CARIS LIFE SCIENCES

FINAL REPORT

PATIENT	SPECIMEN INFORMATION	ORDERED BY
Name: Patient, Test **Date of Birth:** XX-Mon-19XX **Sex:** Female **Case Number:** TN17-XXXXXX **Diagnosis:** Ductal carcinoma, NOS	**Primary Tumor Site:** Breast, NOS **Specimen Site:** Breast, NOS **Specimen ID:** ABC-1234-XX **Specimen Collected:** XX-Mon-2017 **Testing Completed:** XX-Mon-2017	**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**

NONE

★ **Indicates Clinical Trial Opportunity • 2 Targeted Therapy Trials** *(See Clinical Trials Connector™ on page 5 for details.)*

✘ THERAPIES WITH **POTENTIAL LACK OF BENEFIT** (PAGE 3)

dabrafenib, vemurafenib — BRAF		

? THERAPIES WITH **INDETERMINATE BENEFIT** (PAGE 4)

carboplatin, **cisplatin**	**trastuzumab**	oxaliplatin
everolimus	imatinib	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.

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SUMMARY OF BIOMARKER RESULTS (SEE APPENDIX FOR FULL DETAILS)

Biomarker	Method	Result	Biomarker	Method	Result
ABL1	NGS	Mutation Not Detected	HNF1A	NGS	Mutation Not Detected
AKT1	NGS	Mutation Not Detected	HRAS	NGS	Mutation Not Detected
ALK	NGS	Mutation Not Detected	IDH1	NGS	Mutation Not Detected
APC	NGS	Mutation Not Detected	JAK2	NGS	Mutation Not Detected
ATM	NGS	Mutation Not Detected	JAK3	NGS	Mutation Not Detected
BRAF	NGS	Mutation Not Detected	KDR (VEGFR2)	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected	KRAS	NGS	Mutation Not Detected
BRCA2	NGS	Mutation Not Detected	MPL	NGS	Mutation Not Detected
c-KIT	NGS	Mutation Not Detected	NOTCH1	NGS	Mutation Not Detected
CDH1	NGS	Mutation Not Detected	NPM1	NGS	Mutation Not Detected
cMET	NGS	Mutation Not Detected	NRAS	NGS	Mutation Not Detected
CSF1R	NGS	Mutation Not Detected	PDGFRA	NGS	Mutation Not Detected
CTNNB1	NGS	Mutation Not Detected	PIK3CA	NGS	Mutation Not Detected
EGFR	NGS	Mutation Not Detected	PTEN	NGS	Mutation Not Detected
ERBB4	NGS	Mutation Not Detected	PTPN11	NGS	Mutation Not Detected
FBXW7	NGS	Mutation Not Detected	RB1	NGS	Mutation Not Detected
FGFR1	NGS	Mutation Not Detected	RET	NGS	Mutation Not Detected
FGFR2	NGS	Mutation Not Detected	SMAD4	NGS	Mutation Not Detected
FLT3	NGS	Mutation Not Detected	SMARCB1	NGS	Mutation Not Detected
GNA11	NGS	Mutation Not Detected	SMO	NGS	Mutation Not Detected
GNAQ	NGS	Mutation Not Detected	STK11	NGS	Mutation Not Detected
GNAS	NGS	Mutation Not Detected	TP53	NGS	Mutation Not Detected
Her2/Neu (ERBB2)	NGS	Mutation Not Detected	VHL	NGS	Mutation Not Detected

NGS: Next-Generation 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: 46 | Genes with actionable mutations: 0 | Genes with unclassified mutations: 0 | Genes with no mutations detected: 46

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

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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
dabrafenib, vemurafenib	BRAF	NGS	Mutation Not Detected				✔	I / Good	5, 6, 7, 8

* 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	NGS	Mutation Not Detected				✔	II-2 / Good	1, 2, 3, 4#
	BRCA2	NGS	Mutation Not Detected				✔	II-2 / Good	1, 2, 3
everolimus, temsirolimus	PIK3CA	NGS	Mutation Not Detected			✔		II-2 / Good	9#, 10#, 11#
imatinib	c-KIT	NGS	Mutation Not Detected				✔	II-2 / Good	15, 16
	PDGFRA	NGS	Mutation Not Detected				✔	II-3 / Good	12, 13, 14
trastuzumab	PIK3CA	NGS	Mutation Not Detected					II-3 / Good	17#, 18#

* 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.

TARGETED THERAPY CLINICAL TRIALS (2)

Drug Class	Biomarker	Method	Investigational Agent(s)
MDM2 inhibitors (2)	TP53	NGS	CGM097, DS-3032

( ) = 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.	Tan, D.S.P., M.E. Gore, et. Al. (2008) ""BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations." J Clin Oncol. 26(34):5530-6 View Citation Online	II-2 / Good
2.	Hennessy, B.T., G.B. Mills, et al. (2010) "Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer" J Clin Oncol. 28(22):3570-6 View Citation Online	II-3 / Good
3.	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
4.	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
5.	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
6.	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
7.	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
8.	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
9.	Moroney, J.W., R. Kurzrock, et. al. (2011). "A phase I trial of liposomal doxorubicin, bevacizumab, and temsirolimus in patients with advanced gynecologic and breast malignancies." Clin. Cancer Res. 17:6840-6846. View Citation Online	II-3 / Fair
10.	Janku, F., R. Kurzrock, et. al. (2012) "PIK3CA Mutation H1047R Is Associated with Response to PI3K/AKT/mTOR Signaling Pathway Inhibitors in Early-Phase Clinical Trials", Cancer Res; 73(1); 276-84. View Citation Online	II-2 / Good
11.	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
12.	Cassier, P.A., P. Hohenberger, et al. (2012). "Outcome of Patients with Platelet-Derived Growth Factor Receptor Alpha-Mutated Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era." Clin Cancer Res 18:4458-4464. View Citation Online	II-3 / Good
13.	Debiec-Rychter, M., I. Judson, et al. (2006). "KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours." Eur J Cancer 42:1093-1103. View Citation Online	II-3 / Good
14.	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
15.	Guo, J., S. Qin, et. al. (2011). "Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification." J. Clin. Oncol. 29:2904-2909. View Citation Online	II-2 / Good
16.	Carvajal, R.D., G.K. Schwartz, et. al. (2011). "KIT as a therapeutic target in metastatic melanoma." JAMA. 305(22):2327-2334. View Citation Online	II-2 / Good
17.	Dave, B., J.C. Chang, et. al. (2011). "Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers." Journal of Clinical Oncology. 29(2):166-173. View Citation Online	II-3 / Good
18.	Esteva, F.J., D. Yu, et. al. (2010). "PTEN, PIK3CA, p-AKT, and p-p79S6K Status." American Journal of Pathology. 177(4):1647-1656. View Citation Online	II-3 / Good

** See Appendix page 3 for Level of Evidence description.*

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REFERENCES

SOURCE	LEVEL OF EVIDENCE*
19. Wells, S.A., M.J. Schlumberger, et al. (2012). "Vandetanib in Patients with Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial." J Clin Oncol 30: 134-141. View Citation Online	I / Good

** See Appendix page 3 for Level of Evidence description.*

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SPECIMEN INFORMATION

Specimen ID: ABC-1234-XX

Specimen Collected: XX-Mon-2017

Specimen Recieved: XX-Mon-2017

Testing Initiated: XX-Mon-2017

Gross description: 1 (A) Paraffin Block - Client ID (ABC-123-XY) from XYZ Medical Center, Springfield, XY, with the corresponding cytology report labeled "ABC-123-XY".

Pathologic Diagnosis: Right and left breast lesions; ultrasound guided core biopsy: Invasive ductal carcinoma,

Left iliac bone; CT-guided core biopsy: Metastatic carcinoma of breast origin.

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.

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-scraped slides and adequacy of scraping was verified by a board certified Pathologist.

Electronic Signature XX-Mon-2017

CE EC REP

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The Netherlands

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

GENES TESTED WITH NO MUTATIONS DETECTED					
ABL1	cMET	FGFR2	JAK2	PDGFRA	SMO
AKT1	CSF1R	FLT3	JAK3	PIK3CA	STK11
ALK	CTNNB1	GNA11	KDR	PTEN	TP53
APC	EGFR	GNAQ	KRAS	PTPN11	VHL
ATM	ERBB2	GNAS	MPL	RB1	
BRAF	ERBB4	HNF1A	NOTCH1	RET	
c-KIT	FBXW7	HRAS	NPM1	SMAD4	
CDH1	FGFR1	IDH1	NRAS	SMARCB1	

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 46 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

Electronic Signature XX-Mon-2017

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 NO MUTATIONS DETECTED	
BRCA1	BRCA2

Electronic Signature XX-Mon-2017

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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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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