MI PROFILE™

Final Report | CARIS LIFE SCIENCES

Patient

Name: Patient, Test
Date of Birth: XX/Mon/19XX
Sex: Female
Case Number: TN19-XXXXXX
Diagnosis: Carcinoma, metastatic, NOS

Specimen Information

Primary Tumor Site: Breast, NOS
Specimen Site: Pleura, NOS
Specimen ID: ABC-1234-XYZ
Specimen Collected: XX-Mon-2019
Completion of Testing: XX-Mon-2019

Ordered By

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

High Impact Results

BIOMARKER	METHOD	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
BRCA1	**NGS**	**Mutated, Pathogenic Exon 23 | p.R1835***	**BENEFIT**	**olaparib, talazoparib**	**Level 1**
			BENEFIT	carboplatin, cisplatin	Level 3A
ER	**IHC**	**Positive | 3+, 90%**	**BENEFIT**	**endocrine therapy**	**Level 1**
			BENEFIT	abemaciclib, palbociclib, ribociclib	Level 2
			BENEFIT	everolimus	Level 2
PR	**IHC**	**Positive | 2+, 3%**	**BENEFIT**	**endocrine therapy**	**Level 1**
			BENEFIT	abemaciclib, palbociclib, ribociclib	Level 2
ERBB2 (Her2/Neu)	CISH	Not Amplified	LACK OF BENEFIT	ado-trastuzumab emtansine (T-DM1), lapatinib, neratinib, pertuzumab, trastuzumab	Level 1
	IHC	Negative | 1+, 10%			

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or biomarker association included on the drug label; Level 2 - strong evidence of clinical significance and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance (3A - evidence exists in patient's tumor type, 3B - evidence exists in another tumor type).

Additional Results

CANCER TYPE RELEVANT BIOMARKERS

Biomarker	Method	Result
MSI	NGS	Stable
Mismatch Repair Status		Proficient
Tumor Mutational Burden		Intermediate | 11 Mutations/Mb
AKT1	NGS	Mutation Not Detected
AR	IHC	Positive | 2+, 90%
BRCA2	NGS	Mutation Not Detected
ERBB2 (Her2/Neu)	NGS	Mutation Not Detected
ESR1	NGS	Mutation Not Detected
PD-L1	SP142 IHC	Negative | 0

CANCER TYPE RELEVANT BIOMARKERS (cont)

Biomarker	Method	Result
PIK3CA	NGS	Mutated, Pathogenic
		Exon 21 | p.H1047R
PTEN	IHC	Positive | 1+, 100%
	NGS	Mutation Not Detected

OTHER FINDINGS (see page 2 for additional results)

Biomarker	Method	Result
ARID1A	NGS	Mutated, Pathogenic
		Exon 3 | p.P517fs

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 concerning the patient's condition, the FDA prescribing information for any therapeutic, and in accordance with the applicable standard of care. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly. All trademarks and registered trademarks are the property of their respective owners.

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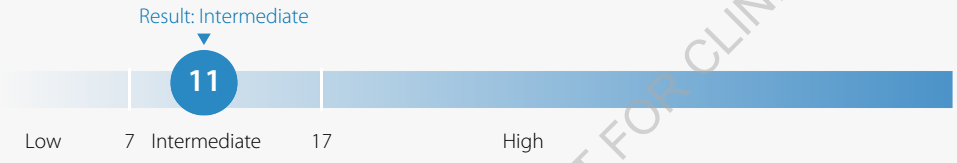
Biomarker Results

This summary includes biomarkers most commonly associated with cancer. Complete details of all biomarkers tested can be found in the Appendix.

GENOMIC SIGNATURES		
Biomarker	**Method**	**Result**
Microsatellite Instability (MSI)	NGS	Stable
Tumor Mutational Burden (TMB)	NGS	

GENES TESTED WITH MUTATIONS/ALTERATIONS						
Gene	**Method**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**
ARID1A	NGS	Mutated, Variant of Unknown Significance	p.P329S	1	c.985C>T	67
	NGS	Mutated, Pathogenic	p.P517fs	3	c.1548 _1549delTC	46
ATM	NGS	Mutated, Presumed Benign	p.I124V	5	c.370A>G	25
BRCA1	NGS	Mutated, Pathogenic	p.R1835*	23	c.5503C>T	52
CDH1	NGS	Mutated, Variant of Unknown Significance	p.V132I	4	c.394G>A	24
PIK3CA	NGS	Mutated, Pathogenic	p.H1047R	21	c.3140A>G	34
RET	NGS	Mutated, Variant of Unknown Significance	p.T75M	2	c.224C>T	35

Unclassified alterations for DNA sequencing can be found in the Appendix.
Formal nucleotide nomenclature and gene reference sequences can be found in the appendix of this report.

Transcript ID and Variants of Unknown Significance can be found in the Appendix.

Other Findings

IMMUNOHISTOCHEMISTRY (IHC)			
Biomarker	**Result**	**Biomarker**	**Result**
AR	Positive | 2+, 90%	PD-L1 (SP142)	Negative | 0
ER	Positive | 3+, 90%	PMS2	Positive | 1+, 5%
ERBB2 (Her2/Neu)	Negative | 1+, 10%	PR	Positive | 2+, 3%
MLH1	Positive | 1+, 20%	PTEN	Positive | 1+, 100%
MSH2	Positive | 1+, 30%	TrkA/B/C	Negative | 0
MSH6	Positive | 1+, 20%		

Additional results continued on the next page. >

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Other Findings

GENES TESTED WITH INDETERMINATE* RESULTS BY NGS										
ASXL1	CHEK2	FANCE	JAK3	KDM5C	KMT2C	NF2	SMARCE1	TERT	TP53	

* Genes in this table were ruled indeterminate due to low coverage for some or all exons. Please see Appendix for a complete list of indeterminate genes.

GENES TESTED WITHOUT POINT MUTATIONS OR INDELS BY NGS											
ABL1	AKT1	ALK	AMER1	APC	AR	ARAF	ARID2	ATR	ATRX	BAP1	BARD1
BCOR	BLM	BMPR1A	BRAF	BRCA2	BRIP1	CARD11	CCND1	CCND2	CCND3	CD79B	CDC73
CDK12	CDK4	CDK6	CDKN1B	CDKN2A	CHEK1	CIC	CREBBP	CSF1R	CTNNB1	CYLD	DDR2
DICER1	DNMT3A	EGFR	EP300	ERBB2 (Her2/ Neu)	ERBB3	ERBB4	ERCC2	ESR1	EZH2	FANCA	FANCC
FANCD2	FANCF	FANCG	FANCL	FBXW7	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3
FLT4	FOXL2	FUBP1	GATA3	GNA11	GNA13	GNAQ	GNAS	H3F3A	H3F3B	HIST1H3B	HNF1A
HRAS	IDH1	IDH2	IRF4	JAK1	JAK2	KDM6A	KDR (VEGFR2)	KIT	KMT2A	KMT2D	KRAS
LCK	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAX	MEN1	MET	MITF	MLH1	MPL	MRE11	MSH2	MSH6
MTOR	MUTYH	MYCN	MYD88	NBN	NF1	NOTCH1	NPM1	NRAS	NSD1	NTRK1	NTRK2
NTRK3	PALB2	PBRM1	PDGFRA	PDGFRB	PHOX2B	PIK3R1	PIM1	PMS1	PMS2	POLE	POT1
PPARG	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTEN	PTPN11	RAD50	RAF1	RB1	RNF43	ROS1
SDHAF2	SDHB	SDHC	SDHD	SETD2	SF3B1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SPOP
SRC	STK11	SUFU	TSC1	TSC2	U2AF1	VHL	WRN	WT1			

GENES TESTED WITHOUT COPY NUMBER ALTERATIONS (AMPLIFICATIONS) BY NGS											
AKT2	ALK	ARID1A	AURKB	CCND1	CCND3	CCNE1	CD274 (PD-L1)	CDK4	CDK6	CDK8	CDKN2A
CREBBP	CRKL	EGFR	EP300	ERBB2 (Her2/ Neu)	EZH2	FGF10	FGF3	FGF4	FGFR1	FGFR2	FGFR3
GATA3	KDR (VEGFR2)	MAP2K1 (MEK1)	MCL1	MDM2	MET	MYC	NF2	NFKBIA	NTRK1	RB1	RICTOR
ROS1	TOP1	WT1									

Additional results continued on the next page. >

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Other Findings

IN SITU HYBRIDIZATION	
Not Amplified	**See Appendix**
ERBB2 (Her2/Neu)	TOP2A

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Notes of Significance

SEE APPENDIX FOR DETAILS

Clinical Trials Connector ™ opportunities based on biomarker expression: 275 Chemotherapy Trials | 417 Targeted Therapy Trials. See page 6 for details.

Specimen Information

Specimen ID: ABC-1234-XX

Specimen Collected: Mon/XX/2019

Specimen Received: Mon/XX/2019

Testing Initiated: Mon/XX/2019

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-XYZ.

Pathologic Diagnosis: Right pleural mass, CT biopsy: Metastatic carcinoma.

Dissection Information: 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 reviewed by a board certified Pathologist.

Interpretation (Caris Life Sciences Microscopic Diagnosis):
Right pleura, biopsy (Formalin Vial): Small focus of metastatic carcinoma.

Electronic Signature
Mon/XX/2019

By my electronic signature, I as the attending pathologist affirm that I have personally reviewed and examined microscopically the prepared slide(s) and that the above diagnosis has been made or confirmed by me.

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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. Therapeutic agents listed below may or may not be currently FDA approved for the tumor type tested.

CHEMOTHERAPY CLINICAL TRIALS (275)			
Drug Class	**Biomarker**	**Method**	**Investigational Agent(s)**
Anti-androgens (15)	AR	IHC	TAK-700, abiraterone, bicalutamide, enzalutamide
Anti-hormonal therapy (155)	ER	IHC	GTx024, TAK-700, abiraterone, anastrozole, bicalutamide, enzalutamide, exemestane, fulvestrant, goserelin, letrozole, leuprolide, tamoxifen, toremifene
	PR	IHC	
	AR	IHC	
Anti-inflammatory agents (1)	PIK3CA	NGS	aspirin
DNA minor groove binding agents (2)	BRCA1	NGS	PM01183 (lurbinectedin)
Platinum compounds (102)	BRCA1	NGS	carboplatin, cisplatin, oxaliplatin

TARGETED THERAPY CLINICAL TRIALS (417)			
Drug Class	**Biomarker**	**Method**	**Investigational Agent(s)**
Akt inhibitors (13)	ARID1A	NGS	ARQ092, AZD5363, MK2206, ipatasertib, triciribine
Chk1/Chk2 inhibitors (5)	BRCA1	NGS	LY2606368
Immunomodulatory agents (246)	AR	IHC	MEDI4736, MK-3475, MPDL3280A, MSB0010718C, atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab
Multikinase inhibitors (24)	RET	NGS	MGCD516, cabozantinib, lenvatinib, regorafenib, sorafenib, sunitinib, vandetanib
PARP inhibitors (61)	BRCA1	NGS	BMN-673, MK4827, niraparib, olaparib, rucaparib, talazoparib, veliparib
PI3K/Akt/mTor inhibitors (68)	PIK3CA	NGS	ARQ092, AZD2014, AZD5363, BAY80-6946, BYL719, GSK2636771, INK1117, MK2206, MLN0128, MLN1117, PF-05212384, everolimus, ipatasertib, sirolimus, taselisib, temsirolimus, triciribine

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

Please refer to the "Notes of Significance" section that may contain additional information regarding therapy associations.

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CLIA 03D1019490 • CAP 7195577 • ISO 15189:2012 • Zoran Gatalica, MD, DSc, Medical Director •

Disclaimer

Decisions regarding care and treatment should not be solely 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 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.

Individual assays that are available through Caris Molecular Intelligence® include both Laboratory Developed Tests (LDT) and U.S. Food and Drug Administration (FDA) approved or cleared tests. Caris MPI, Inc. d/b/a Caris Life Sciences® is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing, including all of the assays that comprise the Caris Molecular Intelligence®. Caris has validated the LDTs and their test performance characteristics were determined by Caris pursuant to CLIA-88 and accompanying regulations. Caris' CLIA certification number is located at the bottom of each page of this report. Tests have not all been cleared or approved by the FDA. The FDA has determined that clearance or approval is not necessary for certain laboratory developed tests. These tests are used for clinical purposes. They should not be regarded as investigational or for research.

This report includes information about therapies that may be associated with clinical benefit based on Caris Life Sciences' review of the NCCN Compendium® guidelines, relevance of tumor lineage, level of published evidence and strength of biomarker results. Associated therapies may or may not be suitable for administration to a particular patient.

Drug associations provided in this report do not guarantee 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 the conclusions drawn from its review of scientific literature, including information and conclusions relating to therapies that are included or omitted from this report. There is no guarantee that any third party will provide reimbursement for any of the tests performed or any treatment decision made based on the results.

The information presented in the Clinical Trials Connector™ section of this report, if applicable, is compiled from sources believed to be reliable and current. However, the accuracy and completeness of the information provided herein cannot be guaranteed. 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 best comprehensive 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 Molecular Intelligence is subject to Caris' intellectual property. Patent www.carislifesciences.com/ip.

Electronic Signature
Mon/XX/2019

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Mutational Analysis by Next-Generation Sequencing (NGS)

TUMOR MUTATIONAL BURDEN	
Mutations / Megabase	**Result**
11	Intermediate

TMB Methods

Tumor Mutational Burden was performed based on Next Generation Sequencing (NGS) analysis from genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina NextSeq platform. NGS was developed and its performance characteristics determined by Caris Life Sciences.

Tumor Mutational Burden is calculated using only missense mutations that have not been previously reported as germline alterations. A high mutational burden 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). Caris Life Sciences has defined threshold levels for Tumor Mutational Burden and establish cutoff points based on published evidence and internal data/experience:

- High: greater than or equal to 17 mutations/Megabase (≥17 mutations/Mb). Approximately 7% of Caris Molecular Intelligence cases reported a High result.
- Intermediate: greater than or equal to 7 but fewer than 17 mutations/ Megabase (≥7 and <17 mutations/Mb). Approximately 34% of Caris Molecular Intelligence cases reported an Intermediate result.
- Low: less than or equal to 6 mutations/Megabase (≤6 mutations/Mb). Approximately 59% of Caris Molecular Intelligence cases reported a Low result.

MICROSATELLITE INSTABILITY ANALYSIS		
Test	**Interpretation**	**Result**
MSI	No microsatellite instability detected	Stable
	Procedure: NGS	

Microsatellite Instability Analysis

Microsatellite instability status by NGS (MSI-NGS) is measured by the direct analysis of known microsatellite regions sequenced in the CMI 592 gene panel. To establish clinical thresholds, MSI-NGS results were compared with results from over 2,000 matching clinical cases analyzed with traditional, PCR-based methods. Genomic variants in the microsatellite loci are detected using the same depth and frequency criteria as used for mutation detection. Only insertions and deletions resulting in a change in the number of tandem repeats are considered in this assay. Some microsatellite regions with known polymorphisms or technical sequencing issues are excluded from the analysis. The total number of microsatellite alterations in each sample are counted and grouped into three categories: High, Equivocal and Stable. MSI-Low results are reported in the Stable category. Equivocal results have a total number of microsatellite alterations in between High and Stable.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

GENES TESTED WITH ALTERATIONS						
Gene	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
ARID1A	Mutated, Pathogenic	p.P517fs	3	c.1548 _1549delTC	46	NM_006015

Interpretation: A pathogenic frameshift mutation was detected in ARID1A

This gene encodes a member of the SWI/SNF family, whose members have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. Inactivating mutations of ARID1A, a member of the SWI/SNF chromatin-remodeling complex, have been identified in a long list of cancers, including ovarian clear-cell carcinoma, gastric, hepatocellular, breast and so on. Mutational and functional data suggest ARID1A is a bona fide tumor suppressor. ARID1A may contribute to tumor suppression via effects on the SWI/SNF complex, control of cell proliferation and differentiation, and/or effects on histone ubiquitylation.

ARID1A	Mutated, Variant of Unknown Significance	p.P329S	1	c.985C>T	67	NM_006015

Interpretation: This is a rare variant with unknown clinical or biological significance

ATM	Mutated, Presumed Benign	p.I124V	5	c.370A>G	25	NM_000051

Interpretation: This variant is presumed to be benign. It is carried by more than 1% of normal African individuals, yet it has not been reported to be pathogenic.

ATM or ataxia telangiectasia mutated is activated by DNA double-strand breaks and DNA replication stress. It encodes a protein kinase that acts as a tumor suppressor and regulates various biomarkers involved in DNA repair, which include p53, BRCA1, CHK2, RAD17, RAD9, and NBS1. Although ATM is associated with hematologic malignancies, somatic mutations have been found in colon (18%), head and neck (14%), and prostate (12%) cancers. Germline mutations in ATM are associated with ataxia-telangiectasia (also known as Louis-Bar syndrome) and a predisposition to malignancy.

BRCA1	Mutated, Pathogenic	p.R1835*	23	c.5503C>T	52	NM_007294

Interpretation: A pathogenic mutation, p.R1835*, was detected in BRCA1. p.R1835* has been reported as a frequent germline mutation, causal for hereditary breast and ovarian cancer (Serova 1996 Am J Hum Genet 58:42).

BRCA1 or breast cancer type 1 susceptibility gene encodes a protein involved in cell growth, cell division, and DNA-damage repair. It is a tumor suppressor gene which plays an important role in mediating double-strand DNA breaks by homologous recombination (HR). Tumors with BRCA1 mutation may be more sensitive to platinum agents and PARP inhibitors.

CDH1	Mutated, Variant of Unknown Significance	p.V132I	4	c.394G>A	24	NM_004360

Interpretation: This rare mutation has been found in breast and colon tumors and it is also present in the general population (SNP ID rs142498771). Because the current clinical information is limited and the impact of this mutation on protein function is currently unknown, it has been classified as a Variant of Uncertain Significance.

This gene is a classical cadherin from the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. The protein plays a major role in epithelial architecture, cell adhesion and cell invasion. Mutations in this gene are correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

GENES TESTED WITH ALTERATIONS						
Gene	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PIK3CA	Mutated, Pathogenic	p.H1047R	21	c.3140A>G	34	NM_006218

Interpretation: The common oncogenic p.H1047R mutation was detected in PIK3CA (Burke 2012 Proc Natl Acad Sci USA 109:15259).

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.

RET	Mutated, Variant of Unknown Significance	p.T75M	2	c.224C>T	35	NM_020975

Interpretation: A rare variant with no known clinical or functional significance was detected in RET.

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.

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.

GENES TESTED WITH UNCLASSIFIED MUTATIONS*					
Gene	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
AKAP9	p.E2829K	33	c.8485G>A	49	NM_005751
ARHGEF12	p.M666V	22	c.1996A>G	75	NM_015313
CAMTA1	p.E1191D	15	c.3573G>C	72	NM_015215
CDX2	p.H124Y	1	c.369 _370 delinsTT	30	NM_001265
CLP1	p.M361T	3	c.1082T>C	60	NM_006831
ELL	p.P386L	8	c.1157C>T	48	NM_006532
ETV5	p.H227Q	8	c.681C>A	26	NM_004454
FGF3	p.*240Q	3	c.718T>C	37	NM_005247
FGFR1	p.V38M	3	c.112G>A	59	NM_023110
IL7R	p.E113D	3	c.339A>C	34	NM_002185
MLLT1	p.P376L	7	c.1127C>T	28	NM_005934
NIN	p.V889L	18	c.2665G>C	38	NM_182946
NR4A3	p.P292A	4	c.874C>G	48	NM_173200
NUP98	p.S306N	8	c.917G>A	75	NM_016320

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	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PAX8	p.P284R	8	c.851C>G	35	NM_003466
PRKDC	p.F1967V	43	c.5899T>G	27	NM_006904
SPEN	p.N2360D	11	c.7077 _7078 delinsTG	75	NM_015001
USP6	p.G365A	14	c.1094G>C	23	NM_004505
ZNF703	p.D169N	2	c.505G>A	43	NM_025069

*** Any mutations in the above genes that are known by Caris to be clinically significant (i.e., pathogenic or presumed pathogenic) are reported with interpretation in the body of the report. Any remaining mutations are listed above and have not been classified by Caris.**

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

COMPLETE LIST OF GENES TESTED WITH INDETERMINATE* RESULTS					
AFF3	CALR	FEV	MALT1	NF2	SMARCE1
AFF4	CD274 (PD-L1)	FNBP1	MED12	NOTCH2	STAT5B
ARNT	CD79A	FSTL3	MKL1	PAX5	TAF15
ASXL1	CHEK2	JAK3	MLLT6	PCSK7	TERT
BCL11A	COL1A1	KDM5C	MN1	PDCD1LG2	TP53
BCL11B	DOT1L	KMT2C	MNX1	PRDM16	VEGFB
BCR	EPS15	KNL1	MUC1	RALGDS	
BIRC3	FANCE	LASP1	MYCL	SEPT5	

*** Genes in this table were ruled indeterminate due to low coverage for some or all exons.**

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	CDK6	FBXW7	KDM6A	NRAS	RNF43
AKT1	CDKN1B	FGFR2	KDR (VEGFR2)	NSD1	ROS1
ALK	CDKN2A	FGFR3	KIT	NTRK1	SDHAF2
AMER1	CHEK1	FGFR4	KMT2A	NTRK2	SDHB
APC	CIC	FH	KMT2D	NTRK3	SDHC
AR	CREBBP	FLCN	KRAS	PALB2	SDHD
ARAF	CSF1R	FLT1	LCK	PBRM1	SETD2
ARID2	CTNNB1	FLT3	MAP2K1 (MEK1)	PDGFRA	SF3B1
ATR	CYLD	FLT4	MAP2K2 (MEK2)	PDGFRB	SMAD2
ATRX	DDR2	FOXL2	MAX	PHOX2B	SMAD4
BAP1	DICER1	FUBP1	MEN1	PIK3R1	SMARCA4
BARD1	DNMT3A	GATA3	MET	PIM1	SMARCB1
BCOR	EGFR	GNA11	MITF	PMS1	SMO
BLM	EP300	GNA13	MLH1	PMS2	SPOP
BMPR1A	ERBB2 (Her2/Neu)	GNAQ	MPL	POLE	SRC
BRAF	ERBB3	GNAS	MRE11	POT1	STK11
BRCA2	ERBB4	H3F3A	MSH2	PPARG	SUFU
BRIP1	ERCC2	H3F3B	MSH6	PPP2R1A	TSC1
CARD11	ESR1	HIST1H3B	MTOR	PRDM1	TSC2
CCND1	EZH2	HNF1A	MUTYH	PRKAR1A	U2AF1
CCND2	FANCA	HRAS	MYCN	PTCH1	VHL
CCND3	FANCC	IDH1	MYD88	PTEN	WRN
CD79B	FANCD2	IDH2	NBN	PTPN11	WT1
CDC73	FANCF	IRF4	NF1	RAD50	
CDK12	FANCG	JAK1	NOTCH1	RAF1	
CDK4	FANCL	JAK2	NPM1	RB1	

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

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 customdesigned 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 with an analytic sensitivity of 96.9% to detect variants with frequency greater than 5%. This may not detect insertion/deletions events that are larger than 44 bases. The Laboratory Developed Tests (LDT) Next Generation Sequencing (NGS) assays were developed and their performance characteristics determined by Caris Life Sciences. These tests have not been cleared or approved by the US Food and Drug Administration. FDA clearance or approval is not currently 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.
The versioned reference identifier used for the transcript ID was Feb.2009 (GRCh37/hg19).

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Copy Number Alterations by Next-Generation Sequencing (NGS)

GENES TESTED WITH NO AMPLIFICATION DETECTED					
AKT2	CD274 (PD-L1)	EGFR	FGFR1	MDM2	RICTOR
ALK	CDK4	EP300	FGFR2	MET	ROS1
ARID1A	CDK6	ERBB2 (Her2/Neu)	FGFR3	MYC	TOP1
AURKB	CDK8	EZH2	GATA3	NF2	WT1
CCND1	CDKN2A	FGF10	KDR (VEGFR2)	NFKBIA	
CCND3	CREBBP	FGF3	MAP2K1 (MEK1)	NTRK1	
CCNE1	CRKL	FGF4	MCL1	RB1	

CNA Methods

The copy number alteration (CNA) of each exon is determined by a calculation using the average sequencing depth of the sample along with the sequencing depth of each exon and comparing this calculated result to a pre-calibrated value. If all exons within the gene of interest have an average of ≥3 copies and the average copy number of the entire gene is ≥6 copies, the gene result is reported as amplified. If an average of ≥ 4, but < 6 copies of a gene are detected, or if the average copy number of the gene is ≥6 copies, but contains exons with an average of < 3 copies, the gene result is reported as intermediate. If an average of < 4 copies of a gene are detected, the gene result is reported as no amplification detected. A complete list of copy number alteration genes are available upon request.

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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:
AR	2 +	90	Positive	Intensity ≥1+ and ≥10% of cells stained
ER	3 +	90	Positive	Intensity ≥1+ and ≥1% of cells stained
ERBB2 (Her2/Neu)	1 +	10	Negative	Intensity ≥3+ and >10% of cells stained
MLH1	1 +	20	Positive	Intensity ≥1+ and ≥1% of cells stained
MSH2	1 +	30	Positive	Intensity ≥1+ and ≥1% of cells stained
MSH6	1 +	20	Positive	Intensity ≥1+ and ≥1% of cells stained
PD-L1 (SP142)	0	100	Negative	Intensity ≥2+ and ≥5% of cells stained
PMS2	1 +	5	Positive	Intensity ≥1+ and ≥1% of cells stained
PR	2 +	3	Positive	Intensity ≥1+ and ≥1% of cells stained
PTEN	1 +	100	Positive	Intensity ≥1+ and ≥1% of cells stained
TrkA/B/C	0	100	Negative	Intensity ≥1+ and ≥1% of cells stained

Clones used: ER (SP1), PR (1E2), AR (AR441), ERBB2 (Her2/Neu) (4B5), MLH1 (M1), MSH2 (G219-1129), MSH6 (44), PMS2 (EPR3947), PD-L1 (SP142), TrkA/B/C (EPR17341), PTEN (6H2.1).

Electronic Signature
Mon/XX/2019

IHC Methods

The Laboratory Developed Tests (LDT) immunohistochemistry (IHC) assays were developed and their performance characteristics determined by Caris Life Sciences. These tests have not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not currently necessary. Interpretations of all immunohistochemistry (IHC) assays were performed manually by a board certified pathologist.

The following IHC assays were performed using FDA-approved companion diagnostic or FDA-cleared tests consistent with the manufacturer's instructions: ALK (VENTANA ALK (D5F3) CDx Assay, Ventana), ER (CONFIRM anti-Estrogen Receptor (ER) (SP1), Ventana), PR (CONFIRM anti-Progesterone Receptor (PR) (1E2), Ventana), HER2/neu (PATHWAY anti-HER-2/neu (4B5), Ventana), Ventana), PD-L1 22c3 (pharmDx, Dako), PD-L1 SP142 (VENTANA, Ventana in Urothelial Carcinomas), and PD-L1 28-8 (pharmDx, Dako).

HER2 results and interpretation follow the ASCO/CAP scoring criteria.

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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
ERBB2 (Her2/Neu) nuc ish (D17Z1x1-2,HER2x1-2)[/30]	20	Not Amplified	2.50	2.30	N/A	N/A	Her2/neu/Chromosome 17	1.09
	Reference Range: Her2 test result is amplified if dual-probe HER2/CEP17 ratio>= 2.0 with an average HER2 copy number >= 4.0 signals per cell; or HER2/CEP17 ratio >= 2.0 with an average HER2 copy number < 4.0 signals/cell; or HER2/CEP17 ratio < 2.0 with an average HER2 copy number >= 6.0 signals/cell. Her2 test result is equivocal if dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number >= 4.0 and < 6.0 signals/cell. Her2 test result is not amplified if dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell. Results and interpretation follow the ASCO/CAP scoring criteria. Wolff, AC. et al. (2013) J Clin Oncol: 31 (31):3997-4013							
TOP2A	N/A	No Hybridization	N/A	N/A	N/A	N/A	TOP2A/Chromosome 17	N/A
	Reference Range: In breast cancer, amplification by CISH has been established as a TOP2A:CEP17 ratio of ≥2.0 or the presence of ≥6 copies of the TOP2A gene in cancer cells.							

Electronic Signature
Mon/XX/2019

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. Analysis of this multiplex probe stain procedure was performed manually. The HER2 CISH testing for cancer lineages other than breast has been developed and their performance characteristics determined by Caris Life Sciences and have not been cleared or approved by the FDA.

TOP2A CISH was carried out using a probe specific for TOP2 and a probe for the pericentromeric region of chromosome 17 (Ventana). Analysis of this multiplex probe stain procedure was performed manually. The TOP2A CISH testing for cancer lineages has been developed and its performance characteristics determined by 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 Life Sciences 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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2	abemaciclib, palbociclib, ribociclib	ER, PR	Cristofanilli, M., D Slamon, et al. (2016) "Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial" Lancet Oncol. 17(4):425-39 View Citation Online
3	abemaciclib, palbociclib, ribociclib	ER, PR	Hortobagyi, G., J. O'Shaughnessy, et al. (2016) "Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer" N Engl J Med 2016; 375:1738-1748 View Citation Online
4	abemaciclib, palbociclib, ribociclib	ER, PR	Sledge, GW, A. Llombart-Cussac et. al. (2017) "MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy." J Clin Oncol 35(25): 2875-2884 View Citation Online
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16	olaparib, talazoparib	BRCA1	Oza, A.M., M. Friedlander, et.al. (2015). "Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial." Lancet Oncol. 16:87-97 View Citation Online

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20	olaparib, talazoparib	BRCA1	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
21	olaparib, talazoparib	BRCA1	Banda, K., V.K. Gadi (2018) "Somatic Reversion of Germline BRCA2 Mutation Confers Resistance to Poly(ADP-ribose) Polymerase Inhibitor Therapy", JCO Precision Oncology, DOI: 10.1200/PO.17.00169. View Citation Online
22	ado-trastuzumab emtansine (T-DM1), lapatinib, neratinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	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
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#	Drug	Biomarker	Reference
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