene was found in the sample. This mutation and substitutions at Thr231 residue have been reported in several sporadic tumors including large intestine, skin, and breast.

TP53, or p53, plays a central role in modulating response to cellular stress through transcriptional regulation of genes involved in cell-cycle arrest, DNA repair, apoptosis, and senescence. Inactivation of the p53 pathway is essential for the formation of the majority of human tumors. Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia, estimated to occur in 30-50% of all cancers. Generally, presence of a disruptive p53 mutation is associated with a poor prognosis in all types of cancers, and diminished sensitivity to radiation and chemotherapy. Germline p53 mutations are associated with the Li-Fraumeni syndrome (LFS) which may lead to early-onset of several forms of cancer currently known to occur in the syndrome, including sarcomas of the bone and soft tissues, carcinomas of the breast and adrenal cortex (hereditary adrenocortical carcinoma), brain tumors and acute leukemias.

GENES TESTED WITH NO MUTATIONS DETECTED

ATM	BRCA2	EGFR	KRAS	PIK3CA
BRAF	c-KIT	Her2/Neu (ERBB2)	NRAS	RET
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
BCR	V949I	KMT2A	K334E	NUP214	I765V	USP6	I67 _R68 delinsMW
CIC	L986V	MLLT6	A327T	PCM1	N159S		
DICER1	E1420del		A447S	RBM15	S26G		

GENES TESTED WITH INDETERMINATE RESULTS

ARID1A	CASP8	EML4	MED12	PCSK7	TAF15
ARNT	CD79A	EPS15	MLF1	PIK3R2	TBL1XR1
ASPSCR1	CEBPA	ETV1	MLLT10	PMS2	TRIM33
ATIC	CHEK2	FANCE	MNX1	PTPRC	UBR5
ATRX	CHN1	FNBP1	MUC1	SMARCE1	VEGFB
BCL11A	CNTRL	GOPC	MYCL	STAT4	YWHAE
BCL3	COL1A1	HOXA11	NOTCH2	STAT5B	
BIRC3	ELK4	KDM5C	NUTM2B	STIL	
CASC5	ELL	MALT1	PAX5	SUZ12	

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 530 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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GENE FUSION AND TRANSCRIPT VARIANT DETECTION BY **RNA SEQUENCING**

GENES TESTED WITH NO GENE FUSION OR TRANSCRIPT VARIANT DETECTED				
ALK	cMET	NTRK1	NTRK3	ROS1
BRAF	EGFRvIII	NTRK2	RET	RSPO3

Gene Fusion Methods

Fusion gene analysis as well as the variant transcript analysis of EGFRvIII (exon 2-7 deletion) and MET (Exon 14 skipping), was performed on mRNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Archer FusionPlex Solid Tumor Panel and the Illumina MiSeq. This assay is designed to detect fusions that occur at known breakpoints within tested fusion genes. Fusions occurring outside of known breakpoints in these genes may not be detected. This assay has the ability to detect a fusion that is present in at least 10% of the cells in the sample tested.

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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 +	5	Negative	Intensity of ≥3+ with ≥10% or ≥2+ with ≥50% of cells stained
Her2/Neu	0	100	Negative	Intensity ≥3+ and >10% of cells stained
PD-L1	0	100	Negative	Intensity ≥2+ and ≥5% of cells stained
RRM1	2 +	20	Negative	Intensity ≥2+ and ≥50% of cells stained
TOP2A	2 +	7	Negative	Intensity ≥1+ and ≥10% of cells stained
TrkA/B/C	1 +	2	Positive	Intensity ≥1+ and ≥1% of cells stained
TS	1 +	10	Positive	Intensity ≥1+ and ≥10% of cells stained
TUBB3	3 +	100	Positive	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: TOP2A(3F6), TUBB3(Polyclonal), Her2/Neu(4B5), ERCC1(8F1), PD-L1(SP142), TrkA/B/C(EPR17341), RRM1(Polyclonal), TS(TS106/4H4B1).

Biomarker	TIL Count/HPF w/40X Objective	Result	Threshold (Condition for a Positive Result)
PD-1	1/HPF	Positive	Intensity ≥1+

IHC Methods

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

* Please note that PD1 staining is read from the tumor infiltrating lymphocytes (TIL).Clones used: PD-1(MRQ-22).

Clones used: PD-1(MRQ-22).

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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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