Patient

Name:
Date of Birth:
Sex:
Case Number: TN26-
Diagnosis: Adenocarcinoma, NOS

Specimen Information

Primary Tumor Site: Sigmoid colon
Specimen Site: Peritoneum, NOS
Specimen ID:
Specimen Collected:
Test Report Date:

Ordered By

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
BRAF	Seq	DNA-Tumor	Pathogenic Variant Exon 15 | p.V600E	BENEFIT	**encorafenib + cetuximab**	**Level 1**
					encorafenib + cetuximab + mFOLFOX6	**Level 2**
					encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	Level 2
				LACK OF BENEFIT	vemurafenib/dabrafenib monotherapy	Level 3
MSI	Seq	DNA-Tumor	High	BENEFIT	**dostarlimab, pembrolizumab**	**Level 1**
					nivolumab, nivolumab/ipilimumab combination	**Level 2**
TMB	Seq	DNA-Tumor	High, 71 mut/Mb	BENEFIT	**pembrolizumab**	**Level 2**

* Biomarker reporting classification - Level 1 – MI Cancer Seek™ or other companion diagnostic (CDx) performed as part of professional services; Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

CARIS | FOLFIRSTai

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

See Page 2 for important details about clinical data regarding Caris FOLFIRSTai™

Important Note

This content is provided as part of the professional services. For MI Cancer Seek™ results, see CDx Associated Findings.

Encorafenib + cetuximab + mFOLFOX6 (NCCN Category 2A) is FDA-approved as first-line therapy for metastatic colorectal cancer (mCRC) patients with BRAF V600E mutation. Encorafenib + cetuximab (NCCN Category 2A) is FDA-approved for use after prior therapy. NCCN guidelines (Colon/Rectal Cancer) also list panitumumab as an alternative to cetuximab, in combination with encorafenib with or without FOLFOX, depending on the line of treatment.

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

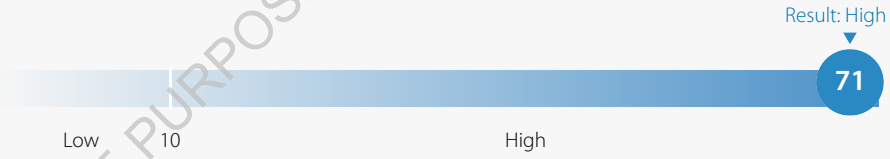
Pembrolizumab monotherapy is FDA-approved for first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer.

Results continued on the next page. >

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
PIK3CA	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 2 | p.R93Q**
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
RET	Seq	RNA-Tumor	Fusion Not Detected
BRAF	Seq	RNA-Tumor	Fusion Not Detected
EGFR	CNA-Seq	DNA-Tumor	Amplification Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected
KRAS	Seq	DNA-Tumor	Mutation Not Detected
NF1	Seq	DNA-Tumor	Mutation Not Detected
NRAS	Seq	DNA-Tumor	Mutation Not Detected
POLE	Seq	DNA-Tumor	Mutation Not Detected

Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	High
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 2% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

CARIS FOLFIRSTai

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.

Caris FOLFIRSTai™ 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 sequencing data and an artificial intelligence algorithm. The signature was validated using two independent data sets, as reported in Abraham, J.P., D.B. Spetzler, et al. (2021). "Clinical Validation of a Machine-learning-derived Signature Predictive of Outcomes from First-line Oxaliplatin-based Chemotherapy in Advanced Colorectal Cancer" Clin Cancer Res 27 (4): 1174-1183.

412 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: 17.5 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 Caris FOLFIRSTai™ methodology.

PATIENT:	TN26-	PHYSICIAN:

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.D1850fs	20	c.5548delG	28
ASXL1	Seq	DNA-Tumor	Pathogenic Variant	p.G645fs	13	c.1934delG	28
ATRX	Seq	DNA-Tumor	Pathogenic Variant	p.K1802fs	21	c.5406delA	26
AXIN1	Seq	DNA-Tumor	Pathogenic Variant	p.W564*	6	c.1691G>A	31
AXIN2	Seq	DNA-Tumor	Pathogenic Variant	p.R671fs	8	c.2011delC	33
BLM	Seq	DNA-Tumor	Pathogenic Variant	p.D757fs	10	c.2268delA	29
BRAF	Seq	DNA-Tumor	Pathogenic Variant	p.V600E	15	c.1799T>A	32
CASP8	Seq	DNA-Tumor	Pathogenic Variant	p.R449*	9	c.1345C>T	23
CDC73	Seq	DNA-Tumor	Pathogenic Variant	c.370+2T>C	4	c.370+2T>C	32
CHEK2	Seq	DNA-Tumor	Pathogenic Variant	p.F292fs	8	c.876delT	33
CREBBP	Seq	DNA-Tumor	Pathogenic Variant	p.S976fs	15	c.2925delC	29
EP300	Seq	DNA-Tumor	Pathogenic Variant	p.T1851fs	31	c.5550delC	28
	Seq	DNA-Tumor	Pathogenic Variant	p.C1177*	19	c.3531C>A	32
EPHA2	Seq	DNA-Tumor	Pathogenic Variant	p.C290fs	4	c.867dupC	32
	Seq	DNA-Tumor	Likely Pathogenic Variant	p.P460fs	6	c.1379delC	30
FANCE	Seq	DNA-Tumor	Pathogenic Variant	p.V311fs	4	c.928 _929dupCC	27
FAT1	Seq	DNA-Tumor	Pathogenic Variant	p.S1011fs	2	c.3031delT	45
	Seq	DNA-Tumor	Pathogenic Variant	p.G3953fs	22	c.11856dupT	40
FBXW7	Seq	DNA-Tumor	Pathogenic Variant	p.R465C	9	c.1393C>T	32
KDM5C	Seq	DNA-Tumor	Likely Pathogenic Variant	p.P1508fs	26	c.4523delC	24
KMT2C	Seq	DNA-Tumor	Pathogenic Variant	p.K4351fs	52	c.13053delA	32
KMT2D	Seq	DNA-Tumor	Pathogenic Variant	p.G2712*	32	c.8134G>T	32
MSH3	Seq	DNA-Tumor	Pathogenic Variant	p.K383fs	7	c.1148delA	66
MSH6	Seq	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3260 _3261dupCC	10
	Seq	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3261dupC	5
PIK3CA	Seq	DNA-Tumor	Pathogenic Variant	p.R93Q	2	c.278G>A	33
PIK3R1	Seq	DNA-Tumor	Likely Pathogenic Variant	p.G588fs	14	c.1761delA	29
PTCH1	Seq	DNA-Tumor	Pathogenic Variant	p.S1203fs	22	c.3606delC	6
RNF43	Seq	DNA-Tumor	Pathogenic Variant	p.P660fs	9	c.1973 _1976dupGGGG	7

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 %
TP53	Seq	DNA-Tumor	Pathogenic Variant	p.S90fs	4	c.267delC	5
	Seq	DNA-Tumor	Likely Pathogenic Variant	p.F113V	4	c.337T>G	23

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 %
FAT1	Seq	DNA-Tumor	Variant of Uncertain Significance	p.S2660N	10	c.7979G>A	43
	Seq	DNA-Tumor	Variant of Uncertain Significance	p.P4007T	22	c.12019C>A	8
KMT2C	Seq	DNA-Tumor	Variant of Uncertain Significance	c.1185-3delT	9	c.1185-3delT	31
KMT2D	Seq	DNA-Tumor	Variant of Uncertain Significance	p.S5341P	50	c.16021T>C	33
MET	Seq	DNA-Tumor	Variant of Uncertain Significance	p.V1377I	21	c.4129G>A	49
	Seq	DNA-Tumor	Variant of Uncertain Significance	p.A1225V	18	c.3674C>T	33
RET	Seq	DNA-Tumor	Variant of Uncertain Significance	p.A217V	4	c.650C>T	30
RNF43	Seq	DNA-Tumor	Variant of Uncertain Significance	p.G659dup	9	c.1974 _1976dupGGG	8

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

Predicted Human Leukocyte Antigen (HLA) Genotype Results

The predicted HLA genotype results are summarized in the table below. Please note that HLA typing via tumor tissue sequencing is not a substitute for histocompatibility testing performed using peripheral blood. It is recommended to confirm the patient's HLA type with an appropriate assay.

Gene	Method	Analyte	Genotype
MHC CLASS I			
HLA-A	Seq	DNA-Tumor	A*01:01, A*02:01
HLA-B	Seq	DNA-Tumor	B*13:02, B*15:01
HLA-C	Seq	DNA-Tumor	C*03:03, C*06:02

HLA genotypes with only one allele are either homozygous or have loss-of-heterozygosity at that position.

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Genes Tested with Indeterminate Results by Tumor DNA Sequencing

ATP6AP2	CYSLTR2	EED	EXO1	KIF1B	MDH2	NPM1	PMS1	PREX2	RABL3	REST	SOS1
CDK6	DACH1	EGLN1	JAK2	LYN	NOTCH2	PLCB4	POLQ	PRKD1	RASA1	RRAS2	SUZ12
CUL3											

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

Genes Tested with Intermediate CNA Results by Tumor DNA Sequencing

AKT2	AXL	CCNE1	RAC1								

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, variants of uncertain significance, or 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

CDx reports are generated through automated bioinformatics processing of a pre-defined list of genes and variants. Pathogenic or likely pathogenic variants identified outside the FDA-approved list will not be included in the CDx report. In addition, downgrading of variants approved by board-eligible/board-certified geneticists and pathologists may have occurred through manual variant annotation carried out by Caris' professional services. To ensure optimal coverage, multiple sequencing runs may be performed for a given case. This may account for some discrepancies observed between CDx reports and professional services.

Clinical Trials Connector ™ opportunities based on biomarker expression: 101 Targeted Therapies. See page 7 for details.

Specimen Information

Specimen ID:

Specimen Collected:

Specimen Received:

Testing Initiated:

Test Ordered*: MI Cancer Seek
* If the submitted specimen is inadequate, only a subset of the ordered testing may be reported.

Gross Description: 1 (A) Paraffin Block 1 (B) Paraffin Block

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™

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.

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

Please see https://clinicaltrials.gov/ for more information.

TARGETED THERAPIES (101)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
Alkylating agents (1)	CHEK2	NGS	DNA-Tumor	LP-184
ATR inhibitors (4)	ARID1A	NGS	DNA-Tumor	ART0380, berzosertib, ceralasertib, IMP9064
	CHEK2	NGS	DNA-Tumor	
BET bromodomain inhibitors (6)	ARID1A	NGS	DNA-Tumor	BET Bromodomain Inhibitor ZEN-3694, tazemetostat
	EP300	NGS	DNA-Tumor	
Biomarker-Inclusion Trial Match (7)	BRAF	NGS	DNA-Tumor	sacituzumab tirumotecan, BET Bromodomain Inhibitor ZEN-3694, STAR0602
	MSI	NGS	DNA-Tumor	
	TMB	NGS	DNA-Tumor	
DNA Polymerase Inhibitor (2)	CHEK2	NGS	DNA-Tumor	GSK4524101, MOMA-313
ERK inhibitors (1)	BRAF	NGS	DNA-Tumor	IPN01194
EZH2 inhibitors (2)	ARID1A	NGS	DNA-Tumor	tazemetostat, tulmimetostat
Immunomodulatory agents (30)	MSH3	NGS	DNA-Tumor	balstilimab, dostarlimab, durvalumab, envafolimab, atezolizumab, nivolumab, pembrolizumab, retifanlimab, volrustomig, cemiplimab
	MSH6	NGS	DNA-Tumor	
	MSI	NGS	DNA-Tumor	
	TMB	NGS	DNA-Tumor	
MEK inhibitors (2)	BRAF	NGS	DNA-Tumor	PF-07799544, PAS-004 Capsules
Multi-targeted TKI (1)	ATRX	NGS	DNA-Tumor	chiauranib
	BRAF	NGS	DNA-Tumor	
Pan-RAS inhibitors (6)	BRAF	NGS	DNA-Tumor	JAB-23E73, NST-628, RMC-6236, YL-17231
PARG inhibitor (2)	CHEK2	NGS	DNA-Tumor	ETX-19477, IDE-161
PARP inhibitors (5)	ARID1A	NGS	DNA-Tumor	niraparib, olaparib, saruparib
	BLM	NGS	DNA-Tumor	
	CHEK2	NGS	DNA-Tumor	

( ) = 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.

Additional Clinical Trials Connector results continued on the next page. >

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Clinical Trials Connector™

TARGETED THERAPIES (101)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
PI3K/Akt/mTOR inhibitors (11)	PIK3CA	NGS	DNA-Tumor	paxalisib, nab-sirolimus, sirolimus, ipatasertib, alpelisib, inavolisib, LY4064809, RLY-2608, ETX-636 dose escalation, STX-478
	PIK3R1	NGS	DNA-Tumor	
Platinum compounds (3)	CHEK2	NGS	DNA-Tumor	cisplatin, oxaliplatin
RAF inhibitors (8)	BRAF	NGS	DNA-Tumor	dabrafenib, encorafenib, Plixorafenib, tovorafenib, vemurafenib, avutometinib, S241656
RAS Interaction Breakers (1)	PIK3CA	NGS	DNA-Tumor	BBO-10203
RNA polymerase inhibitor (1)	CHEK2	NGS	DNA-Tumor	CX-5461
SWI/SNF complex inhibitors (1)	ARID1A	NGS	DNA-Tumor	LY4050784
T-cell therapy (2)	HLA-A	NGS	DNA-Tumor	brenetafusp, IMA203 Product
TEAD inhibitors (1)	FAT1	NGS	DNA-Tumor	SW-682
Ubiquitin Specific Protease Inhibitor (1)	CHEK2	NGS	DNA-Tumor	XL309
Wnt pathway inhibitors (2)	AXIN2	NGS	DNA-Tumor	E7386, FOG-001
	RNF43	NGS	DNA-Tumor	
WRN helicase inhibitor 1 (1)	MSI	NGS	DNA-Tumor	NDI-219216

( ) = 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, 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 and the tests should not be considered a companion diagnostic.

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 Caris molecular profiling assays. Individual assays that are available through Caris molecular profiling include both Laboratory Developed Tests (LDT) and U.S. Food and Drug Administration (FDA) approved or cleared tests. In addition, certain tests have been CE-marked as a general IVD under the In Vitro Diagnostic Directive (IVDD) 98/79/EC. Offered LDTs were developed and their performance characteristics determined by Caris. Certain tests have not been cleared or approved by the FDA. Caris LDTs are used for clinical purposes. They are not investigational or for research. Caris' CLIA certification number is located at the bottom of each page of this report.

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.

All materials, documents, data, data software, information and/or inventions supplied to customers by or on behalf of Caris or created by either party relating to the services shall be and remain the sole and exclusive property of Caris. Customer shall not use or disclose the information provided by Caris through the services or related reports except in connection with the treatment of the patient for whom the services were ordered and shall not use such property for, or disseminate such property to, any third parties without expressed written consent from Caris. Customer shall deliver all such property to Caris immediately upon demand or upon Caris ceasing to provide the services. The technical and professional component of all testing was performed at the laboratory location displayed in the footer unless otherwise notated in the report.

Caris molecular testing is subject to Caris' intellectual property. Patent www.CarisLifeSciences.com/ip.

Professional Component Performed:

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Patient

Name:
Date of Birth:
Sex:
Case Number: TN26-
CDx Report Generated:

Specimen Information

Diagnosis and Tumor Type: Adenocarcinoma, NOS, Sigmoid colon
Specimen Site: Peritoneum, NOS
Specimen ID:
Specimen Type: Formalin-fixed paraffin embedded
Specimen Collected

Ordered By

CDx Associated Findings

Genomic Findings Detected	FDA-approved Therapeutic Options
BRAF V600E	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)
KRAS Wild-Type (Exons 2, 3, 4) ***NRAS Wild-Type (Exons 2, 3, 4)***	VECTIBIX® (panitumumab)
Microsatellite Instability (MSI) MSI-H	JEMPERLI® (dostarlimab-gxly), KEYTRUDA® (pembrolizumab)

Tumor Profiling Results

MI Cancer Seek is FDA-approved to provide tumor mutation profiling results for previously diagnosed oncology patients with solid tumors.

Other Alterations and Biomarkers Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
Confirmation of tumor mutation status using an FDA-approved CDx test is needed for therapeutic use.

Tumor Mutational Burden (TMB)	71 mut/Mb	***FAT1***	G3953fs
ARID1A	D1850fs	***FBXW7***	R465C
ASXL1	G645fs	***KDM5C***	P1508fs
ATRX	K1802fs	***KMT2C***	K4351fs
AXIN2	R671fs	***KMT2D***	G2712*
BLM	D757fs	***MSH3***	K383fs
CDC73	c.370+2T>C	***MSH6***	F1088fs F1088fs
CHEK2	F292fs	***PIK3CA***	R93Q
CREBBP	S976fs	***PIK3R1***	G588fs
EP300	C1177* T1851fs	***PTCH1***	S1203fs
EPHA2	C290fs	***RNF43***	G659fs

	P460fs		P660fs
FANCE	V311fs	***TP53***	F113V S90fs

MI Cancer Seek™

Intended Use:

MI Cancer Seek is a next-generation sequencing (NGS) based in vitro diagnostic (IVD) device using total nucleic acid (TNA) isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens for the detection of single nucleotide variants (SNVs) and insertions and deletions (indels) in 228 genes, microsatellite instability (MSI), tumor mutational burden (TMB) in patients with previously diagnosed solid tumors, and copy number amplification (CNA) in one gene in patients with breast cancer.

MI Cancer Seek is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 below, in accordance with the approved therapeutic product labeling.

Additionally, MI Cancer Seek is intended to provide tumor mutational profiling to be used by qualified healthcare professionals in accordance with professional oncology guidelines for cancer patients with previously diagnosed solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. MI Cancer Seek Companion Diagnostic Indications

INDICATION	BIOMARKER	THERAPY
Breast Cancer	PIK3CA (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, H1047Y)	PIQRAY® (alpelisib)
Colorectal Cancer (CRC)	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild-type (absence of mutations in exons 2, 3, and 4)	VECTIBIX® (panitumumab)
	BRAF V600E	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)
Melanoma	BRAF V600E	BRAF Inhibitors approved by FDA*
	BRAF V600E or BRAF V600K	MEKINIST® (trametinib) or BRAF/MEK Inhibitor Combinations approved by FDA*
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors approved by FDA*
Solid Tumors	MSI-H	KEYTRUDA® (pembrolizumab), JEMPERLI® (dostarlimab-gxly)
Endometrial Carcinoma	Not MSI-H	KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenvatinib)

* For the most current information about the therapeutic products in this group, go to:

www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group_Labeling

MI Cancer Seek™ is a single-site assay performed at Caris Life Sciences, Phoenix, AZ.

Contraindications:

There are no known contraindications.

Warnings and Precautions:

Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

Limitations:

- For in vitro diagnostic use.
- CAUTION: Federal law restricts this device to sale by or on the order of a physician.
- The acceptable preparation method for MI Cancer Seek CDx specimens is FFPE. Other preparations have not been evaluated.
- The test is designed to report out somatic variants and is not intended to report germline variants.
- MI Cancer Seek requires a minimum tumor percentage of 20% for detection of alterations, with tumor content enrichment recommended for specimens with tumor percentage lower than 20%.

- Genomic findings other than those listed in the Companion Diagnostic Indications table are not prescriptive or conclusive for labeled use of any specific therapeutic product. Confirmation of tumor mutation status using an FDA-approved CDx test is needed for therapeutic use.
- A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
- MI Cancer Seek is only approved for use with Caris Life Sciences pre-qualified Illumina NovaSeq 6000 instruments.
- The test is intended to be performed on specific serial number-controlled instruments by Caris Life Sciences.
- MI Cancer Seek does not report TMB for values lower than 3 mut/Mb as the accuracy of TMB values below 3 mut/Mb are unreliable.
- 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, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
- Based on the low positive percent agreement (PPA) in the accuracy study for ERBB2 copy number amplifications (CNAs) in breast cancer patients, this alteration may not be detected. Additional clinical investigation to confirm the presence of ERBB2 CNAs in the breast cancer patient's tumor with another FDA approved or cleared test is strongly recommended.
- Patients with breast cancer whose specimens have intermediate ERBB2 CNA status should be tested with another FDA approved or cleared test to ascertain ERRB2 CNA status in their tumor.
- Test may have reduced sensitivity and may yield false negative results in samples where necrotic tissue is >15%, melanin is >5%, fat cells are >10%.

Test Principle:

MI Cancer Seek is a single-site assay performed at Caris Life Sciences located at 4610 South 44th Place, Phoenix, AZ 85040. The test includes reagents, software, and procedures for testing of total nucleic acid (TNA) from formalin fixed paraffin embedded (FFPE) tumor tissue. The test uses a custom bait panel to measure all coding regions of the exome to detect and report SNVs and indels within 228 genes outlined in Table 2 across solid tumors and amplifications in ERBB2 in patients with breast cancer only. The test also detects MSI (determined from 3,210 genes) and whole exome based TMB in patients with solid tumors.

Table 2. MI Cancer Seek Reportable Gene List for SNVs and indels

ABL1	BARD1	CDH1	EP300	FAT1	H3F3B	KMT2D	MSH3	NTRK2	PRKAR1A	SDHA	STAT3
ACVR1	BCL2	CDK12	EPHA2	FBXW7	HIST1H3B	KRAS	MSH6	NTRK3	PRKDC	SDHAF2	STK11
AIP	BCL9	CDK4	ERBB2	FGFR1	HNF1A	LZTR1	MTOR	PALB2	PTCH1	SDHB	SUFU
AKT1	BCOR	CDKN1B	ERBB3	FGFR2	HOXB13	MAP2K1	MUTYH	PBRM1	PTEN	SDHC	TCF7L2
AKT2	BLM	CDKN2A	ERBB4	FGFR3	HRAS	MAP2K2	MYC	PDGFRA	PTPN11	SDHD	TERT
AKT3	BMPR1A	CHEK1	ERCC2	FGFR4	IDH1	MAP2K4	MYCN	PDGFRB	RAC1	SETD2	TET2
ALK	BRAF	CHEK2	ESR1	FH	IDH2	MAP3K1	MYD88	PIK3CA	RAD50	SF3B1	TMEM127
AMER1	BRCA1	CIC	EZH2	FLCN	IRF4	MAPK1	NBN	PIK3CB	RAD51B	SMAD2	TNFAIP3
APC	BRCA2	CREBBP	FANCA	FLT1	JAK1	MAX	NF1	PIK3R1	RAD51C	SMAD4	TNFRSF14
AR	BRIP1	CSF1R	FANCB	FLT3	JAK2	MED12	NF2	PIK3R2	RAD51D	SMARCA4	TP53
ARAF	BTK	CTCF	FANCC	FOXA1	JAK3	MEF2B	NFE2L2	PIM1	RAD54L	SMARCB1	TRAF7
ARID1A	CALR	CTNNA1	FANCD2	FOXL2	KDM5C	MEN1	NFKBIA	PMS2	RAF1	SMARCE1	TSC1
ARID2	CARD11	CTNNB1	FANCE	FUBP1	KDM6A	MET	NOTCH1	POLD1	RASA1	SMO	TSC2
ASXL1	CBFB	CXCR4	FANCF	GATA3	KDR	MITF	NPM1	POLE	RB1	SOCS1	U2AF1
ATM	CCND1	CYLD	FANCG	GNA11	KEAP1	MLH1	NRAS	POT1	RET	SOS1	VHL
ATRX	CCND2	DDR2	FANCI	GNA13	KIT	MLH3	NSD1	PPP2R1A	RHOA	SPEN	WRN
AXIN2	CCND3	DICER1	FANCL	GNAQ	KLF4	MPL	NSD2	PPP2R2A	RNF43	SPOP	WT1
B2M	CD79B	DNMT3A	FANCM	GNAS	KMT2A	MRE11	NTHL1	PRDM1	ROS1	SRC	XPO1
BAP1	CDC73	EGFR	FAS	H3F3A	KMT2C	MSH2	NTRK1	PRKACA	RUNX1	STAG2	XRCC1

FDA Evidence Levels:

Genomic findings other than those listed in the Intended Use are not prescriptive or conclusive for labeled use of any specif ic therapeutic product. Test results should be interpreted in the context of pathological evaluation of tumors, treatment history, clinical findings, and other laboratory data. The test report includes genomic findings reported in the following levels (Table 3).

Table 3. Classification Criteria for FDA Evidence Levels

LEVEL	CRITERIA
Level 1	Biomarker is FDA-approved as a companion diagnostic as part of MI Cancer Seek™
Level 2	Cancer alterations that are well-established with strong clinical evidence that the clinician must know according to professional consensus guidelines in the specific tumor type.
Level 3	Cancer alterations with potential clinical significance, e.g., biomarkers deemed useful for directing patients to a clinical trial or simply for informational purposes. i. Clinical data such as case reports, single or several case series, or Phase I/II clinical trial data that support the utility of specific biomarker alteration to direct a patient to clinical trials, or ii Pre-clinical and/or in vitro studies provide structural analysis of the mutation, fusion, or isoform to confirm pathogenicity (tumor-promoting), sensitivity, or resistance through colony forming assays, growth inhibition or drug sensitivity assays, etc.

Gene Expression

Gene	Percentile in Cancer Type	Gene	Percentile in Cancer Type	Gene	Percentile in Cancer Type
ADAM9	58	EREG	44	NTRK1	84
ADORA2A	87	FGFR2	38	NTRK2	40
ALK	72	FGFR3	48	NTRK3	62
APC	96	FN1	38	PDCD1	57
AREG	73	FOLR1	58	PDCD1LG2	93
ATM	30	GNAS	52	PIK3CA	65
BRAF	32	HRAS	98	PIWIL1	0
BRCA1	74	IGF1R	38	PRAME	90
BRCA2	30	ITGB6	46	PTEN	37
BRD4	57	KDM1A	100	PVRIG	84
CCND1	100	KDR	2	RB1	72
CCNE1	100	KRAS	68	RET	68
CD274	89	LAG3	88	ROR1	16
CD276	9	MAGEA4	88	ROR2	52
CDH17	0	MDM2	94	ROS1	24
CDH6	1	MET	100	SRC	0
CDKN2A	96	MGMT	89	SSTR2	88
CEACAM5	28	MKI67	58	SSTR3	88
CLDN18	43	MSLN	13	SSTR5	90
CLDN4	16	MTAP	100	TACSTD2	14
CLDN6	74	MTOR	36	TGFB1	100
CTLA4	80	MUC1	58	TNFRSF1B	86
DKK1	90	MUC16	40	TOP1	10
EGFR	46	MYC	32	TP53	80
EPHA2	99	NECTIN4	60	TSC1	75
EPHA5	48	NF1	38	TSC2	12
ERBB2	89	NRAS	74	VEGFA	76
ERBB3	18	NRG1	82	XPO1	59

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Gene Expression of Selected Genes by Whole Transcriptome Sequencing (WTS) Methods:
Gene expression is derived from whole transcriptome sequencing. Relative expression of genes are calculated as normalized values using Transcripts per Million Molecules or TPM. TPM is presented as a percentile derived by comparison to a distribution of Caris' internal cohort of the tumor-type profiled. Selected genes reported in this section were chosen based on their tumor-type specific relevance for matching to clinical trials, or tumor type subclassification.

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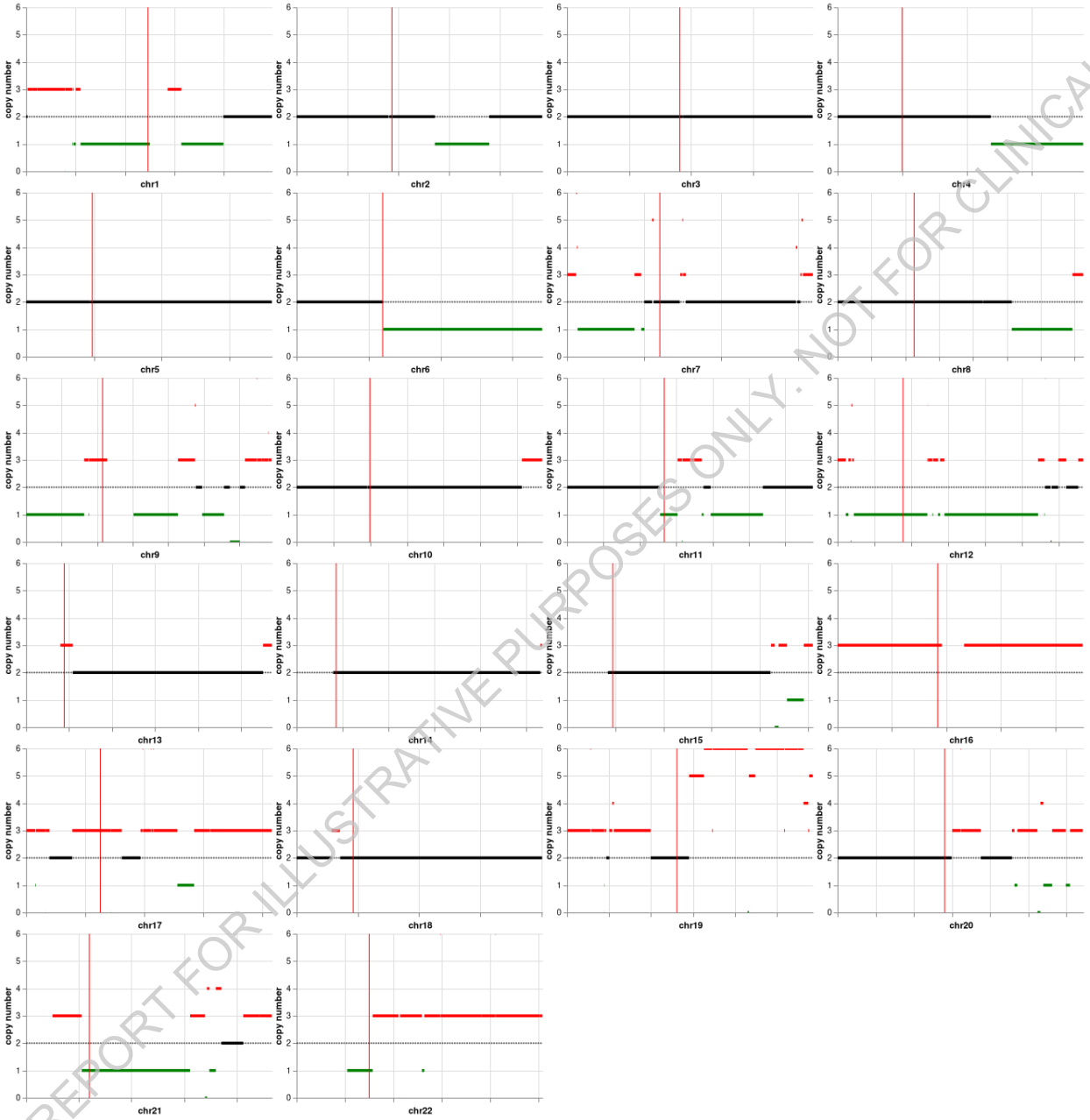
Karyotype



Karyotyping using Copy Number Analysis by Whole Exome Sequencing (WES) Methods:
Whole exome sequencing in combination with interrogation of single nucleotide polymorphisms (SNPs) tiled throughout the genome, allows for the identification and visualization of cytogenetic aberrations.

Somatic structural variants like whole or partial chromosome duplications or deletions, are important for cancer development and progression, and may identify clinically actionable alterations.

PATIENT:	TN26-	PHYSICIAN:

Colorectal Cancer Consensus Molecular Subtype (CMS) Classification

Result
CMS1

Gene expression data was utilized to validate a CMS classifier. Chowdhury S, Xiu J, Ribeiro JR, et al. Consensus molecular subtyping of metastatic colorectal cancer expands biomarker-directed therapeutic benefit for patients with CMS1 and CMS2 tumors. Br J Cancer. 2024;131(8):1328-1339.

Colorectal Cancer (CRC) Consensus Molecular Subtypes was established by an International Consortium described in Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer.#Nat Med. 2015;21(11):1350-1356.

Four molecular subtypes of CRC are defined below, though this classification is not recommended for clinical practice (NCCN Guidelines Colon/Rectal 2024).

CMS Subtypes
(1) CMS1- Microsatellite Instability (MSI-H) Immune, hypermutated, microsatellite instability high, with strong immune activation.
(2) CMS2 - Canonical, epithelial, chromosomal instability, with Wnt and MYC signaling pathway activation
(3) CMS3 - Metabolic, epithelial, metabolic dysregulation
(4) CMS4 - Mesenchymal, TGFB signaling pathway activation, angiogenic and stromal invasive features

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Mutational Analysis by Next-Generation Sequencing (NGS)

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

TMB

Tumor Mutational Burden (TMB) is defined as the number of somatic non-synonymous mutations per million bases of sequenced DNA in a tumor sample. Tumors with high TMB may increase the number of neoantigens which is hypothesized to increase T-cell reactivity and potential for response to immune checkpoint inhibitors. TMB analysis was performed based on next generation sequencing analysis of genomic DNA isolated from a tumor sample.

MICROSATELLITE INSTABILITY ANALYSIS	
Test	**Result**
MSI	High

MSI

Microsatellite instability (MSI) status is a measure of the number of somatic mutations with short, repeated sequences of DNA (microsatellites). MSI-High status can indicate that the tumor has a defect in mismatch repair (MMR) abrogating the ability to correct mistakes during DNA replication. Tumors with MSI-high status may increase the number of neoantigens which is hypothesized to increase T-cell reactivity and potential for response to immune checkpoint inhibitors. Tumor-only microsatellite instability status by NGS (MSI-NGS) is measured by the direct analysis of known microsatellite regions sequenced in the CMI NGS panel.

GENOMIC LOSS OF HETEROZYGOSITY	
Test	**Result**
Genomic Loss of Heterozygosity (LOH)	Low - 2% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

LOH

To calculate genomic loss-of-heterozygosity (LOH), the 22 autosomal chromosomes are split into 552 segments and the LOH of single nucleotide polymorphisms (SNPs) within each segment is calculated. Caris WES data consist of approximately 250k SNPs spread across the genome. SNP alleles with frequencies skewed towards 0 or 100% indicate LOH (heterozygous SNP alleles have a frequency of 50%). The final call of genomic LOH is based on the percentage of all 552 segments with observed LOH.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ARID1A	DNA-Tumor	Pathogenic Variant	p.D1850fs	20	c.5548delG	28	NM_006015.5

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.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ASXL1	DNA-Tumor	Pathogenic Variant	p.G645fs	13	c.1934delG	28	NM_015338.5

Interpretation: A common truncating mutation, p.G645fs, was detected in ASXL1. Pathogenic somatic ASXL1 mutations are frequent in myeloid neoplasms and solid tumors, such as colorectal adenocarcinomas (PMID: 26095772).

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
ATRX	DNA-Tumor	Pathogenic Variant	p.K1802fs	21	c.5406delA	26	NM_000489.4

Interpretation: A pathogenic frameshift mutation was detected in ATRX.

The protein encoded by this gene contains an ATPase/helicase domain, and thus it belongs to the SWI/SNF family of chromatin remodeling proteins. This protein is found to undergo cell cycle-dependent phosphorylation, which regulates its nuclear matrix and chromatin association, and suggests its involvement in the gene regulation at interphase and chromosomal segregation in mitosis. Mutations in this gene are associated with an X-linked mental retardation (XLMR) syndrome most often accompanied by alpha-thalassemia (ATRX) syndrome. These mutations have been shown to cause diverse changes in the pattern of DNA methylation, which may provide a link between chromatin remodeling, DNA methylation, and gene expression in developmental processes. In cancer, ATRX mutation is the most prevalent in central nervous system malignacies.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
AXIN1	DNA-Tumor	Pathogenic Variant	p.W564*	6	c.1691G>A	31	NM_003502.3

Interpretation: A pathogenic variant was detected in AXIN1.

This gene encodes a cytoplasmic protein which contains a regulation of G-protein signaling (RGS) domain and a dishevelled and axin (DIX) domain. The encoded protein interacts with adenomatosis polyposis coli (APC), catenin beta-1 (CTNNB1), glycogen synthase kinase 3 beta(GSK3B), protein phosphate 2, and itself. This protein functions as a negative regulator of the wingless-type MMTV integration site family, member 1 (WNT) signaling pathway and can induce apoptosis. The crystal structure of a portion of this protein, alone and in a complex with other proteins, has been resolved. Mutations in this gene have been associated with hepatocellular carcinoma, hepatoblastomas, ovarian endometriod adenocarcinomas, and medullablastomas.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
AXIN2	DNA-Tumor	Pathogenic Variant	p.R671fs	8	c.2011delC	33	NM_004655.3

Interpretation: A pathogenic frameshift mutation was detected in AXIN2

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
BLM	DNA-Tumor	Pathogenic Variant	p.D757fs	10	c.2268delA	29	NM_000057.3

Interpretation: A pathogenic mutation was detected in BLM.

The Bloom syndrome gene product is related to the RecQ subset of DExH box-containing DNA helicases and has both DNA-stimulated ATPase and ATP-dependent DNA helicase activities. Participates in DNA replication and repair. Exhibits a magnesium-dependent ATP-dependent DNA-helicase activity that unwinds single- and double-stranded DNA in a 3'-5' direction. Involved in 5'-end resection of DNA during double-strand break (DSB) repair. Mutations causing Bloom syndrome delete or alter helicase motifs and may disable the 3'-5' helicase activity. The normal protein may act to suppress inappropriate recombination.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
BRAF	DNA-Tumor	Pathogenic Variant	p.V600E	15	c.1799T>A	32	NM_004333.5

Interpretation: The oncogenic p.V600E mutation was detected in BRAF.

BRAF encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway initiated by EGFR activation, which affects cell division, differentiation, and secretion. BRAF somatic mutations have been found in melanoma (43%), thyroid (39%), biliary tree (14%), colon (12%), and ovarian tumors (12%). BRAF inherited mutations are associated with Noonan/Cardio-Facio-Cutaneous (CFC) syndrome, syndromes associated with short stature, distinct facial features, and potential heart/skeletal abnormalities.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CASP8	DNA-Tumor	Pathogenic Variant	p.R449*	9	c.1345C>T	23	NM_001228.4

Interpretation: A pathogenic variant was detected in CASP8.

This gene encodes a member of the cysteine-aspartic acid protease (caspase) family. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspases exist as inactive proenzymes composed of a prodomain, a large protease subunit, and a small protease subunit. Activation of caspases requires proteolytic processing at conserved internal aspartic residues to generate a heterodimeric enzyme consisting of the large and small subunits. This protein is involved in the programmed cell death induced by Fas and various apoptotic stimuli. The N-terminal FADD-like death effector domain of this protein suggests that it may interact with Fas-interacting protein FADD. Many alternatively spliced transcript variants encoding different isoforms have been described, although not all variants have had their full-length sequences determined.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CDC73	DNA-Tumor	Pathogenic Variant	c.370+2T>C	4	c.370+2T>C	32	NM_024529.4

Interpretation: A pathogenic variant that is predicted to disrupt splicing of the transcript was found. Such mutations typically lead to abnormal splicing and loss of protein function.

This gene encodes a tumor suppressor that is involved in transcriptional and post-transcriptional control pathways. The protein is a component of the the PAF protein complex, which associates with the RNA polymerase II subunit POLR2A and with a histone methyltransferase complex. This protein appears to facilitate the association of 3' mRNA processing factors with actively-transcribed chromatin. Mutations in this gene have been linked to hyperparathyroidism-jaw tumor syndrome, familial isolated hyperparathyroidism, and parathyroid carcinoma.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CHEK2	DNA-Tumor	Pathogenic Variant	p.F292fs	8	c.876delT	33	NM_007194.3

Interpretation: A pathogenic frameshift mutation was detected.

The CHEK2 gene encodes a protein Chek2 (Checkpoint kinase 2) that is involved in the initiation of cell cycle arrest and DNA repair following the detection of DNA damage, in particular, double strand breaks. Chek2 stabilizes p53, leading to cell cycle arrest in G1, and activates BRCA1, facilitating DNA repair. Mutations or deletions in CHEK2 have been associated with colon, prostate, breast, pancreas and ovarian cancers.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CREBBP	DNA-Tumor	Pathogenic Variant	p.S976fs	15	c.2925delC	29	NM_004380.2

Interpretation: A pathogenic frameshift mutation was detected in CREBBP.

CREBBP encodes a protein involved in the transcriptional co-activation of many different transcription factors. This gene is known to play critical roles in embryonic development, growth control, and homeostasis. The protein encoded by this gene has intrinsic histone acetyltransferase activity and also acts as a scaffold to stabilize additional protein interactions with the transcription complex. Mutations in this gene cause Rubinstein-Taybi syndrome (RTS). Chromosomal translocations involving this gene have been associated with acute myeloid leukemia.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EP300	DNA-Tumor	Pathogenic Variant	p.T1851fs	31	c.5550delC	28	NM_001429.3

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

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.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EP300	DNA-Tumor	Pathogenic Variant	p.C1177*	19	c.3531C>A	32	NM_001429.3

Interpretation: A pathogenic mutation was detected in EP300

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EPHA2	DNA-Tumor	Pathogenic Variant	p.C290fs	4	c.867dupC	32	NM_004431.4

Interpretation: A pathogenic frameshift variant was detected in EPHA2.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EPHA2	DNA-Tumor	Likely Pathogenic Variant	p.P460fs	6	c.1379delC	30	NM_004431.4

Interpretation: A likely pathogenic frameshift mutation was found in EPHA2. Loss of EPHA2 has been shown to promote cell proliferation by activating ERK MAP kinase signaling and hedgehog signaling pathways (PMID 26542681). EPHA2 has been reported to be both tumor-promoting and tumor-inhibiting (PMID 20179713) therefore this frameshift mutation is likely to be pathogenic. This mutation deletes a nucleotide in a mononucleotide repeat tract and frequently occurs in tumors with microsatellite instability.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FANCE	DNA-Tumor	Pathogenic Variant	p.V311fs	4	c.928_929dupCC	27	NM_021922.2

Interpretation: A pathogenic frameshift mutation was detected in FANCE.

Family member of the fanconi anemia complementation group (FANC).This gene encodes the protein for complementation group E. As part of the Fanconi anemia (FA) complex, functions in DNA cross-links repair. Required for the nuclear accumulation of FANCC and provides a critical bridge between the FA complex and FANCD2. Deficiencies in this family may lead to hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FAT1	DNA-Tumor	Pathogenic Variant	p.S1011fs	2	c.3031delT	45	NM_005245.3

Interpretation: A pathogenic frameshift variant was detected in FAT1.

FAT1 is a gene that encodes for the Protocadherin FAT1 protein, which has been nextGenDescribed as both a tumor suppressor or oncogene in different contexts. FAT1 is a single pass transmembrane protein with an extracellular portion consisting of cadherin repeats. Loss of heterozygosity for FAT1 has been reported in primary oral carcinomas and astrocytic tumors. FAT1 has also been reported to be overexpressed in different cancers including breast cancer, melanoma, and leukemia.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FAT1	DNA-Tumor	Variant of Uncertain Significance	p.S2660N	10	c.7979G>A	43	NM_005245.3

Interpretation: A variant with no known clinical or functional significance was detected in FAT1.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FAT1	DNA-Tumor	Pathogenic Variant	p.G3953fs	22	c.11856dupT	40	NM_005245.3

Interpretation: A loss of function pathogenic frameshift mutation was found in FAT1.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FAT1	DNA-Tumor	Variant of Uncertain Significance	p.P4007T	22	c.12019C>A	8	NM_005245.3

Interpretation: A variant with no known clinical or functional significance was detected in FAT1.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
FBXW7	DNA-Tumor	Pathogenic Variant	p.R465C	9	c.1393C>T	32	NM_033632.3

Interpretation: A pathogenic mutation, p.R465C, was detected in FBXW7. Substitutions at codon 465 are frequent in cancers.

FBXW7 or E3 ligase F-box and WD repeat domain containing 7, also known as Cdc4, encodes three protein isoforms which constitute a component of the ubiquitin-proteasome complex. Mutation of FBXW7 occurs in hotspots and disrupts the recognition of and binding with substrates which inhibits the proper targeting of proteins for degradation (e.g. Cyclin E, c-Myc, SREBP1, c-Jun, Notch-1, mTOR and MCL1). Mutation frequencies identified in cholangiocarcinomas, acute T-lymphoblastic leukemia/lymphoma, and carcinomas of endometrium, colon and stomach are 35%, 31%, 9%, 9%, and 6%, respectively. Targeting an oncoprotein downstream of FBXW7, such as mTOR or c-Myc, may provide a novel therapeutic strategy.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KDM5C	DNA-Tumor	Likely Pathogenic Variant	p.P1508fs	26	c.4523delC	24	NM_004187.3

Interpretation: A likely pathogenic frameshift mutation was detected in KDM5C last exon. This mutation has been reported in the somatic mutation cancer database.

This gene is a member of the SMCY homolog family and encodes a protein with one ARID domain, one JmjC domain, one JmjN domain and two PHD-type zinc fingers. The DNA-binding motifs suggest this protein is involved in the regulation of transcription and chromatin remodeling. Mutations in this gene have been associated with X-linked mental retardation.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2C	DNA-Tumor	Variant of Uncertain Significance	c.1185-3delT	9	c.1185-3delT	31	NM_170606.2

Interpretation: An intronic variant with no known clinical or functional significance was detected in KMT2C.

This gene is a member of the myeloid/lymphoid or mixed-lineage leukemia (MLL) family and encodes a nuclear protein with an AT hook DNA-binding domain, a DHHC-type zinc finger, six PHD-type zinc fingers, a SET domain, a post-SET domain and a RING-type zinc finger. This protein is a member of the ASC-2/NCOA6 complex (ASCOM), which possesses histone methylation activity and is involved in transcriptional coactivation.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2C	DNA-Tumor	Pathogenic Variant	p.K4351fs	52	c.13053delA	32	NM_170606.2

Interpretation: A pathogenic frameshift mutation was detected in KMT2C.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2D	DNA-Tumor	Pathogenic Variant	p.G2712*	32	c.8134G>T	32	NM_003482.3

Interpretation: A pathogenic mutation was detected in KMT2D.

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.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KMT2D	DNA-Tumor	Variant of Uncertain Significance	p.S5341P	50	c.16021T>C	33	NM_003482.3

Interpretation: A variant with no known clinical or functional significance was detected in KMT2D.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
MET	DNA-Tumor	Variant of Uncertain Significance	p.V1377I	21	c.4129G>A	49	NM_001127500.2

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

C-Met is a proto-oncogene that encodes the tyrosine kinase receptor of hepatocyte growth factor (HGF) or scatter factor (SF). c-Met mutation causes aberrant MET signaling in various cancer types including renal papillary, hepatocellular, head and neck squamous, gastric carcinomas and non-small cell lung cancer. Mutations in the juxtamembrane domain (exon 14, 15) results in the constitutive activation and show enhanced tumorigenicity. Germline mutations in c-MET have been associated with hereditary papillary renal cell carcinoma.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
MET	DNA-Tumor	Variant of Uncertain Significance	p.A1225V	18	c.3674C>T	33	NM_001127500.2

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
MSH3	DNA-Tumor	Pathogenic Variant	p.K383fs	7	c.1148delA	66	NM_002439.4

Interpretation: A pathogenic frameshift mutation was detected in MSH3.

The protein encoded by this gene forms a heterodimer with MSH2 to form MutS beta, which is part of the post-replicative DNA mismatch repair system. MutS beta initiates mismatch repair by binding to a mismatch and subsequently forming a complex with the MutL alpha heterodimer. As a result, the function of these complexes ensures the stability of the genome and to promote tumor suppression by repairing somatic mutations. Defects in this gene are a cause of susceptibility to endometrial cancer.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
MSH6	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3260 _3261dupCC	10	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
MSH6	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3261dupC	5	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).

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PIK3CA	DNA-Tumor	Pathogenic Variant	p.R93Q	2	c.278G>A	33	NM_006218.3

Interpretation: This PIK3CA mutation, and other substitutions at the same position in the protein, have been identified in a number of tumors. The incidence of this mutation in cancers indicates it is pathogenic.

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
PIK3R1	DNA-Tumor	Likely Pathogenic Variant	p.G588fs	14	c.1761delA	29	NM_181523.2

Interpretation: This PIK3R1 mutation is presumed to be pathogenic due to similar mutations reported in this region.

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PTCH1	DNA-Tumor	Pathogenic Variant	p.S1203fs	22	c.3606delC	6	NM_000264.4

Interpretation: A pathogenic frameshift mutation was detected in PTCH1. Germline mutations in the PTCH1 gene are causal for Nevoid Basal Cell Carcinoma Syndrome.

PTCH1 is a tumor suppressor in the patched gene family and is the receptor for sonic hedgehog, a secreted molecule implicated in the formation of embryonic structures and in tumorigenesis. The PTCH1 gene product, is a transmembrane protein that suppresses the release of another protein called smoothened, and when sonic hedgehog binds PTCH1, smoothened is released and signals cell proliferation. Mutations in PTCH1 are associated with basal cell carcinoma and medulloblastoma. Germline mutations in PTCH1 cause Gorlin syndrome.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
RET	DNA-Tumor	Variant of Uncertain Significance	p.A217V	4	c.650C>T	30	NM_020975.5

Interpretation: A 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.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
RNF43	DNA-Tumor	Pathogenic Variant	p.P660fs	9	c.1973 _1976dupGGGG	7	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
RNF43	DNA-Tumor	Variant of Uncertain Significance	p.G659dup	9	c.1974 _1976dupGGG	8	NM_017763.5

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

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

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
TP53	DNA-Tumor	Pathogenic Variant	p.S90fs	4	c.267delC	5	NM_000546.5

Interpretation: A pathogenic frameshift mutation was detected in TP53.

TP53, or p53, plays a central role in modulating response to cellular stress through transcriptional regulation of genes involved in cell-cycle arrest, DNA repair, apoptosis, and senescence. Inactivation of the p53 pathway is essential for the formation of the majority of human tumors. Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia, estimated to occur in 30-50% of all cancers. Generally, presence of a disruptive p53 mutation is associated with a poor prognosis in all types of cancers, and diminished sensitivity to radiation and chemotherapy. Germline p53 mutations are associated with the Li-Fraumeni syndrome (LFS) which may lead to early-onset of several forms of cancer currently known to occur in the syndrome, including sarcomas of the bone and soft tissues, carcinomas of the breast and adrenal cortex (hereditary adrenocortical carcinoma), brain tumors and acute leukemias.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
TP53	DNA-Tumor	Likely Pathogenic Variant	p.F113V	4	c.337T>G	23	NM_000546.5

Interpretation: This TP53 mutation, and other substitutions at the same position in the protein, have been identified in a number of tumors. The high incidence of this mutation in cancers suggests it is pathogenic.

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					
ATP6AP2	EED	LYN	PMS1	RASA1	
CDK6	EGLN1	MDH2	POLQ	REST	
CUL3	EXO1	NOTCH2	PREX2	RRAS2	
CYSLTR2	JAK2	NPM1	PRKD1	SOS1	
DACH1	KIF1B	PLCB4	RABL3	SUZ12	

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

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

NGS Methods

Direct sequence analysis was performed on genomic DNA isolated from a micro-dissected tumor sample using Illumina NovaSeq 6000 sequencers. A hybrid pull-down panel of baits was used to enrich more than 700 clinically relevant genes along with > 20,000 other genes. Sequence data is analyzed using a customized bioinformatics pipeline to detect sequencing variants, copy number alterations (amplifications and deletions) indels and HLA genotypes. In addition, genomic signatures for tumor mutational burden (TMB), microsatellite instability (MSI), genomic loss-of-heterozygosity (LOH) or HRD-Genomic Scar Score (HRD-GSS), and homologous recombination deficiency (HRD) are reported when applicable. For a complete list of what is covered by the assay, and genes with partial coverage, please contact Caris Customer Support.

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Copy Number Alterations by Next-Generation Sequencing (NGS)

GENES TESTED WITH INTERMEDIATE CNA RESULTS					
AKT2	AXL	CCNE1	RAC1		

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. A complete list of genes for reporting copy number alterations, including amplifications and deletions, is available upon request.

Caris FOLFIRSTai™ by Next-Generation Sequencing (NGS)

CARIS | FOLFIRSTai

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

Methods

The Caris FOLFIRSTai™ 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 Whole Exome 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) 412 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 17.5 months (71%) longer than the median predicted DB with a hazard ratio 0.466 (95% CI: 0.325-0.670, $p < 0.001$). 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. Abraham et al., "Clinical validation of a machine-learning derived signature predictive of outcomes from first-line oxaliplatin-based chemotherapy in patients with advanced colorectal cancer". (December 8, 2020), Clinical Cancer Res., 10.1158/1078-0432.CCR-20-3286.

Gene Fusion and Transcript Variant Detection by RNA Sequencing

Whole Transcriptome Sequencing (WTS) Methods

Gene fusion and variant transcript detection were performed on RNA isolated from a tumor sample using next generation sequencing. The assay also detects fusions occurring at known and novel breakpoints within genes. The genes included in this report represent the subset of genes associated with cancer. The complete list of unclassified alterations is available by request.

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References

#	Drug	Biomarker	Reference
1	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	Kopetz, S., J. Tabernero, et al., (2025). "BREAKWATER: Analysis of first-line encorafenib + cetuximab + chemotherapy in BRAF V600E-mutant metastatic colorectal cancer." J Clin Oncol 43:4 (suppl; abstract 16). View Citation Online
2	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	Kopetz, S., J. Taberno, et al. (2019). "Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer." N Engl J Med doi: 10.1056/NEJMoa1908075. View Citation Online
3	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	Kopetz, S., J. Taberno, et al. (2020). "Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC)." J Clin Oncol 38: suppl 4; abstr 8. View Citation Online
4	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer Version 2.2020
5	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer Version 2.2024 View Citation Online
6	encorafenib + cetuximab, encorafenib + cetuximab + mFOLFOX6, encorafenib + panitumumab, encorafenib + panitumumab + FOLFOX	BRAF	Van Cutsem, E., J. Tabernero, et al. (2019) "Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study", J Clin Oncol. JCO1802459. doi: 10.1200
7	vemurafenib/dabrafenib monotherapy	BRAF	Kopetz, S., L. Saltz, et al. (2015). "Phase II Pilot Study of Vemurafenib in Patients with Metastatic BRAF-Mutated Colorectal Cancer." J Clin Oncol 33:1-7. View Citation Online
8	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	MSI	Andre, T., N. Starling, et al. (2021). "Safety and efficacy of anti-PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Result from GARNET study." J Clin Oncol 39 (suppl 3; abstr 9). View Citation Online
9	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	MSI	Le, D.T., L.A. Diaz, et al. (2015). "PD-1 blockade in tumors with mismatch-repair deficiency". N Engl J Med. 372:2509-2520. View Citation Online
10	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	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
11	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	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
12	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	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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References

#	Drug	Biomarker	Reference
13	pembrolizumab	TMB	Marabelle, A., Y.J. Bang, et al., (2019). "Association of Tumor Mutational Burden with Outcomes in Patients with Select Advanced Solid Tumors Treated with Pembrolizumab in KEYNOTE-158." AnnOncol 30(suppl_5): v475-v532 View Citation Online

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