Final Report

CARIS LIFE SCIENCES

Patient

Name: PATIENT, TEST
Date of Birth:
Sex: Female
Case Number: TN20-
Diagnosis: Adenocarcinoma, intestinal type

Specimen Information

Primary Tumor Site: Sigmoid colon
Specimen Site: Overlapping lesion of colon
Specimen ID:
Specimen Collected:
All Testing Completed:

Ordered By

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
KRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**	**BENEFIT**	**cetuximab, panitumumab**	**Level 1**
Mismatch Repair Status	**IHC**	**Protein**	**Deficient**	**BENEFIT**	**nivolumab, nivolumab/ipilimumab combination, pembrolizumab**	**Level 1**
MSI	**Seq**	**DNA-Tumor**	**High**			
NRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**	**BENEFIT**	**cetuximab, panitumumab**	**Level 1**
NTRK1	**Seq**	**RNA-Tumor**	**Pathogenic Fusion**	**BENEFIT**	**entrectinib, larotrectinib**	**Level 1**
TMB	**Seq**	**DNA-Tumor**	**High, 29 mut/Mb**	**BENEFIT**	**pembrolizumab**	**Level 1**
BRAF	Seq	DNA-Tumor	Mutation Not Detected	BENEFIT	cetuximab, panitumumab	Level 2
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 2

* 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).

MI FOLFOXai™ **Result:** **DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC**

See Page 2 for important details about clinical data regarding MI FOLFOXai

Important Note

An SNRNP70-NTRK1 fusion was detected in this tumor. This specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic NTRK fusions.

TMB-High status should only be used to guide pembrolizumab treatment when no satisfactory alternative treatment options are available.

Pembrolizumab monotherapy is FDA-approved for first-line treatment of patients with unresectable or metastatic MSI-H or dMMR coloretal cancer.

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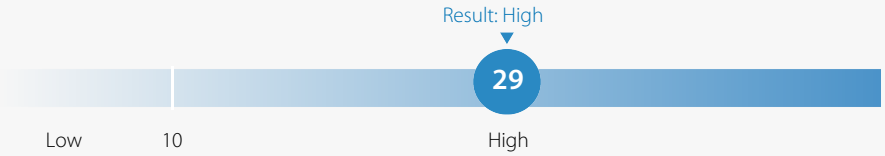
Cancer Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
NTRK2	Seq	RNA-Tumor	Fusion Not Detected
NTRK3	Seq	RNA-Tumor	Fusion Not Detected
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected

Biomarker	Method	Analyte	Result
PIK3CA	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 10 | p.Q546R**
PTEN	IHC	Protein	Positive | 1+, 90%

Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	High
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	

MI FOLFOXai™ **Result:** **DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC**

Intended Use and Result Interpretation:

To determine the sequencing of therapy for patients who are not being considered for FOLFOXIRI:

This patient may achieve improved results by receiving an alternative to FOLFOX, such as FOLFIRI, as their initial regimen.

As an adjustment to frontline FOLFOXIRI following toxicity:

This patient may achieve improved results by removing the oxaliplatin portion of their regimen.

MI FOLFOXai is a molecular signature that predicts relative benefit from FOLFOX + bevacizumab therapy given as the first-line treatment in metastatic colorectal cancer patients. The signature was developed using Caris Molecular Intelligence NGS 592 sequencing data and an artificial intelligence algorithm. The signature was validated using two independent data sets:

296 manually curated cases with real world evidence (insurance claims, electronic medical records and death registries):

Median Overall Survival difference between the increased benefit arm and the decreased benefit arm: 11.2 months

149 cases analyzed retrospectively from the randomized, prospective Phase III TRIBE2 study:

Median Overall Survival difference between the increased benefit arm and the decreased benefit arm: 6.0 months

All patients in the validation studies above had stage IV CRC and received FOLFOX + bevacizumab.

Any therapeutic decision should be based on the physician's judgement considering all of the patient's clinical conditions. Please see the Appendix of this report for MI FOLFOXai methodology.

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
AMER1	Seq	DNA-Tumor	Pathogenic Variant	p.F173fs	2	c.519delT	23
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.G276fs	1	c.827delG	26

Additional results continued on the next page. >

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Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ASXL1	Seq	DNA-Tumor	Pathogenic Variant	p.G646fs	13	c.1934dupG	9
BCOR	Seq	DNA-Tumor	Pathogenic Variant	p.S336fs	4	c.1005delC	29
EP300	Seq	DNA-Tumor	Pathogenic Variant	p.T278fs	3	c.832delA	16
KMT2A	Seq	DNA-Tumor	Pathogenic Variant	p.D877fs	3	c.2629 _2630delGA	25
KMT2D	Seq	DNA-Tumor	Pathogenic Variant	p.R4960*	48	c.14878C>T	16
	Seq	DNA-Tumor	Pathogenic Variant	p.R755fs	10	c.2263dupC	11
MSH6	Seq	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3261delC	20
NSD1	Seq	DNA-Tumor	Pathogenic Variant	p.M1531fs	11	c.4591delA	9
NTRK1	Seq	RNA-Tumor	Pathogenic Fusion	SNRNP70-NTRK1	12	-	-
PIK3CA	Seq	DNA-Tumor	Pathogenic Variant	p.Q546R	10	c.1637A>G	31
RNF43	Seq	DNA-Tumor	Pathogenic Variant	p.G659fs	9	c.1976delG	48
SMARCA4	Seq	DNA-Tumor	Likely Pathogenic Variant	p.G1194R	27	c.3580G>A	25

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

Genes Tested with Variants of Uncertain Significance

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
EP300	Seq	DNA-Tumor	Variant of Uncertain Significance	p.Q1904P	31	c.5711A>C	52
KMT2D	Seq	DNA-Tumor	Variant of Uncertain Significance	p.R5392H	51	c.16175G>A	23
NSD1	Seq	DNA-Tumor	Variant of Uncertain Significance	p.R1578S	12	c.4734A>C	27

Additional Variants of Uncertain Significance can be found in the MI Portal.

Immunohistochemistry Results

Biomarker	Result	Biomarker	Result
ERBB2 (Her2/Neu)	Negative | 0	PD-L1 (SP142)	Negative | 0%
MLH1	Negative | 0	PMS2	Negative | 0
MSH2	Positive | 2+, 100%	PTEN	Positive | 1+, 90%
MSH6	Positive | 1+, 90%		

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Genes Tested with Indeterminate Results by Tumor DNA Sequencing

ATRX	FANCE	FLT3	KMT2C	PMS2	PTCH1	RUNX1	TERT ¶				

¶TERT Promoter region not sequenced
* Genes in this table were ruled indeterminate due to low coverage for some or all exons.

The results in this report were curated to represent biomarkers most relevant for the submitted cancer type. These include results important for therapeutic decision-making, as well as notable alterations in other biomarkers known to be involved in oncogenesis. Additional results, including genes with normal findings, additional variants of uncertain significance and unclassified alterations can be found in the MI Portal at **miportal.carismolecularintelligence.com.** If you do not have an MI Portal account, or need assistance accessing it, please contact Caris Customer Support at (888) 979-8669.

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Notes of Significance

SEE APPENDIX FOR DETAILS

An SNRNP70-NTRK1 fusion was detected in this tumor. This specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic NTRK fusions.

Clinical Trials Connector ™ opportunities based on biomarker expression: 205 Chemotherapy Trials | 323 Targeted Therapy Trials. See page 6 for details.

Specimen Information

Specimen ID:

Specimen Collected:

Specimen Received:

Other Testing Initiated:

Gross Description:

Pathologic Diagnosis: Colon, descending and sigmoid, hemicolectomy: Adenocarcinoma, poorly to moderately differentiated, intestinal type, 6.5 cm, arising in sigmoid colon.

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.

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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)

The Clinical Trials Connector lists agents that are matched to available clinical trials according to biomarker status. In some instances, older-generation agents may still be relevant in the context of new combination strategies and, therefore, will still appear on this report.

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 (205)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
Antifolates (11)	MSH6	NGS	DNA-Tumor	methotrexate, pemetrexed
Anti-inflammatory agents (16)	PIK3CA	NGS	DNA-Tumor	aspirin
Platinum compounds (178)	MSH6	NGS	DNA-Tumor	carboplatin, cisplatin, oxaliplatin

TARGETED THERAPY CLINICAL TRIALS (323)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
Akt inhibitors (2)	ARID1A	NGS	DNA-Tumor	AZD5363, ipatasertib
Immunomodulatory agents (280)	Mismatch Repair Status	IHC	Protein	atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, mRNA-4157, nivolumab, pembrolizumab
	MSH6	NGS	DNA-Tumor	
	MSI	NGS	DNA-Tumor	
	TMB	NGS	DNA-Tumor	
Multikinase inhibitors (1)	NTRK1	RNA-Seq	RNA-Tumor	MGCD516
NTRK inhibitors (12)	NTRK1	RNA-Seq	RNA-Tumor	LOXO-195, MGCD516, cabozantinib, entrectinib, larotrectinib, repotrectinib (TPX-0005)
PI3K/Akt/mTor inhibitors (27)	PIK3CA	NGS	DNA-Tumor	AZD2014, AZD5363, BAY80-6946, GSK2636771, INK1117, MLN1117, PF-05212384, everolimus, ipatasertib, sapanisertib, sirolimus, temsirolimus
Wnt pathway inhibitors (1)	RNF43	NGS	DNA-Tumor	LGK974

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

The Clinical Trials Connector may include trials that enroll patients with additional screening of molecular alterations. In some instances, only specific gene variants may be eligible.

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Disclaimer

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. Drug associations provided in this report do not guarantee that any particular agent will be effective for the treatment of any patient or for any particular condition. Caris Life Sciences expressly disclaims and makes no representation or warranty whatsoever relating, directly or indirectly, to the performance of services, including any information provided and/or conclusions drawn from therapies that are included or omitted from this report. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly. The selection of therapy, if any, resides solely in the discretion of the treating physician.

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 (CLIA) as qualified to perform high complexity clinical laboratory testing, including all of the assays that comprise the Caris Molecular Intelligence®. The LDTs were developed and their performance characteristics determined by Caris. The LDTs have not been cleared or approved by the U.S. Food and Drug Administration. Caris' CLIA certification number is located at the bottom of each page of this report. Certain tests have not been cleared or approved by the FDA. The FDA has determined that clearance or approval is not necessary for certain laboratory developed tests. Caris LDTs are used for clinical purposes. They are not investigational or for research.

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.

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Caris Molecular Intelligence is subject to Caris' intellectual property. Patent www.carislifesciences.com/ip.

Electronic Signature

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Mutational Analysis by Next-Generation Sequencing (NGS)

TUMOR MUTATIONAL BURDEN	
Mutations / Megabase	**Result**
29	High

TMB Methods

Tumor Mutational Burden (TMB) analysis was performed based on Next Generation Sequencing analysis from genomic DNA isolated from a formalin-fixed paraffin embedded tumor sample using the Illumina platform. TMB is calculated using nonsynonymous, in-frame indel, and frameshift indel mutations that have not been previously reported as germline alterations in the Genome Aggregation Database (gnomAD) and dbSNP151 or as common benign variants identified by Caris geneticists. The cutoff point (≥10) is based on the KEYNOTE-158 pembrolizumab trial (Marabelle et al., ESMO 2019), which showed that patients with a TMB of ≥ 10 mutations per megabase across several tumor types had higher response rates than patients with fewer than 10 mutations per megabase. Caris Life Sciences is a participant in the Friends of Cancer Research TMB Harmonization Project (Merino et al., 2020).

MICROSATELLITE INSTABILITY ANALYSIS		
Test	**Interpretation**	**Result**
MSI	Major microsatellite instability detected.	High
	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 NGS 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.

GENES TESTED WITH ALTERATIONS							
Gene	**Analyte**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
AMER1	DNA-Tumor	Pathogenic Variant	p.F173fs	2	c.519delT	23	NM_152424.3

Interpretation: A pathogenic mutation was detected in AMER1 (WTX). Somatic mutations in AMER1 are frequent in colorectal cancers and Wilms tumors (Sanz-Pamplona 2015 Clin Cancer Res 21:4709).

AMER1 is a regulator of the canonical Wnt signaling pathway by specifically binding phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2), translocating to the cell membrane and interacting with key regulators of the canonical Wnt signaling pathway, such as components of the beta-catenin destruction complex. Acts both as a positive and negative regulator of the Wnt signaling pathway, depending on the context. It also promotes CTNNB1 ubiquitination and degradation. It upregulates trancriptional activation by the Wilms tumor protein. Defects in this gene are a cause of osteopathia striata with cranial sclerosis (OSCS).

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

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GENES TESTED WITH ALTERATIONS							
Gene	**Analyte**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
ARID1A	DNA-Tumor	Pathogenic Variant	p.G276fs	1	c.827delG	26	NM_006015.4

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.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ASXL1	DNA-Tumor	Pathogenic Variant	p.G646fs	13	c.1934dupG	9	NM_015338.5

Interpretation: A common truncating mutation, p.G646fs, was detected in ASXL1. Pathogenic somatic ASXL1 mutations are frequent in myeloid neoplasms and solid tumors, such as colorectal adenocarcinomas (Balasubramani 2015 Cancer-associated ASXL1 mutations may act as gain-of-function mutations of the ASXL1-BAP1 complex. Nat Commun 6:7307).

The protein is a member of the Polycomb group of proteins, which are necessary for the maintenance of stable repression of homeotic and other loci. The protein is thought to disrupt chromatin in localized areas, enhancing transcription of certain genes while repressing the transcription of other genes. The protein encoded by this gene functions as a ligand-dependent co-activator for retinoic acid receptor in cooperation with nuclear receptor coactivator 1. Mutations in this gene are associated with myelodysplastic syndromes and chronic myelomonocytic leukemia.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
BCOR	DNA-Tumor	Pathogenic Variant	p.S336fs	4	c.1005delC	29	NM_017745.5

Interpretation: A pathogenic frameshift mutation was detected in BCOR.

The protein encoded by this gene was identified as an transcriptional corepressor of BCL6, a POZ/zinc finger transcription repressor that is required for germinal center formation and may influence apoptosis. This protein selectively interacts with the POZ domain of BCL6, but not with eight other POZ proteins. Specific class I and II histone deacetylases (HDACs) have been shown to interact with this protein, which suggests a possible link between the two classes of HDACs.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EP300	DNA-Tumor	Pathogenic Variant	p.T278fs	3	c.832delA	16	NM_001429.3

Interpretation: A pathogenic frameshift mutation was detected in EP300.

EP300 encodes the adenovirus E1A-associated cellular p300 transcriptional co-activator protein. It functions as histone acetyltransferase that regulates transcription via chromatin remodeling and is important in the processes of cell proliferation and differentiation. It mediates cAMP-gene regulation by binding specifically to phosphorylated CREB protein. This gene has also been identified as a co-activator of HIF1A (hypoxia-inducible factor 1 alpha), and thus plays a role in the stimulation of hypoxia-induced genes such as VEGF. Defects in this gene are a cause of Rubinstein-Taybi syndrome and may also play a role in epithelial cancer.

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	**Analyte**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
EP300	DNA-Tumor	Variant of Uncertain Significance	p.Q1904P	31	c.5711A>C	52	NM_001429.3

Interpretation: A variant with no known clinical or functional significance was detected in EP300.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ERBB2 (Her2/Neu)	DNA-Tumor	Likely Benign Variant	p.G1189fs	27	c.3566delG	25	NM_004448.3

Interpretation: This loss of function mutation is predicted to be of no clinical significance in this tumor, since oncogenic ERBB2 mutations are expected to activate the protein.

ERBB2 (HER2) or v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. This gene binds to other ligand-bound EGF receptor family members to form a heterodimer and enhances kinase-mediated activation of downstream signaling pathways, leading to cell proliferation. Most common mechanism for activation of HER2 are gene amplification and over-expression with somatic mutations being rare.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2A	DNA-Tumor	Pathogenic Variant	p.D877fs	3	c.2629 _2630delGA	25	NM_005933.3

Interpretation: A loss of function pathogenic frameshift mutation was found.

This gene encodes a transcriptional coactivator that plays an essential role in regulating gene expression during early development and hematopoiesis. The encoded protein contains multiple conserved functional domains. This protein is processed by the enzyme Taspase 1 into two fragments, MLL-C and MLL-N. These fragments reassociate and further assemble into different multiprotein complexes that regulate the transcription of specific target genes, including many of the HOX genes. Multiple chromosomal translocations involving this gene are the cause of certain acute lymphoid leukemias and acute myeloid leukemias.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2D	DNA-Tumor	Pathogenic Variant	p.R4960*	48	c.14878C>T	16	NM_003482.3

Interpretation: A loss of function pathogenic nonsense mutation was found.

The protein encoded by this gene is a histone methyltransferase that methylates the Lys-4 position of histone H3. The encoded protein is part of a large protein complex called ASCOM, which has been shown to be a transcriptional regulator of the beta-globin and estrogen receptor genes. Mutations in this gene have been shown to be a cause of Kabuki syndrome.

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	**Analyte**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
KMT2D	DNA-Tumor	Variant of Uncertain Significance	p.R5392H	51	c.16175G>A	23	NM_003482.3

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

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2D	DNA-Tumor	Pathogenic Variant	p.R755fs	10	c.2263dupC	11	NM_003482.3

Interpretation: A pathogenic frameshift mutation was detected in KMT2D.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
MSH6	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3261delC	20	NM_000179.2

Interpretation: A pathogenic frameshift mutation, p.F1088fs, was detected in MSH6. This specific mutation frequently occurs as a somatic mutation in tumors with microsatellite instability due to other causes. It has also been reported as a germline mutation, causal for Lynch syndrome (ClinVar database).

This gene encodes a member of the DNA mismatch repair MutS family. Mutations in this gene may be associated with hereditary nonpolyposis colon cancer, colorectal cancer, and endometrial cancer. THe protein product is a component of the DNA mismatch repair system (MMR), and heterodimerizes with MSH2 to form MutS alpha, which binds to DNA mismatches thereby initiating DNA repair.MutS alpha may also play a role in DNA homologous recombination repair. Recruited on chromatin in G1 and early S phase via its PWWP domain that specifically binds trimethylated 'Lys-36' of histone H3 (H3K36me3): early recruitment to chromatin to be replicated allowing a quick identification of mismatch repair to initiate the DNA mismatch repair reaction.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
NSD1	DNA-Tumor	Pathogenic Variant	p.M1531fs	11	c.4591delA	9	NM_022455.4

Interpretation: A pathogenic frameshift mutation was detected in NSD1.

This gene encodes a protein containing a SET domain, 2 LXXLL motifs, 3 nuclear translocation signals (NLSs), 4 plant homeodomain (PHD) finger regions, and a proline-rich region. The encoded protein enhances androgen receptor (AR) transactivation, and this enhancement can be increased further in the presence of other androgen receptor associated coregulators. This protein may act as a nucleus-localized, basic transcriptional factor and also as a bifunctional transcriptional regulator. Mutations of this gene have been associated with Sotos syndrome and Weaver syndrome. One version of childhood acute myeloid leukemia is the result of a cryptic translocation with the breakpoints occurring within nuclear receptor-binding Su-var, enhancer of zeste, and trithorax domain protein 1 on chromosome 5 and nucleoporin, 98-kd on chromosome 11.

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	**Analyte**	**Variant Interpretation**	**Protein Alteration**	**Exon**	**DNA Alteration**	**Variant Frequency %**	**Transcript ID**
NSD1	DNA-Tumor	Variant of Uncertain Significance	p.R1578S	12	c.4734A>C	27	NM_022455.4

Interpretation: A rare NSD1 mutation with unknown clinical or biological significance was found in this sample.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PIK3CA	DNA-Tumor	Pathogenic Variant	p.Q546R	10	c.1637A>G	31	NM_006218.3

Interpretation: A pathogenic mutation was detected in PIK3CA. Substitutions at codon 546 have been reported in numerous tumors.

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.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
RNF43	DNA-Tumor	Pathogenic Variant	p.G659fs	9	c.1976delG	48	NM_017763.5

Interpretation: A pathogenic frameshift mutation was detected in RNF43. This specific mutation frequently occurs as a somatic mutation in tumors with microsatellite instability.

E3 ubiquitin-protein ligase that acts as a negative regulator of the Wnt signaling pathway by mediating the ubiquitination, endocytosis and subsequent degradation of Wnt receptor complex components Frizzled. Acts on both canonical and non-canonical Wnt signaling pathways. Acts as a tumor suppressor in the intestinal stem cell zone by inhibiting the Wnt signaling pathway, thereby resticting the size of the intestinal stem cell zone.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
SMARCA4	DNA-Tumor	Likely Pathogenic Variant	p.G1194R	27	c.3580G>A	25	NM_001128844.1

Interpretation: This missense SMARCA4 mutation is presumed to be pathogenic due to its recurrence in somatic cancers.

The protein encoded by this gene is a member of the SWI/SNF family of proteins and is similar to the brahma protein of Drosophila. Members of this family have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. In addition, this protein can bind BRCA1, as well as regulate the expression of the tumorigenic protein CD44. Mutations in this gene cause rhabdoid tumor predisposition syndrome type 2.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

GENES TESTED WITH INDETERMINATE* RESULTS BY TUMOR DNA SEQUENCING					
ATRX	FLT3	PMS2	RUNX1		
FANCE	KMT2C	PTCH1	TERT ¶		

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

¶TERT Promoter region not sequenced

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 WITH INDETERMINATE CNA RESULTS					
AKAP9	HGF	KMT2C	KNL1	LIFR	STAT4

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.

FOLFOX predictor by Next-Generation Sequencing (NGS)

MI FOLFOXai™ **Result:** **DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC**

Methods

The MI FOLFOXai predictor is comprised of 5,000 machine learning algorithms which are trained to identify patients with metastatic colorectal cancer (mCRC) that may exhibit increased benefit (IB) to first-line FOLFOX + bevacizumab from those that may exhibit decreased benefit (DB). The algorithms use information from the Caris Life Sciences 592-gene Next Generation Sequencing panel to make a single aggregated prediction for each patient. The prediction is not a guarantee that IB or DB status will be realized on a regimen of FOLFOX + bevacizumab. The predictor was validated against two blinded, stage IV CRC cohorts: i) 296 cases from a manually curated real world evidence dataset of insurance claims and electronic medical records that received first-line FOLFOX combined with bevacizumab, ii) 149 patients from the TRIBE2 phase III clinical trial (all TRIBE2 patients received bevacizumab in addition to the chemotherapy backbone). In the manually curated real world evidence cohort (i), the median predicted IB patient had an overall survival 11.2 months (51%) longer than the median predicted DB with a hazard ratio 0.486 (95% CI: 0.337-0.699, p < 0.001). In the TRIBE2 cohort (ii), the median predicted IB patient had an overall survival 6.0 months (32%) longer than the median predicted DB patient with a hazard ratio of 0.629 (95% CI: 0.404-0.981, p=0.04). When the algorithm cannot place a patient's results in either the IB or DB categories, the result is reported as "No Call". In both of the independent, blinded testing sets there was no statistical difference between these no-call cases and the total population with respect to overall survival or hazard.

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Gene Fusion and Transcript Variant Detection by RNA Sequencing

GENES TESTED WITH GENE FUSION OR TRANSCRIPT VARIANT DETECTED				
Biomarker	**Fusion/Isoform**	**Splice Site**	**Transcript ID**	**Variant Interpretation**
NTRK1	SNRNP70:NTRK1	exon 8:exon 12	NM_001301069.1/NM_002529.3	Pathogenic Fusion

Interpretation: An SNRNP70-NTRK1 fusion was detected in this tumor. This specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic NTRK fusions. Exon 8 of SNRNP70 (NM_001301069.1) is joined to exon 12 of NTRK1 (NM_002529.3)

NTRK1 encodes the TrkA protein, which is a member of the neurotrophic tyrosine kinase receptor (NTKR) family. This kinase is a membrane-bound receptor that, when activated, phosphorylates members of the MAPK pathway. TrkA is an oncoprotein and is mutated (typically by gene rearrangement) in papillary thyroid and colon cancers. TrkA rearrangements have also been found in gliomas, cholangiocarcinomas, certain subtypes of melanoma and neuroendocrine tumors.

Gene Fusion Methods

Gene fusion and variant transcript detection were performed on mRNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Agilent SureSelectXT Low Input Library prep chemistry, optimized for FFPE tissue, in conjunction with the SureSelect Human All Exon V7 bait panel (48.2 Mb) and the Illumina NovaSeq. This assay is designed to detect fusions occurring at known and novel breakpoints within genes. Only a portion of genes tested are included in this report. The genes included in this report represent the subset of genes most commonly associated with cancer. All results can be provided by request. Analytical validation of this test demonstrated ≥97% Positive Percent Agreement (PPA), ≥99% Negative Percent Agreement (NPA) and ≥99% Overall Percent Agreement (OPA) with a validated comparator method.
The versioned reference identifier used for the transcript ID was Feb.2009 (GRCh37/hg19).
The complete list of unclassified alterations for RNA Whole Transcriptome Sequencing are available by 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:
ERBB2 (Her2/Neu)	0	100	Negative	Intensity ≥3+ and >10% of cells stained
MLH1	0	100	Negative	Intensity ≥1+ and ≥1% of cells stained
MSH2	2 +	100	Positive	Intensity ≥1+ and ≥1% of cells stained
MSH6	1 +	90	Positive	Intensity ≥1+ and ≥1% of cells stained
PD-L1 (SP142)	0	100	Negative	Intensity ≥2+ and ≥5% of cells stained
PMS2	0	100	Negative	Intensity ≥1+ and ≥1% of cells stained
PTEN	1 +	90	Positive	Intensity ≥1+ and ≥1% of cells stained

Clones used: ERBB2 (Her2/Neu) (4B5), MLH1 (M1), MSH2 (G219-1129), MSH6 (44), PMS2 (A16-4), PD-L1 (SP142), PTEN (6H2.1).

Electronic Signature

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 using a microscope and/or digital whole slide image(s).

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, breast carcinoma and non-small cell lung cancer; drug association only in urothelial, triple negative breast cancers and non-small cell lung cancer), and PD-L1 28-8 (pharmDx, Dako).

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

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References

#	Drug	Biomarker	Reference
1	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Valtorta, E., M. Gambacorta, et al. (2015) "Assessment of a HER2 scoring system for colorectal cancer: results from a validation study". Modern Pathology 28, 1481-1491. View Citation Online
2	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Meric-Bernstam, F., J., Hainsworth, et al. (2019) "Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study." Lancet Oncol. 20(4):518-530. View Citation Online
3	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer Version 3.2019
4	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer Version 4.2019
5	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Sartore-Bianchi, A., S. Siena, (2018) "Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial." Lancet Oncol.17(6):738-746 View Citation Online
6	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Hainsworth, J.D., R. Kurzrock, et al (2018) "Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study." J Clin Oncol. 36(6):536-542. View Citation Online
7	entrectinib, larotrectinib	NTRK1	Drilon, A., D.M. Hyman, et al. (2018). "Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children". N Engl J Med. 378(8):731-739. View Citation Online
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11	cetuximab, panitumumab	KRAS, NRAS	Douillard, J-Y, S.D. Patterson, et al. (2013). "Panitumumab-FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer" N. Engl. J. Med. 369;11: 1023-1034 View Citation Online
12	cetuximab, panitumumab	KRAS	Lievre, A., Laurent-Puge, P., (2008). "KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab". J Clin Oncol, 26(3):374-9. View Citation Online
13	cetuximab, panitumumab	KRAS	Chen, J., G. Shi, et al. (2012). "Association between KRAS codon 13 mutations and clinical response to anti-EGFR treatment in patients with metastatic colorectal cancer: results from a meta-analysis"Cancer Chemother Pharmacol. 2012 Oct 23. [Epub ahead of print] View Citation Online
14	cetuximab, panitumumab	KRAS	Amado, R.G., et. al. (2008). "Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer." J. Clin. Oncol. 26:1626-1634. View Citation Online
15	cetuximab, panitumumab	KRAS	Douillard, J.Y., J. Gansert (2010). "Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study." J. Clin. Oncol. 28:4697-4705. View Citation Online
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References

#	Drug	Biomarker	Reference
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18	cetuximab, panitumumab	KRAS	Tejpar, S., E. Van Cutsem, et al. (2012). ""Association of KRAS G13D Tumor Mutations With Outcome in Patients With Metastatic Colorectal Cancer Treated With First-Line Chemotherapy With or Without Cetuximab.""J Clin Oncol. 30(29):3570-7. View Citation Online
19	cetuximab, panitumumab	BRAF	Di Nicolantonio,F. , A. Bardelli, et. al. (2008). "Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer." J. Clin. Oncol. 2008 View Citation Online
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21	cetuximab, panitumumab	BRAF, NRAS	De Roock, W., S. Tejpar, et. al. (2010). "Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis." Lancet Oncol. 11: 753-62. View Citation Online
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26	cetuximab, panitumumab	NRAS	Peeters, M., S.D. Patterson, et al. (2013). "Massively Parallel Tumor Multigene Sequencing to Evaluate Response to Panitumumab in a Randomized Phase III Study of Metastatic Colorectal Cancer. "Clin Cancer Res; 19(7): 1902-1912. View Citation Online
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28	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Le, DT, LA Diaz, et al. (2017). ""Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade"". Science. 357:409-413. View Citation Online
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30	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Overman, M.J., T. Andre, et. al. (2018) "Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer" J Clin Oncol 36:773-779. View Citation Online
31	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Overman, M.J., T., Andre, et al. (2016) "Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results." J Clin Oncol 34, (suppl; abstr 3501). View Citation Online

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