

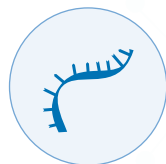
Comprehensive Tumor Profiling

Caris Life Sciences' comprehensive molecular profiling approach to assess DNA, RNA and proteins reveals a molecular blueprint to help guide more precise and individualized treatment decisions.



DNA

Whole Exome Sequencing
SNVs, Indels, CNAs, Karyotyping, Viruses



RNA

Whole Transcriptome Sequencing
Gene Fusions and Variant Transcripts



Protein

Immunohistochemistry
Tumor-Relevant Protein Biomarkers

Technical Specifications

Sufficient tumor content ($\geq 20\%$ tumor nuclei) must be present to complete all analyses.

Technical Information	IHC	CISH
Sample Requirements <i>(see requisition for full details)</i>	1 unstained slide at 4 μ m thickness from FFPE block, with evaluable tumor present, per IHC test	1 unstained slide at 4 μ m thickness from FFPE block, with at least 100 evaluable tumor cells present, per CISH test
Sensitivity/Specificity	>95%	>95%

Technical Information	NGS (Whole Exome – DNA)	NGS (Whole Transcriptome – RNA)
Sample Requirements	$\geq 20\%$ tumor nuclei. Accepted specimen types: FFPE block, unstained slides, core needle biopsy, fine needle aspirate, malignant fluid cell block, bone/bone metastasis. See <i>Tumor Profiling Requisition</i> for complete details.	
Tumor Enrichment (when necessary)	Microdissection to isolate and increase the number of cancer cells to improve test performance and increase the chance for successful testing from small tumor samples	
Number of Genes	23,000+ genes	23,000+ genes
Average Depth of Coverage (DNA) Average Read Count (RNA)	1,500x for clinical genes	17 million reads
Positive Percent Agreement (PPA)	>97% for base substitutions at $\geq 5\%$ mutant allele frequency; >97% for indels at $\geq 5\%$ mutant allele frequency; >95% for copy number alterations (amplifications ≥ 6 copies)	>96%
Negative Percent Agreement (NPA)	>99%	>99%
Alterations	SNVs, Indels, CNAs, Karyotyping, Viruses	Fusions and Variant Transcripts
Viruses	HPV 16 & 18 (Head & Neck, Anal, Genital, CUP) EBV (Head & Neck, Esophagogastric Junction, Gastric Adenocarcinoma, CUP. If positive result in cancer type not listed here, EBER ISH reflex to confirm EBV result) MCPyV (Merkel Cell, Neuroendocrine – Poorly Differentiated (High-Grade)/Large or Small Cell Carcinoma, CUP)	
Genomic Signatures/Other	Genomic Loss of Heterozygosity (gLOH) Homologous Recombination Deficiency (HRD) Microsatellite Instability (MSI) Tumor Mutational Burden (TMB) Human Leukocyte Antigen (HLA) Genotype Caris FOLFIRSTai™ Caris GPSai™	

Caris Molecular Profiling Associations List

The list below details the biomarkers assessed, technology platforms utilized and associated therapies or clinical trials. **Biomarkers and therapy associations may vary by the tumor type submitted.** *Individual assay results are always included with the final report.*

Biomarker	Technology/Alteration	Agent
ALK	IHC, RNA Fusion	crizotinib, ceritinib, alectinib, brigatinib (NSCLC only), lorlatinib (NSCLC only)
	DNA Mutation	resistance to crizotinib, alectinib
AR	IHC	bicalutamide, leuprolide (salivary gland tumors only)
BRAF	DNA Mutation	vemurafenib, dabrafenib, cobimetinib, trametinib
		encorafenib + binimetinib (melanoma only)
		dabrafenib+trametinib
		atezolizumab + cobimetinib + vemurafenib (melanoma only)
		cetuximab + encorafenib (CRC only)
BRCA1/2	DNA Mutation, DNA Deletion	carboplatin, cisplatin, oxaliplatin
		niraparib (ovarian), olaparib (breast, cholangiocarcinoma, ovarian, pancreatic, prostate), rucaparib (ovarian, pancreatic, prostate), talazoparib (breast only), veliparib combination (pancreatic only), niraparib + abiraterone (prostate), olaparib + abiraterone (prostate), talazoparib + enzalutamide (prostate)
		resistance to olaparib, niraparib, rucaparib with reversion mutation
CLDN18	IHC	zolbetuximab (gastric/GEJ only)
COL1A1-PDGFB	RNA Fusion	imatinib (DFSP only)
EGFR	DNA Mutation	afatinib (NSCLC and CUP only)
		afatinib + cetuximab (T790M; NSCLC only)
		amivantamab, mobocertinib (Exon 20 insertion; NSCLC only)
		erlotinib, gefitinib (NSCLC and CUP only)
		osimertinib, dacomitinib (NSCLC and CUP only)
ER	IHC	endocrine therapies
		everolimus (breast only)
		palbociclib, ribociclib, abemaciclib (breast only)
ERBB2 (HER2)	IHC, CISH, CNA	trastuzumab, lapatinib, neratinib (breast only), pertuzumab, T-DM1, fam-trastuzumab deruxtecan-nxki, tucatinib, margetuximab
	DNA Mutation	fam-trastuzumab deruxtecan-nxki, T-DM1 (NSCLC only)
ER/PR/ERBB2 (HER2)	IHC, CISH	sacituzumab govitecan
ESR1	DNA Mutation	elacestrant
FGFR2/3	DNA Mutation, RNA Fusion	erdafitinib (urothelial bladder only), pemigatinib, infigratinib (biliary tract cancers only), futibatinib (intrahepatic cholangiocarcinoma only)
FOLR1	IHC	mirvetuximab soravtansine (epithelial ovarian only)
gLOH (Genomic)	DNA Mutation	rucaparib (ovarian only)
HLA Genotype	DNA Mutation	tebentafusp (uveal melanoma)
HRD	DNA Mutation	niraparib, olaparib, rucaparib (epithelial ovarian only)
HRR	DNA Mutation, DNA Deletion	olaparib, talazoparib + enzalutamide (prostate only)
IDH1	DNA Mutation	temozolomide (glioma only)
		ivosidenib (biliary tract cancers only)
KIT	DNA Mutation	imatinib
		regorafenib, ripretinib, sunitinib (GIST only)
KRAS	DNA Mutation	resistance to cetuximab, panitumumab (CRC only)
		resistance to erlotinib/gefitinib (NSCLC only)
		sotorasib, adagrasib (G12C-mutated, NSCLC and pancreatic only)
		binimetinib, trametinib (low grade serous ovarian cancer only)
MEK1/2	DNA Mutation	resistance to BRAF and MEK inhibitor monotherapy
MET	RNA Exon Skipping, DNA Exon Skipping, CNA	capmatinib, crizotinib, tepotinib (all NSCLC only)
MGMT	Pyrosequencing (Methylation)	temozolomide (glioma only)
MMR Deficiency		pembrolizumab, dostarlimab (pan-tumors)
MSI	IHC, DNA Mutation	pembrolizumab, nivolumab (CRC, small bowel adenocarcinoma), nivolumab+ipilimumab (CRC, small bowel adenocarcinoma)
MMR Proficiency		
MSS	IHC, DNA Mutation	pembrolizumab + levatinib (endometrial only)
NF1	DNA Mutation	selumetinib (neurofibroma only)
NRAS	DNA Mutation	resistance to cetuximab, panitumumab (CRC only)
NTRK1/2/3	RNA Fusion	entrectinib, larotrectinib
	DNA Mutation	resistance to larotrectinib, entrectinib
PALB2	DNA Mutation	olaparib (pancreatic and prostate), veliparib combination (pancreatic only)
PDGFRA	DNA Mutation	imatinib, avapritinib (GIST only), sunitinib
PD-L1	IHC	pembrolizumab (22c3 TPS in NSCLC; 22c3 CPS in cervical, esophageal, head & neck, urothelial and non-urothelial bladder, vulvar)
		atezolizumab (SP142 IC & TC, SP263 TC NSCLC)
		pembrolizumab + chemotherapy (22c3 CPS in TNBC only)
		nivolumab/ipilimumab combination (28-8 NSCLC only)
		nivolumab (22c3 gastric/GEJ only)
		cemiplimab (22c3 TPS, SP263 CPS NSCLC only)
PIK3CA	DNA Mutation	alpelisib + fulvestrant (breast only)
POLE	DNA Mutation	pembrolizumab (endometrial, CRC, small bowel adenocarcinoma only)
PR	IHC	endocrine therapies
RET	RNA Fusion	cabozantinib, vandetanib, selpercatinib, pralsetinib (NSCLC only)
	DNA Mutation	vandetanib, cabozantinib, selpercatinib (thyroid only); resistance to vandetanib, cabozantinib
ROS1	IHC, RNA Fusion	crizotinib, ceritinib, entrectinib, lorlatinib (NSCLC only)
TMB	DNA Mutation	pembrolizumab
VHL	DNA Mutation	belzutifan (renal cell carcinoma, CNS hemangioblastomas, pancreatic neuroendocrine tumors)

IHC: Immunohistochemistry CISH: Chromogenic in situ Hybridization CNA: Copy Number Alteration (DNA) HRD: Homologous Recombination Deficiency
HRR (Homologous Recombination Repair) genes: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, MLH1, MRE11, FANCA, NBN
 Note: in certain instances, some biomarkers included in MI Profile or genes ordered individually will not associate with commercially available cancer therapies or clinical trials.

Tumor Profiling Menu

The information below details the biomarkers analyzed by technology for the tumor type submitted. Before ordering testing services, please refer to the profile menu online (www.CarisLifeSciences.com/profiling-menu) to view the most up-to-date listing of biomarkers that will be performed. Tests may vary if insufficient tumor samples are submitted.

	WES	WTS	IHC/Other	AI Signatures
MI Profile™ Comprehensive Testing MI Tumor Seek Hybrid™ + IHCs and Other Tests by Tumor Type: Tissue-based WES and WTS analysis, plus additional tumor-type relevant biomarker testing (see below). Caris FOLFIRSTai™ reported for mCRC cases.	✓	✓	✓	✓
Next-Generation Sequencing Only MI Tumor Seek Hybrid™: Tissue-based WES and WTS analysis. Caris FOLFIRSTai™ reported for mCRC cases.	✓	✓	–	✓

AI-Powered Molecular Signatures

Caris GPSai™

Cancer type similarity assessment that is intended to help identify the tumor of origin by comparing the molecular characteristics of the patient's tumor against other tumors in the Caris database.

Caris FOLFIRSTai™

Chemotherapy response predictor that is intended to gauge a mCRC patient's likelihood of benefit from first-line FOLFOX+BV followed by FOLFIRI+BV, versus FOLFIRI+BV followed by FOLFOX+BV treatment.

Other Testing by Tumor Type

Tumor Type	Immunohistochemistry (IHC)	Other
Bladder	Her2/Neu, MMR, PD-L1 (22c3)	
Breast	AR, ER, Her2/Neu, PD-L1 (22c3), PR, PTEN	
Cancer of Unknown Primary – Female	AR, ER, Her2/Neu, MMR, PD-L1 (SP142)	
Cancer of Unknown Primary – Male	AR, Her2/Neu, MMR, PD-L1 (SP142)	
Cervical	ER, Her2/Neu, MMR, PD-L1 (22c3), PR	
Cholangiocarcinoma/Hepatobiliary	Her2/Neu, MMR, PD-L1 (SP142)	
Colorectal and Small Intestinal	Her2/Neu, MMR, PD-L1 (SP142), PTEN	
Endometrial (all except uterine sarcoma)	ER, Her2/Neu, MMR, PD-L1 (SP142), PR, PTEN	
Esophageal Cancer	Her2/Neu, MMR, PD-L1 (22c3)	
Gastric/GEJ	CLDN18, Her2/Neu, MMR, PD-L1 (22c3)	EBER (Chromogenic <i>in situ</i> Hybridization)
GIST	MMR, PD-L1 (SP142), PTEN	
Glioma	–	MGMT Methylation (Pyrosequencing)
Head & Neck	MMR, p16, PD-L1 (22c3)	EBER, HPV (Chromogenic <i>in situ</i> Hybridization), HPV reflex to confirm p16 result
Kidney	MMR, PD-L1 (SP142)	

Tumor Type	Immunohistochemistry (IHC)	Other
Melanoma	MMR, PD-L1 (SP142)	
Merkel Cell	MMR, PD-L1 (SP142)	
Neuroendocrine	MMR, PD-L1 (SP142)	
Non-Small Cell Lung	ALK [†] , PD-L1 (22c3, 28-8, SP142, SP263), PTEN	
Ovarian	ER, FOLR1 [‡] , Her2/Neu [‡] , MMR, PD-L1 (22c3), PR	
Pancreatic	MMR, PD-L1 (SP142)	
Prostate	AR, MMR, PD-L1 (SP142)	
Salivary Gland	AR, Her2/Neu, MMR, PD-L1 (SP142)	
Sarcoma	MMR, PD-L1 (SP142)	
Small Cell Lung	PD-L1 (22c3)	
Thyroid	MMR, PD-L1 (SP142)	
Uterine Sarcoma	ER, MMR, PD-L1 (SP142), PR, PTEN	
Vulvar Cancer (SCC)	MMR, PD-L1 (22c3)	
Other Tumors	MMR, PD-L1 (SP142)	

MMR = Mismatch Repair proteins: MLH1, MSH2, MSH6, PMS2

[†]ALK IHC only performed for NSCLC adenocarcinoma

[‡]FOLR1 IHC, Her2/Neu IHC and HRD Status only performed for epithelial ovarian cancer.

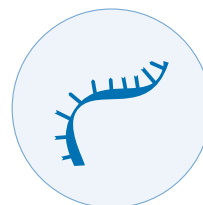
Caris Molecular Testing – Complete Gene Coverage

As the pioneer in precision medicine, Caris was the first to provide WES and WTS for every patient. All molecular profiling orders include next-generation sequencing of 23,000+ genes.



Whole Exome Sequencing (WES) DNA

- 23,000+ genes
- 1,500x for clinical genes
- SNVs, Indels, CNAs & Karyotyping
- Viruses
- Genomic signatures:
 - Genomic Loss of Heterozygosity (gLOH)
 - Homologous Recombination Deficiency (HRD)
 - Microsatellite Instability (MSI)
 - Tumor Mutational Burden (TMB)
- Other:
 - HLA Genotype



Whole Transcriptome Sequencing (WTS) RNA

- 23,000+ genes
- 17 million read count
- Gene fusions and variant transcripts
- Novel translocation detection independent of intronic breakpoint

Gene List

Listed below are the genes most commonly associated with cancer. Full gene search is available on CarisLifeSciences.com.

ABL1	BCR	CSF1R	FANCC	GNAQ	LZTR1	MUTYH	PIK3CB	RAD51D	SOCS1
ABL	BLM	CTNNA1	FANCD2	GNAS	MAML2	MYB	PIK3R1	RAD54L	SPEN
ACVR1	BMPR1A	CTNNB1	FANCE	H3F3A	MAP2K1	MYC	PIK3R2	RAF1	SPOP
AIP	BRAF	CXCR4	FANCF	H3F3B	MAP2K2	MYCN	PIM1	RASA1	SRC
AKT1	BRCA1	CYLD	FANCG	HDAC1	MAP2K4	MYD88	PKN1	RB1	SSBP1
AKT2	BRCA2	CYP17A1	FANCI	HIST1H3B	MAP3K1	NBN	PMS1	RELA	STAG2
AKT3	BRD3	DDR2	FANCL	HIST1H3C	MAPK1	NF1	PMS2	RET	STAT3
ALK	BRD4	DICER1	FANCM	HNF1A	MAPK3	NF2	POLD1	RHOA	STK11
AMER1	BRIP1	DNMT3A	FAS	HOXB13	MAST1	NFE2L2	POLD2	RNF43	SUFU
APC	BTK	EGFR	FAT1	HRAS	MAST2	NFKBIA	POLD3	ROS1	TERT
AR	CALR	EGFRV8	FBXW7	IDH1	MAX	NOTCH1	POLD4	RPA1	TET2
ARAF	CARD11	EGLN1	FGFR1	IDH2	MED12	NOTCH2	POLE	RPA2	TFE3
ARHGAP26	CASP8	ELF3	FGFR2	INSR	MEF2B	NPM1	POLQ	RPA3	TFEB
ARHGAP35	CBFB	EP300	FGFR3	IRF4	MEN1	NRAS	POT1	RPA4	THADA
ARID1A	CCND1	EPHA2	FGFR4	JAK1	MET	NRG1	PPARG	RSP02	TMEM127
ARID2	CCND2	ERBB2	FGR	JAK2	MET Exon 14 Skipping	NSD1	PPP2R1A	RSP03	TMPRSS2
AR-V7	CCND3	ERBB3	FH	JAK3	MGA	NTHL1	PPP2R2A	RUNX1	TNFAIP3
ASXL1	CD274	ERBB4	FLCN	KDM5C	MGMT	NTRK1	PRDM1	SDHA	TNFRSF14
ATM	CD79B	ERCC2	FLT1	KDM6A	MIF	NTRK2	PRKACA	SDHAF2	TP53
ATR	CDC73	ERG	FLT3	KDR	MLH1	NTRK3	PRKAR1A	SDHB	TRAF7
ATRX	CDH1	ESR1	FLT4	KEAP1	MLH3	NUMBL	PRKCA	SDHC	TSC1
AXIN1	CDK12	ETV1	FOXA1	KIF1B	MPL	NUTM1	PRKCB	SDHD	TSC2
AXIN2	CDK4	ETV4	FOXL2	KIT	MRE11	PALB2	PTCH1	SETD2	U2AF
AXL	CDK6	ETV5	FUBP1	KLF4	MSH2	PARP1	PTEN	SF3B1	VHL
B2M	CDKN1B	ETV6	FYN	KMT2A	MSH3	PBRM1	PTPN11	SMAD2	WRN
BAP1	CDKN2A	EWSR1	GALNT12	KMT2C	MSH4	PCNA	RABL3	SMAD4	WT1
BARD1	CHEK1	EXO1	GATA3	KMT2D	MSMB	PDGFRA	RAC1	SMARCA4	XPO1
BCL2	CHEK2	EZH2	GLI2	KRAS	MST1R	PDGFRB	RAD50	SMARCB1	XRCC1
BCL9	CIC	FANCA	GNA11	LCK	MTOR	PHOX2B	RAD51B	SMARCE1	XRCC2
BCOR	CREBBP	FANCB	GNA13	LYN	MUSK	PIK3CA	RAD51C	SMO	YES1

Certain assays and features may vary by location. Check website for complete details.

To order or learn more, visit www.CarisLifeSciences.com.
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