MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS® LIFE SCIENCES

FINAL REPORT

PATIENT

Name: Patient, Test
Date of Birth: XX-Mon-19XX
Sex: Male
Case Number: TN16-XXXXXX
Diagnosis: Glioblastoma multiforme

SPECIMEN INFORMATION

Primary Tumor Site: Brain, NOS
Specimen Site: Brain, NOS
Specimen ID: ABC-1234-XY
Specimen Collected: XX-Mon-2016
Testing Completed: XX-Mon-2016

ORDERED BY

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

Bold Therapies = On NCCN Compendium® Therapies

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

carboplatin, cisplatin	ERCC1	**temozolomide**	MGMT★	oxaliplatin	ERCC1
irinotecan	TOPO1	dacarbazine	MGMT★	topotecan	TOPO1

★ **Indicates Clinical Trial Opportunity • 93 Chemotherapy Trials • 160 Targeted Therapy Trials** *(See Clinical Trials Connector™ on page 7 for details.)*

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

dabrafenib, vemurafenib	BRAF	

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

everolimus, temsirolimus	imatinib	

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

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CE

SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

Assay	Result
Total Mutational Load	Low | 6 Mutations / Megabase

Biomarker	Method	Result
AKT2	NGS	Amplification Not Detected
ALK	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
ARID1A	NGS	Amplification Not Detected
ATM	NGS	Mutated, Variant of Unknown Significance
		Exon 47 | L2307F
AURKB	NGS	Amplification Not Detected
BRAF	RNA-Seq	Fusion Not Detected
	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected
BRCA2	NGS	Mutated, Variant of Unknown Significance
		Exon 6 | K169R
	NGS	Mutated, Variant of Unknown Significance
		Exon 11 | F1031S
c-KIT	NGS	Mutation Not Detected
CCND1	NGS	Amplification Not Detected
CCND3	NGS	Amplification Not Detected
CCNE1	NGS	Amplification Not Detected
CDK4	NGS	Amplification Not Detected
CDK6	NGS	Amplification Not Detected
CDK8	NGS	Amplification Not Detected
CDKN2A	NGS	Amplification Not Detected
CHEK1	NGS	Mutated, Pathogenic
		Exon 10 | Q346X
cMET	NGS	Amplification Not Detected
cMET - exon 14	RNA-Seq	Variant Transcript Not Detected
CREBBP	NGS	Amplification Not Detected
CRKL	NGS	Amplification Not Detected

Biomarker	Method	Result
EGFR	NGS	Amplification Not Detected
EGFRvIII	RNA-Seq	Variant Transcript Not Detected
EP300	NGS	Amplification Not Detected
ERCC1	IHC	Negative | 2+, 30%
EZH2	NGS	Amplification Not Detected
FGF10	NGS	Amplification Not Detected
FGF3	NGS	Amplification Not Detected
FGF4	NGS	Amplification Not Detected
FGFR1	NGS	Amplification Not Detected
FGFR2	NGS	Amplification Not Detected
FGFR3	NGS	Amplification Not Detected
GATA3	NGS	Amplification Not Detected
Her2/Neu	NGS	Amplification Not Detected
IDH1	NGS	Mutation Not Detected
KDR (VEGFR2)	NGS	Amplified
MCL1	NGS	Amplification Not Detected
MDM2	NGS	Amplification Not Detected
MEK1	NGS	Amplification Not Detected
MGMT	PyroSeq	Methylated
MYC	NGS	Amplification Not Detected
NF2	NGS	Amplification Not Detected
NFKBIA	NGS	Amplification Not Detected
NTRK1	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
NTRK2	RNA-Seq	Fusion Not Detected
NTRK3	RNA-Seq	Fusion Not Detected
PD-L1	IHC	Negative | 2+, 1%
PDGFRA	NGS	Mutation Not Detected
PIK3CA	NGS	Mutation Not Detected
PTEN	NGS	Mutated, Pathogenic
		Exon 6 | I203fs

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

Biomarker Results continued on the next page. >

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SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

Biomarker	Method	Result
RB1	NGS	Amplification Not Detected
RET	RNA-Seq	Fusion Not Detected
	NGS	Mutation Not Detected
RICTOR	NGS	Amplification Not Detected
ROS1	RNA-Seq	Fusion Not Detected
	NGS	Amplification Not Detected
RSPO3	RNA-Seq	Fusion Not Detected
TOP1	NGS	Amplification Not Detected
TOPO1	IHC	Positive | 2+, 70%
WT1	NGS	Amplification Not Detected

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

The Next-Generation Sequencing results above include only the genes most commonly associated with cancer. See summary below and for full Next-Generation Sequencing results, see Appendix page 1.
Genes tested: 592 | Genes with actionable mutations: 4 | Genes with unclassified mutations: 16 | Genes with no mutations detected: 527

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

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✔ THERAPIES WITH **POTENTIAL BENEFIT**

Therapies	Test	Method	Result	Value†	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
carboplatin, cisplatin, oxaliplatin	ATM	NGS	Mutated, Variant of Unknown Significance	L2307F					
	BRCA1	NGS	Mutation Not Detected					II-2 / Good	1, 2, 3, 4
	BRCA2	NGS	Mutated, Variant of Unknown Significance	K169R					
	ERCC1	IHC	Negative	2+ 30%	✔			II-2 / Good	5, 6, 7, 8, 9
dacarbazine, temozolomide	IDH1	NGS	Mutation Not Detected			✔		II-3 / Good	19#
	MGMT	PyroSeq	Methylated		✔			II-1 / Good	14#, 15#, 16#, 17#, 18#
irinotecan, topotecan	TOPO1	IHC	Positive	2+ 70%	✔			II-1 / Good	28, 29, 30

* 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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✘ 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	10#, 11, 12, 13#

* 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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? THERAPIES WITH **INDETERMINATE BENEFIT**

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

Therapies	Test	Method	Result	Value†	Clinical Association				
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
everolimus, temsirolimus	PIK3CA	NGS	Mutation Not Detected			✔		II-2 / Good	20, 21, 22
imatinib	c-KIT	NGS	Mutation Not Detected				✔	II-2 / Good	26, 27
	PDGFRA	NGS	Mutation Not Detected				✔	II-3 / Good	23, 24, 25

* 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 (93)

Drug Class	Biomarker	Method	Investigational Agent(s)
Alkylating agents (50)	MGMT	Pyrosequencing	carmustine, dacarbazine, lomustine, temozolomide
DNA minor groove binding agents (3)	BRCA2	NGS	PM01183 (lurbinectedin), trabectedin
Platinum compounds (40)	ATM	NGS	carboplatin, cisplatin, oxaliplatin
	BRCA2	NGS	
	CHEK1	NGS	

TARGETED THERAPY CLINICAL TRIALS (160)

Drug Class	Biomarker	Method	Investigational Agent(s)
Anti-angiogenic agents (78)	KDR	NGS	X-82, aflibercept, axitinib, bevacizumab, cabozantinib, cediranib, lenvatinib, nintedanib, pazopanib, ponatinib, ramucirumab, regorafenib, sorafenib, sunitinib, vandetanib
Cell cycle inhibitors (8)	RB1	NGS	LEE011, palbociclib
HDAC inhibitors (16)	ATM	NGS	CUDC-907, FK228, PCI-24781, abexinostat, belinostat, entinostat, mocetinostat, panobinostat, valproic acid, vorinostat
	CHEK1	NGS	
PARP inhibitors (20)	ATM	NGS	BMN-673, olaparib, rucaparib, veliparib
	BRCA2	NGS	
	CHEK1	NGS	
	PTEN	NGS	
PI3K/Akt/mTor inhibitors (38)	PTEN	NGS	ARQ092, AZD2014, AZD5363, BAY80-6946, BKM120, BYL719, GDC0941, GSK2110183, GSK2141795, GSK2636771, MLN0128, MLN1117, PF-05212384, ZSTK474, everolimus, sirolimus, temsirolimus

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

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** See Appendix page 8 for Level of Evidence description.*

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** See Appendix page 8 for Level of Evidence description.*

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** See Appendix page 8 for Level of Evidence description.*

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** See Appendix page 8 for Level of Evidence description.*

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SPECIMEN INFORMATION

Specimen ID: ABC-12345-XY

Specimen Collected: XX-Mon-2016

Specimen Received: XX-Mon-2016

Testing Initiated: XX-Mon-2016

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

Pathologic Diagnosis: Brain, parietal-temporal region (biopsy, mass, for frozen and permanent sections): Glioblastoma multiforme.

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

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MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS LIFE SCIENCES

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

TOTAL MUTATIONAL LOAD

Result	Mutations / Megabase (Mb)	Threshold
Low	6	≥ 17 Mutations per Mb

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

GENES TESTED WITH ALTERATIONS

Gene	Alteration	Frequency (%)	Exon	Result
ATM	L2307F	60	47	Mutated, Variant of Unknown Significance

Interpretation: This variant has been previously reported in the germline of rare individuals; however, its clinical significance is unknown at this time.

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.

BRCA2	K169R	81	6	Mutated, Variant of Unknown Significance

Interpretation: This variant has been previously reported in the germline of rare individuals; however, its clinical significance is unknown at this time.

BRCA2 or breast cancer type 2 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 BRCA2 mutation may be more sensitive to platinum agents and PARP inhibitors.

BRCA2	F1031S	84	11	Mutated, Variant of Unknown Significance

Interpretation: This variant has been reported as germline in the breast cancer mutation database BIC. No other association with cancer is known for this variant, therefore, it is unclear if this variant is pathogenic.

CHEK1	Q346X	37	10	Mutated, Pathogenic

Interpretation: A nonsense mutation was identified. Germline inheritance of this mutation has not been reported.

The CHEK1 gene encodes a protein Chek1 (Checkpoint kinase 1) that is involved in the initiation of cell cycle arrest and DNA repair following the detection of DNA damage, in particular, single strand breaks. Preclinical studies have demonstrated the potential of CHEK1 inhibitors to increase the sensitivity of tumor cells to DNA-damaging therapeutics but this hypothesis is still under investigation in the clinic. Mutations in CHEK1 have been observed in several tumor types including pancreatic and breast cancers.

PTEN	I203fs	69	6	Mutated, Pathogenic

Interpretation: A pathogenic mutation has been detected in this sample

PTEN or phosphatase and tensin homolog is a tumor suppressor gene that prevents cells from proliferating. PTEN is an important mediator in signaling downstream of EGFR, and loss of PTEN gene function/expression due to gene mutations or allele loss is associated with reduced benefit to EGFR-targeted monoclonal antibodies. Mutation in PTEN is found in 5-14% of colorectal cancer and 7% of breast cancer. PTEN mutation leads to loss of function of the encoded phosphatase, and an upregulation of the PIK3CA/AKT pathway. Germline PTEN mutations associate with Cowden disease and Bannayan-Riley-Ruvalcaba syndrome. These dominantly inherited disorders belong to a family of hamartomatous polyposis syndromes which feature multiple tumor-like growths (hamartomas) accompanied by an increased risk of breast carcinoma, follicular carcinoma of the thyroid, glioma, prostate and endometrial cancer. Trichilemmoma, a benign, multifocal neoplasm of the skin is also associated with PTEN germline mutations.

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

BRAF	c-KIT	PDGFRA	RET
BRCA1	IDH1	PIK3CA	

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

GENES TESTED WITH UNCLASSIFIED MUTATIONS

Gene	Alteration
AFF3	T619 _A621 delinsS
ARHGAP26	I388T
BARD1	V507M
CCND3	S259A
ELK4	T240I

Gene	Alteration
FANCE	M437T
HNF1A	P394S
IKBKE	V460A
IL21R	T68M
LRP1B (continued next column)	T3122I

Gene	Alteration
LRP1B	N895Y
MAML2	G174D
PCM1	N159S
PCSK7	R441W
PDE4DIP	R2145T

Gene	Alteration
RBM15	A668V
USP6	I67 _R68 delinsMW

GENES TESTED WITH INDETERMINATE RESULTS

ABI1	CASC5	HOOK3	MNX1	PAK3	STAT5B
ARID1A	CDKN2A	KDM5C	MRE11A	PAX5	SUZ12
ARNT	CHN1	KIF5B	MUC1	PHF6	TAF15
ASPSCR1	COL1A1	KMT2C	MYH11	PTPRC	TBL1XR1
ATRX	COPB1	LIFR	NFIB	RAD50	VEGFB
BCL11A	EML4	MALT1	NOTCH2	RICTOR	
BIRC3	EPS15	MED12	NT5C2	SMARCE1	
BTK	GOPC	MLLT10	NUTM2B	STAT4	

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

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

For Next-Generation Sequencing, a total of 592 genes were analyzed. The results above include genes most commonly associated with cancer and any additional mutations identified. No alterations were identified in 527 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

Comments on NGS Analysis

This assay is unable to determine if the two BRCA2 mutations are on the same or separate alleles.

NGS Methods

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

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

GENES TESTED WITH AMPLIFICATION DETECTED
KDR

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

The CNV results reported in the table below have been assessed for general quality but have not been evaluated by a board-certified molecular geneticist or evaluated for clinical significance. They are reported for informational purposes only.

GENES TESTED WITH UNEVALUATED AMPLIFICATION DETECTED			
c-KIT	CHIC2	FIP1L1	PDGFRA

CNV Methods

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

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

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

Gene Fusion Methods

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

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MUTATIONAL ANALYSIS BY **PYROSEQUENCING**

Gene	Interpretation	Result
MGMT	MGMT promoter hypermethylation detected	Methylated
	Procedure: Pyrosequencing	
48% MGMT promoter methylation detected in this sample.		

MGMT Methylation Testing

DNA extraction from paraffin-embedded tumor samples was performed for subsequent pyrosequencer-based analysis of 5 CpG sites (CpGs 74-78). All DNA samples undergo a bisulfite treatment and are PCR amplified with primers specific for exon 1 of MGMT (GRCh37/hgl9 – chr10: 131,265,448- 131,265,560). Methylation status of PCR amplified products is determined using the PyroMark system. Samples with ≥7% and <9% methylation are considered to be equivocal or gray zone results. This assay requires samples to have at least 60% tumor nuclei.

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PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

Biomarker	Patient Tumor			Thresholds*
	Staining Intensity (0, 1+, 2+, 3+)	Percent of cells	Result	Conditions for a Positive Result:
ERCC1	2 +	30	Negative	Intensity of ≥3+ with ≥10% or ≥2+ with ≥50% of cells stained
PD-L1	2 +	1	Negative	Intensity ≥2+ and ≥5% of cells stained
TOPO1	2 +	70	Positive	Intensity ≥2+ and ≥30% of cells stained

Electronic Signature

IHC Methods

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

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

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

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

Clones used: TOPO1(1D6), ERCC1(8F1), PD-L1(SP142).

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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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