




FINAL REPORT

PATIENT	SPECIMEN INFORMATION	ORDERED BY
Name: Patient, Test Date of Birth: XX-Mon-1980 Sex: Female Case Number: TN14-111111 Diagnosis: Carcinoma, metastatic, NOS	Primary Tumor Site: Unknown primary site Specimen Site: Supraclavicular lymph node Specimen ID: ABC-12345-YZ Specimen Collected: XX-Mon-2015 Completion of Testing: XX-Mon-2015	Ordering Physician, MD Cancer Center Main Street Australia 1234 (123) 456-78910

 THERAPIES WITH POTENTIAL BENEFIT (PAGE 4)					
docetaxel, paclitaxel	TLE3 [★] , PGP, TUBB3	doxorubicin, epirubicin, liposomal-doxorubicin	PGP, Her2/Neu, TOP2A	nab-paclitaxel	SPARC Polyclonal, SPARC Monoclonal

★ Indicates Clinical Trial Opportunity • 65 Chemotherapy Trials • 81 Targeted Therapy Trials (See *Clinical Trials Connector™* on page 8 for details.)

 THERAPIES WITH POTENTIAL LACK OF BENEFIT (PAGE 5)					
abarelix, degarelix, goserelin, leuprolide, triptorelin	ER, PR, Androgen Receptor	anastrozole, exemestane, fulvestrant, letrozole, megestrol acetate, tamoxifen, toremifene	PR, ER	gemcitabine	RRM1
abiraterone, bicalutamide, enzalutamide, flutamide	Androgen Receptor	capecitabine, fluorouracil, pemetrexed	TS	irinotecan, topotecan	TOPO1
ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab	Her2/Neu	dabrafenib, vemurafenib	BRAF	lapatinib	Her2/Neu
		dacarbazine, temozolomide	MGMT		

 THERAPIES WITH INDETERMINATE BENEFIT (PAGE 7)			
carboplatin, cisplatin, oxaliplatin	imatinib	vandetanib	everolimus, temsirolimus

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.

SUMMARY OF BIOMARKER RESULTS (SEE APPENDIX FOR FULL DETAILS)

Biomarker	Method	Result	Biomarker	Method	Result
ABL1	NGS	Mutation Not Detected	JAK3	NGS	Mutation Not Detected
AKT1	NGS	Mutation Not Detected	KDR (VEGFR2)	NGS	Mutation Not Detected
ALK	NGS	Mutation Not Detected	KRAS	NGS	Mutated G13D
Androgen Receptor	IHC	Negative	MGMT	IHC	Positive
APC	NGS	Mutation Not Detected	MPL	NGS	Mutation Not Detected
ATM	NGS	Mutation Not Detected	NOTCH1	NGS	Mutation Not Detected
BRAF	NGS	Mutation Not Detected	NPM1	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected	NRAS	NGS	Mutation Not Detected
BRCA2	NGS	Mutated E3071K	PD-1 IHC	IHC	Positive
CDH1	NGS	Mutation Not Detected	PDGFRA	NGS	Mutation Not Detected
c-KIT	NGS	Mutation Not Detected	PD-L1 IHC	IHC	Negative
cMET	NGS	Mutation Not Detected	PGP	IHC	Negative
cMET	IHC	Negative	PIK3CA	NGS	Mutated E545K
cMET	CISH	Not Amplified	PR	IHC	Negative
CSF1R	NGS	Mutation Not Detected	PTEN	IHC	Positive
CTNNB1	NGS	Mutation Not Detected	PTEN	NGS	Mutation Not Detected
EGFR	IHC	Positive	PTPN11	NGS	Mutation Not Detected
EGFR	NGS	Mutation Not Detected	RB1	NGS	Mutation Not Detected
ER	IHC	Negative	RET	NGS	Mutation Not Detected
ERBB4	NGS	Mutation Not Detected	RRM1	IHC	Positive
FBXW7	NGS	Mutated R505C	SMAD4	NGS	Mutation Not Detected
FGFR1	NGS	Mutation Not Detected	SMARCB1	NGS	Mutation Not Detected
FGFR2	NGS	Mutation Not Detected	SMO	NGS	Mutation Not Detected
FLT3	NGS	Mutation Not Detected	SPARC Monoclonal	IHC	Negative
GNA11	NGS	Mutation Not Detected	SPARC Polyclonal	IHC	Positive
GNAQ	NGS	Mutation Not Detected	STK11	NGS	Mutation Not Detected
GNAS	NGS	Mutation Not Detected	TLE3	IHC	Positive
Her2/Neu	IHC	Negative	TOP2A	IHC	Positive
Her2/Neu	CISH	Not Amplified	TOPO1	IHC	Negative
Her2/Neu (ERBB2)	NGS	Mutation Not Detected	TP53	NGS	Mutation Not Detected
HNF1A	NGS	Mutation Not Detected	TS	IHC	Positive
HRAS	NGS	Mutation Not Detected	TUBB3	IHC	Positive
IDH1	NGS	Mutation Not Detected	VHL	NGS	Mutation Not Detected
JAK2	NGS	Mutation Not Detected			

IHC: Immunohistochemistry

CISH: Chromogenic *in situ* hybridization **NGS:** Next-Generation Sequencing

Biomarker Results continued on the next page. >

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SUMMARY OF BIOMARKER RESULTS (SEE APPENDIX FOR FULL DETAILS)

For Next-Generation Sequencing, a total of 46 genes were analyzed. The results above include genes most commonly associated with cancer and any additional mutations identified. No alterations were identified in 42 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

Footnote(s):

Mutation analysis of BRCA1 and BRCA2 identified a E3071K (Mutated, Variant of Unknown Significance) mutation in BRCA2.

Current assay is not intended to identify or diagnose a hereditary condition, and all mutations detected in this assay may be somatic or germ line in origin and are used primarily for theranostic purposes. Appropriate genetic counseling and testing is recommended.

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

SAMPLE REPORT. ILLUSTRATIVE PURPOSES ONLY. NOT FOR CLINICAL USE.

✓ 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
docetaxel, paclitaxel	PGP	IHC	Negative	0+ 100%	✓			II-3 / Fair	38, 39
	TLE3	IHC	Positive	2+ 30%	✓			II-2 / Good	37
	TUBB3	IHC	Positive	3+ 60%		✓		I / Good	40, 41, 42, 43
doxorubicin, epirubicin, liposomal-doxorubicin	Her2/Neu	CISH	Not Amplified	1.32		✓		I / Good	46, 47
	PGP	IHC	Negative	0+ 100%	✓			II-1 / Fair	44, 45
	TOP2A	IHC	Positive	2+ 20%	✓			I / Good	48, 49
nab-paclitaxel	SPARC Monoclonal	IHC	Negative	1+ 50%		✓		II-2 / Good	65, 66
	SPARC Polyclonal	IHC	Positive	2+ 30%	✓			II-2 / Good	65, 66

* 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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X 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
abarelix, degarelix, goserelin, leuprolide, triptorelin	Androgen Receptor	IHC	Negative	0+ 100%			✓	II-3 / Good	2
	ER	IHC	Negative	0+ 100%			✓	I / Good	1
	PR	IHC	Negative	0+ 100%			✓	I / Good	1
abiraterone, bicalutamide, enzalutamide, flutamide	Androgen Receptor	IHC	Negative	0+ 100%			✓	I / Good	2, 3, 4, 5
ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab	Her2/Neu	CISH	Not Amplified	1.32			✓	I / Good	6, 7, 8, 9, 10, 11, 12, 13
	Her2/Neu	IHC	Negative	0+ 100%			✓	I / Good	6, 7, 8, 9, 10, 11, 12
anastrozole, exemestane, fulvestrant, letrozole, megestrol acetate, tamoxifen, toremifene	ER	IHC	Negative	0+ 100%			✓	I / Good	14, 17, 18, 19, 20, 21, 22, 23
	PR	IHC	Negative	0+ 100%			✓	I / Good	14, 15, 16, 17, 18, 19, 20, 21
capecitabine, fluorouracil, pemetrexed	TS	IHC	Positive	1+ 30%			✓	I / Good	24, 25, 26
dabrafenib, vemurafenib	BRAF	Next Gen SEQ	Wild Type				✓	I / Good	31, 32, 33, 34
dacarbazine, temozolomide	MGMT	IHC	Positive	1+ 50%			✓	II-2 / Good	35, 36
gemcitabine	RRM1	IHC	Positive	2+ 80%			✓	I / Good	53
irinotecan, topotecan	TOPO1	IHC	Negative	2+ 20%			✓	II-1 / Good	59, 60, 61

Additional Therapies Associated with Potential Lack of Benefit continued on the next page. >

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Therapies	Test	Method	Result	Value [†]	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
lapatinib	Her2/Neu	CISH	Not Amplified	1.32			✓	I / Good	13, 62, 63, 64
	Her2/Neu	IHC	Negative	0+ 100%			✓	I / Good	62, 63, 64

* 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
carboplatin , cisplatin , oxaliplatin	BRCA1	Next Gen SEQ	Mutation Not Detected				✓	II-2 / Good	27, 28, 29, 30
	BRCA2	Next Gen SEQ	Mutation Not Detected						
everolimus , temsirolimus	PIK3CA	Next Gen SEQ	Mutated, Pathogenic	E545K		✓		II-2 / Good	50, 51, 52
imatinib	c-KIT	Next Gen SEQ	Wild Type				✓	II-2 / Good	54, 55
	PDGFRA	Next Gen SEQ	Wild Type				✓	II-3 / Good	56, 57, 58
vandetanib	RET	Next Gen SEQ	Wild Type					I / Good	67

* 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 (65)			
Drug Class	Biomarker	Method	Investigational Agent(s)
Platinum compounds (48)	BRCA2	Next Gen SEQ	carboplatin, cisplatin
Taxanes (17)	TLE3	IHC	docetaxel

TARGETED THERAPY CLINICAL TRIALS (81)			
Drug Class	Biomarker	Method	Investigational Agent(s)
EGFR monoclonal antibody (16)	EGFR	IHC	cetuximab
ERK inhibitors (1)	KRAS	Next Gen SEQ	BVD-523
Immunomodulatory agents (3)	PD-1	IHC	MK-3475, lambrolizumab, lambrolizumab (MK-3475)
MDM2 inhibitors (3)	TP53	Next Gen SEQ	CGM097, DS-3032, Kevetrin (thioureidobutyronitrile)
MEK inhibitors (2)	KRAS	Next Gen SEQ	GDC-0973
PARP inhibitors (2)	BRCA2	Next Gen SEQ	BMN-673
PI3K/Akt/mTor inhibitors (54)	PIK3CA	Next Gen SEQ	ARQ092, AZD2014, AZD5363, BAY80-6946, BEZ235, BKM120, BYL719, CC-223, GDC-0068, GSK2110183, GSK2141795, INK1117, LY2780301, MK2206, MLN0128, MLN1117, everolimus

() = 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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2. El Sheikh, S. S., H. M. Romanska, et al. (2008). "Predictive value of PTEN and AR coexpression of sustained responsiveness to hormonal therapy in prostate cancer—a pilot study." <i>Neoplasia</i> . 10(9): 949-53. View Citation Online	II-3 / Good
3. Jaspers, H.C., C.M. van Herpen, et al. (2011). "Androgen-receptor-positive salivary duct carcinoma: a disease entity with promising new treatment options". <i>J Clin Oncol</i> . 29(16):e473-476. View Citation Online	II-3 / Fair
4. Scher, H.I., J.S. de Bono, et al. (2012). "Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy". <i>N Engl J Med</i> . 367:1187-1197. View Citation Online	I / Good
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8. Yin, W., J. Lu, et al. (2011). "Trastuzumab in adjuvant treatment HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials." <i>PLoS ONE</i> 6(6): e21030. doi:10.1371/journal.pone.0021030. View Citation Online	I / Good
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11. Slamon, D., M. Buyse, et al. (2011). "Adjuvant trastuzumab in HER2-positive breast cancer." <i>N. Engl. J. Med</i> . 365:1273-83. View Citation Online	I / Good
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13. Bartlett, J.M.S., K. Miller, et al. (2011). "A UK NEQAS ISH multicenter ring study using the Ventana HER2 dual-color ISH assay." <i>Am. J. Clin. Pathol</i> . 135:157-162. View Citation Online	II-3 / Good
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16. Yamashita, H., Y. Yando, et al. (2006). "Immunohistochemical evaluation of hormone receptor status for predicting response to endocrine therapy in metastatic breast cancer." <i>Breast Cancer</i> 13(1): 74-83. View Citation Online	II-3 / Good
17. Stuart, N.S.A., H. Earl, et al. (1996). "A randomized phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer." <i>European Journal of Cancer</i> . 32(11):1888-1892. View Citation Online	II-2 / Fair

* See Appendix page 7 for Level of Evidence description.

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
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19. Thurlimann, B., A. Goldhirsch, et al. (1997). "Formestane versus Megestrol Acetate in Postmenopausal Breast Cancer Patients After Failure of Tamoxifen: A Phase III Prospective Randomised Cross Over Trial of Second-line Hormonal Treatment (SAKK 20/90). <i>E J Cancer</i> 33 (7): 1017-1024. View Citation Online	II-2 / Fair
20. Lewis, J.D., M.J. Edwards, et al. (2010). "Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer." <i>Cancer</i> 116:2307-15. View Citation Online	I / Good
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22. Anderson, H., M. Dowsett, et al. (2011). "Relationship between estrogen receptor, progesterone receptor, HER-2 and Ki67 expression and efficacy of aromatase inhibitors in advanced breast cancer. <i>Annals of Oncology</i> . 22:1770-1776. View Citation Online	II-3 / Good
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25. 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." <i>Int. J. Cancer</i> : 123, 2384-2389. View Citation Online	I / Good
26. 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." <i>Cancer Chemother. Pharmacol.</i> DOI 10.1007/s00280-010-1545-0. View Citation Online	II-3 / Good
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* See Appendix page 7 for Level of Evidence description.

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
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* See Appendix page 7 for Level of Evidence description.

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PHYSICIAN: Ordering Physician, MD

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SOURCE	LEVEL OF EVIDENCE*
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* See Appendix page 7 for Level of Evidence description.

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SPECIMEN(S) RECEIVED (GROSS DESCRIPTION)

Specimen ID: ABC-12345-YZ

Specimen Collected: XX-Mon-2015

The specimen(s) consist of: 1 (A) Paraffin Block - Client ID (ABC-12345-YZ) with the corresponding surgical pathology report labeled "ABC-12345-YZ".

Clinical History: Per the submitted documents, the patient is a 34 year-old female with metastatic carcinoma of uncertain origin.

Pathologic Diagnosis: Carcinoma, metastatic, NOS

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.



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

GENES TESTED WITH ALTERATIONS				
Gene	Alteration	Frequency (%)	Exon	Result
FBXW7	R505C	45	10	Mutated, Pathogenic
<p>Interpretation: A pathogenic mutation was detected in FBXW7</p> <p>FBXW7 or E3 ligase F-box and WD repeat domain containing 7, also known as Cdc4, encodes three protein isoforms which constitute a component of the ubiquitin-proteasome complex. Mutation of FBXW7 occurs in hotspots and disrupts the recognition of and binding with substrates which inhibits the proper targeting of proteins for degradation (e.g. Cyclin E, c-Myc, SREBP1, c-Jun, Notch-1, mTOR and MCL1). Mutation frequencies identified in cholangiocarcinomas, acute T-lymphoblastic leukemia/lymphoma, and carcinomas of endometrium, colon and stomach are 35%, 31%, 9%, 9%, and 6%, respectively. Targeting an oncoprotein downstream of FBXW7, such as mTOR or c-Myc, may provide a novel therapeutic strategy.</p>				
KRAS	G13D	47	2	Mutated, Pathogenic
<p>Interpretation: A pathogenic mutation was detected in KRAS</p> <p>KRAS or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog encodes a signaling intermediate involved in many signaling cascades including the EGFR pathway. KRAS somatic mutations have been found in pancreatic (57%), colon (35%), lung (16%), biliary tract (28%), and endometrial (15%) cancers. Mutations at activating hotspots are associated with resistance to EGFR tyrosine kinase inhibitors (erlotinib, gefitinib) in NSCLC and monoclonal antibodies (cetuximab, panitumumab) in CRC patients. Retrospective clinical studies raised the possibility that KRAS G13D mutations may not be absolutely predictive of non-response; however, this finding is not supported by published analysis of 3 randomized controlled phase III trials. Various clinical trials (on www.clinicaltrials.gov) investigating agents which target this gene may be available for KRAS mutated patients. Several germline mutations of KRAS (V14I, T58I, and D153V amino acid substitutions) are associated with Noonan syndrome.</p>				
PIK3CA	E545K	33	9	Mutated, Pathogenic
<p>Interpretation: A pathogenic mutation was detected in PIK3CA</p> <p>PIK3CA or phosphoinositide-3-kinase catalytic alpha polypeptide encodes a protein in the PI3 kinase pathway. This pathway is an active target for drug development. PIK3CA somatic mutations have been found in breast (26%), endometrial (23%), urinary tract (19%), colon (13%), and ovarian (11%) cancers. Somatic mosaic activating mutations in PIK3CA are said to cause CLOVES syndrome. PIK3CA exon 20 mutations have been associated with benefit from mTOR inhibitors (everolimus, temsirolimus). Evidence suggests that breast cancer patients with PIK3CA mutation have a significantly shorter survival following trastuzumab treatment. PIK3CA mutated colorectal cancer patients are less likely to respond to EGFR targeted monoclonal antibody therapy. Various clinical trials (on www.clinicaltrials.gov) investigating agents which target this gene may be available for PIK3CA mutated patients.</p>				

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

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

GENES TESTED WITH NO MUTATIONS DETECTED

ABL1	AKT1	ALK	APC	ATM	BRAF
c-KIT	CDH1	cMET	CSF1R	CTNNB1	EGFR
ERBB2	ERBB4	FGFR1	FGFR2	FLT3	GNA11
GNAQ	GNAS	HNF1A	HRAS	IDH1	JAK2
JAK3	KDR	MPL	NOTCH1	NPM1	NRAS
PDGFRA	PTEN	PTPN11	RB1	RET	SMAD4
SMARCB1	SMO	STK11	TP53	VHL	

For Next-Generation Sequencing, a total of 46 genes were analyzed. The results above include genes most commonly associated with cancer and any additional mutations identified. No alterations were identified in 42 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

Electronic Signature

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Comments on NGS Analysis

Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique. Candidate slides were examined 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. The areas marked and extracted were examined on post-microdissected slides and adequacy of microdissection was verified by a board certified Pathologist.

NGS Methods

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of the genome were amplified using the Illumina TruSeq Amplicon Cancer Hotspot panel. This panel only sequences selected regions of 44 genes and the amino acids sequenced by this assay can be found at www.carislifesciences.com. All variants reported by this 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 a sequenced amplicon. 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. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.

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

GENES TESTED WITH ALTERATIONS				
Gene	Alteration	Frequency (%)	Exon	Result
BRCA2	E3071K	36	24	Mutated, Variant of Unknown Significance

Interpretation: This variant has not been reported in the literature. As such, its clinical significance is not currently known.

GENES TESTED WITH NO MUTATIONS DETECTED
BRCA1

Electronic Signature

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BRCA1 Sequencing Methods

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of BRCA1 were amplified using primers flanking coding regions of this gene. All variants reported by this 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 20% population of cells containing a mutation a sequenced amplicon. 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. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.

BRCA2 Sequencing Methods

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of BRCA2 were amplified using primers flanking coding regions of this gene. All variants reported by this 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 20% population of cells containing a mutation a sequenced amplicon. 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. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.

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PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

Biomarker	Patient Tumor			Threshold * Biomarker Intensity/Percentage
	Staining Intensity	Percent Staining	Result	
SPARC Monoclonal	1	50	Negative	<30% or <2+ or ≥2+ and ≥30%
SPARC Polyclonal	2	30	Positive	<30% or <2+ or ≥2+ and ≥30%
ER	0	100	Negative	=0+ or <10% or ≥1+ and ≥10%
PR	0	100	Negative	=0+ or <10% or ≥1+ and ≥10%
Androgen Receptor	0	100	Negative	=0+ or <10% or ≥1+ and ≥10%
TOPO1	2	20	Negative	=0+ or <30% or <2+ or ≥2+ and ≥30%
TOP2A	2	20	Positive	=0+ or <10% or ≥1+ and ≥10%
TLE3	2	30	Positive	<30% or <2+ or ≥2+ and ≥30%
TUBB3	3	60	Positive	<30% or <2+ or ≥2+ and ≥30%
PGP	0	100	Negative	=0+ or <10% or ≥1+ and ≥10%
EGFR	2	80	Positive	=0+ or <10% or ≥1+ and ≥10%
Her2/Neu	0	100	Negative	≤1+ or =2+ and ≤10% or ≥3+ and >10%
cMET	1	95	Negative	<50% or <2+ or ≥2+ and ≥50%
MGMT	1	50	Positive	=0+ or ≤35% or ≥1+ and >35%
PD-L1	0	100	Negative	<5% or <2+ or ≥2+ and ≥5%
PTEN	1	60	Positive	=0+ or ≤50% or ≥1+ and >50%
RRM1	2	80	Positive	=0+ or <50% or <2+ or ≥2+ and ≥50%
TS	1	30	Positive	=0+ or ≤3+ and <10% or ≥1+ and ≥10%

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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.

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

Clones used: SPARC Monoclonal(122511), SPARC Polyclonal(Polyclonal), ER(SP1), PR(1E2), Androgen Receptor(AR27), TOPO1(1D6), TOP2A(3F6), TLE3(Polyclonal), TUBB3(Polyclonal), PGP(C494), EGFR(H11), Her2/Neu(4B5), cMET(SP44), MGMT(MT23.2), PD-L1(130021), PTEN(6H2.1), RRM1(Polyclonal), TS(TS106/4H4B1).

Additional IHC results continued on the next page. >

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PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

Biomarker	TIL Count/HPF w/40X Objective	Result	Threshold *
PD-1	>5/HPF	Positive	=0+ or ≥1+

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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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AMPLIFICATION BY **CHROMOGENIC IN SITU HYBRIDIZATION (CISH)**

Gene / ISCN	Cells Counted	Result	Total/Avg Gene Copy Number	Total/Avg Control Copy Number	Cells with ≥ 4 Copies	Cells with ≥ 15 Copies	Ratio Calculation	Ratio
Her2/Neu nuc ish (D17Z1x1-2,HER2x1-2)[/30]	20	Not Amplified	2.70	2.05	N/A	N/A	Her2/neu/ Chromosome 17	1.32
<i>Reference Range:</i> Her2/Neu:CEP 17 signal ratio of ≥ 2.0 ; and non-amplification as < 2.0 per Ventana INFORM HER2 CISH Package insert.								
cMET nuc ish (D7Z1x1-2,cMETx1-2)[100/100]	20	Not Amplified	2.15	2.60	N/A	N/A		0.83
<i>Reference Range:</i> Positivity for increased gene copy number for cMET CISH has been defined as ≥ 5 copies of mean MET gene copy number per cell in NSCLC based on cMET FISH evidence (Cappuzzo et al 2009). The gene copy number threshold for other tumor types has not been determined.								

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CISH Methods

HER2 CISH test was carried out using the INFORM DUAL HER2 ISH Assay (Ventana Medical Systems, Inc.), which has been cleared by the US Food and Drug Administration (FDA) for enumerating the ratio of HER2/Chr 17 in Breast Cancer samples. The HER2 CISH testing for cancer lineages other than breast has been developed and their performance characteristics determined by Caris MPI, Inc. (d/b/a Caris Life Sciences), and have not been cleared or approved by the FDA.

cMET CISH was carried out using a probe specific for cMET and a probe for the pericentromeric region of chromosome 7 (Ventana). The cMET CISH testing for cancer lineages has been developed and its performance characteristics determined by Caris MPI, Inc. (d/b/a Caris Life Sciences), and has not been cleared or approved by the FDA.

The FDA has determined that such clearance or approval is not currently necessary. These tests should not be regarded as investigational or research as they are used for clinical purpose and determined to be medically necessary by the ordering physician, who is not employed by Caris MPI, Inc. or its affiliates. This laboratory is certified under Clinical Laboratory Improvement Amendment of 1988 (CLIA-88) and is qualified to perform high complexity testing. CLIA 03D1019490

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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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