

UC San Diego Health

# Oncology Updates: Colorectal Cancer

Gregory Botta MD/PhD

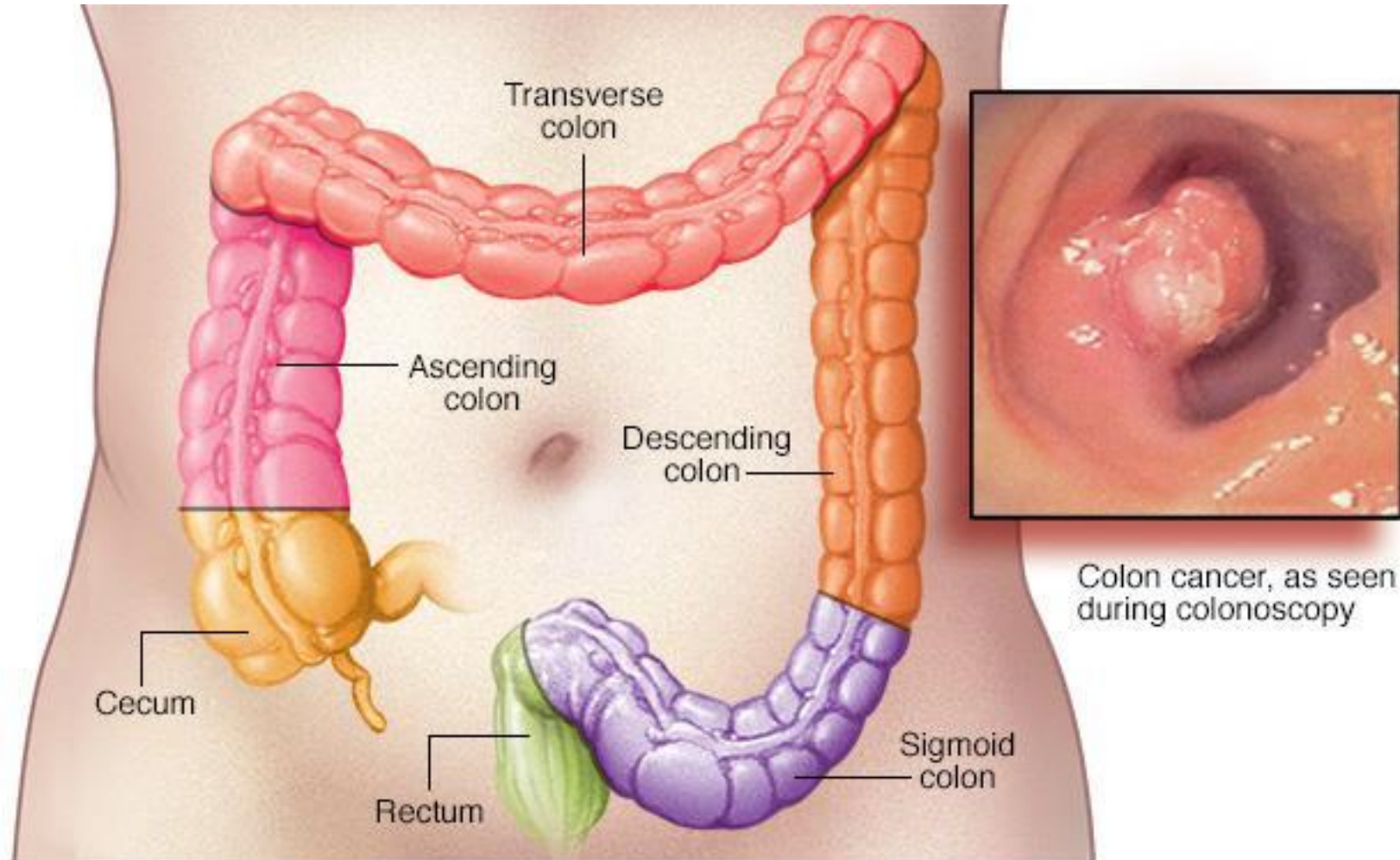
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Gastrointestinal Oncology

3/18/2026

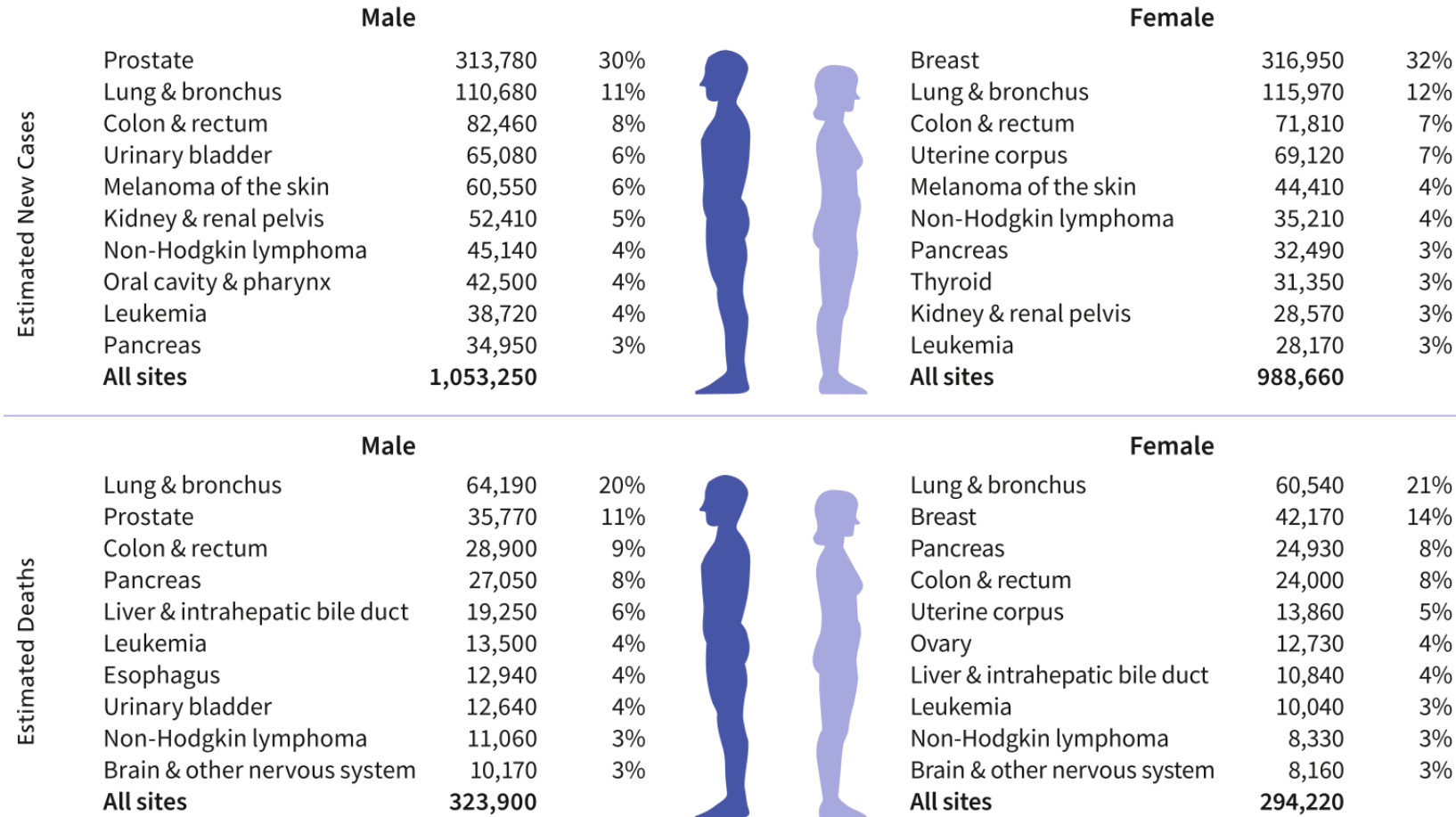


# Anatomy

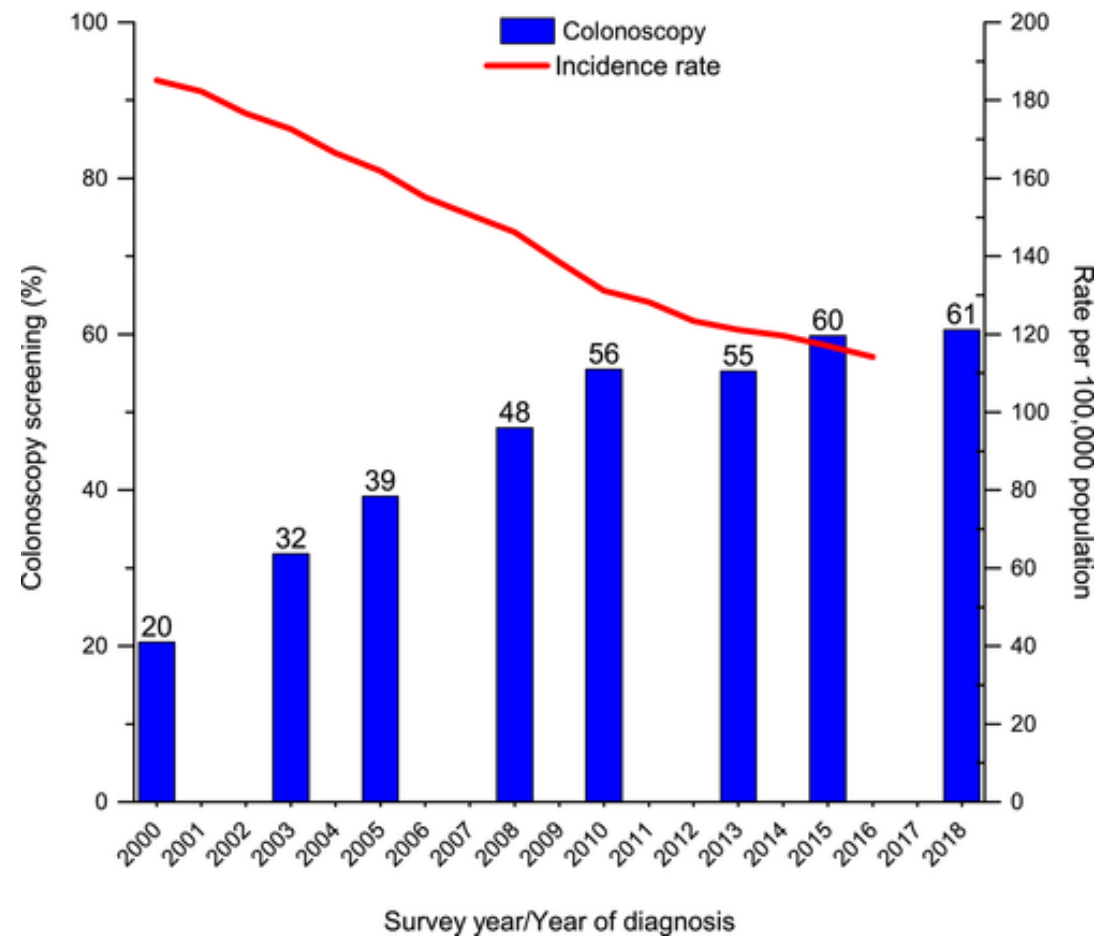
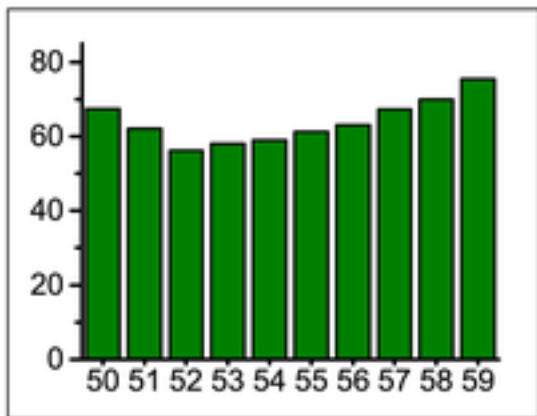
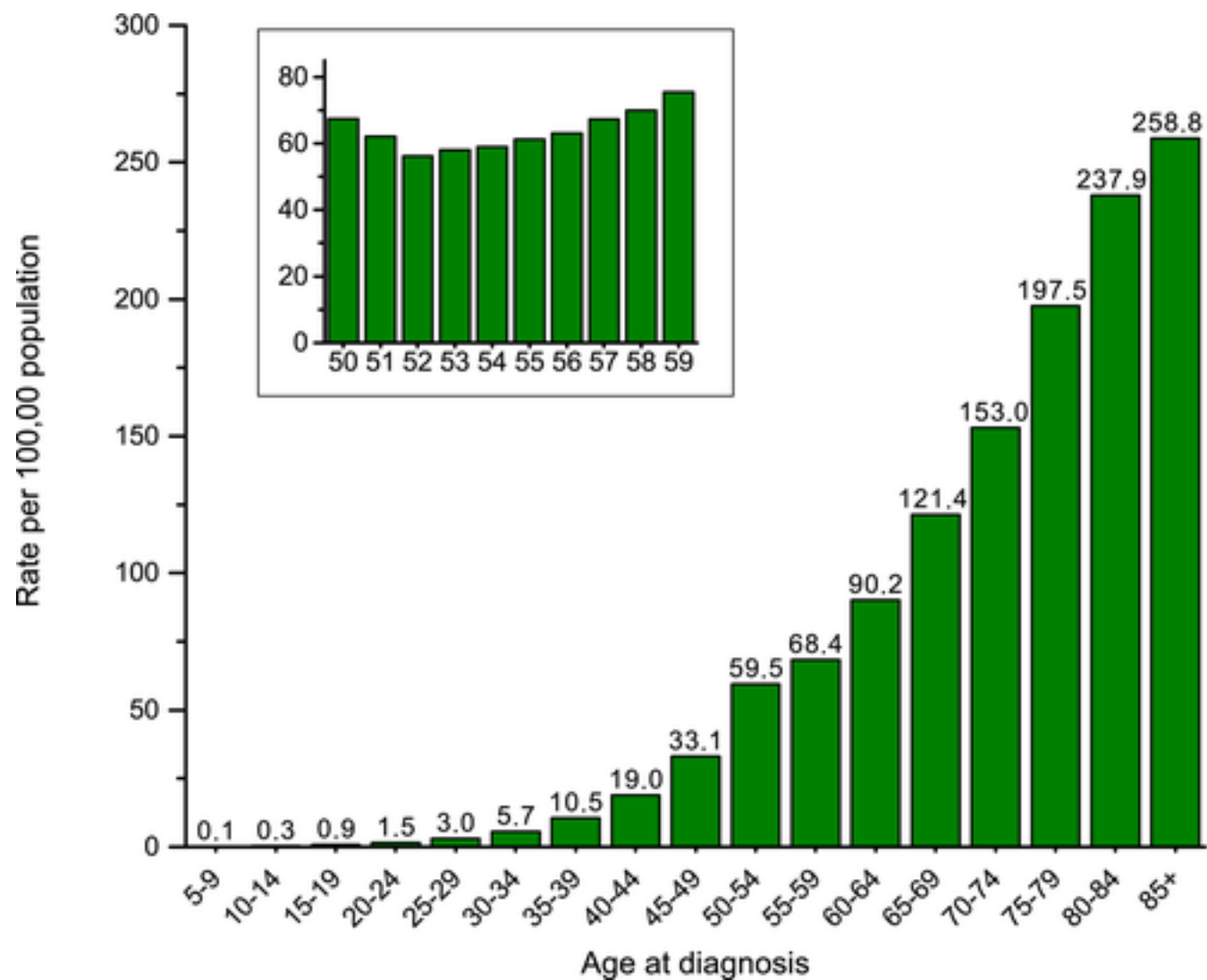


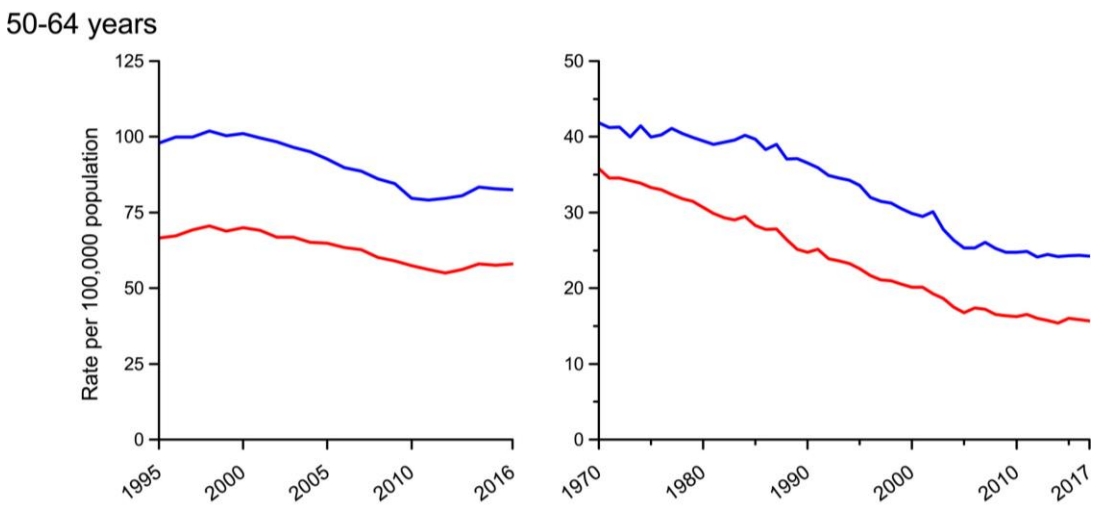
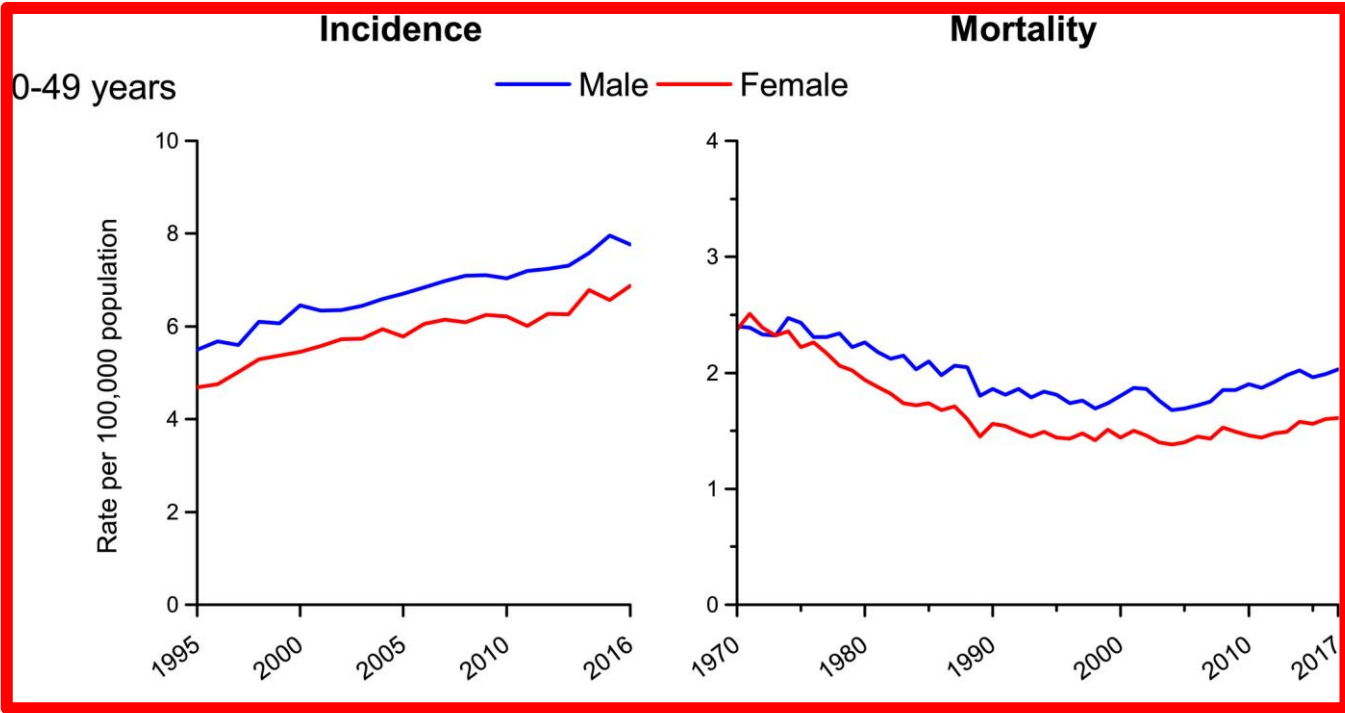
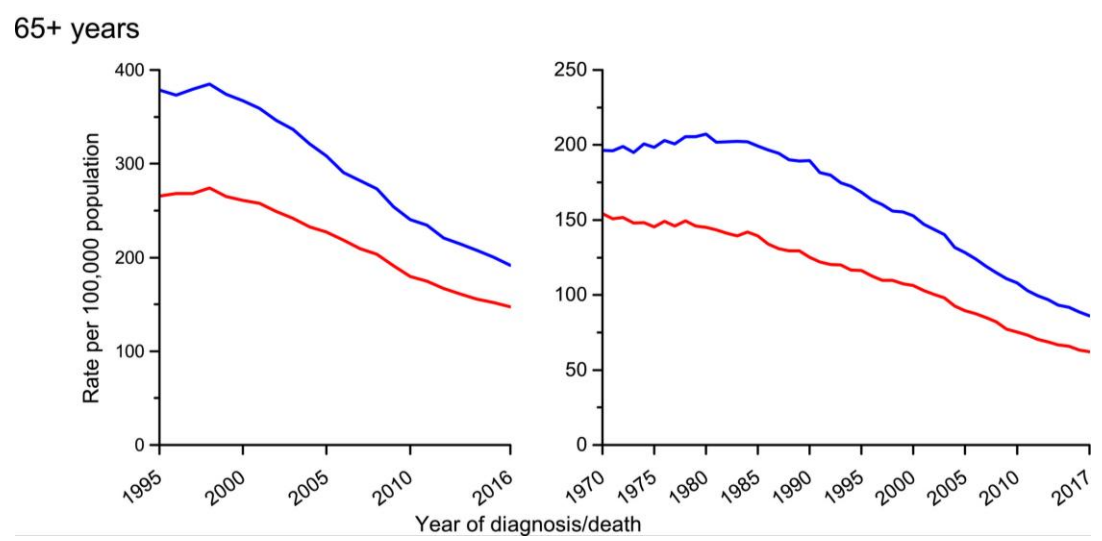
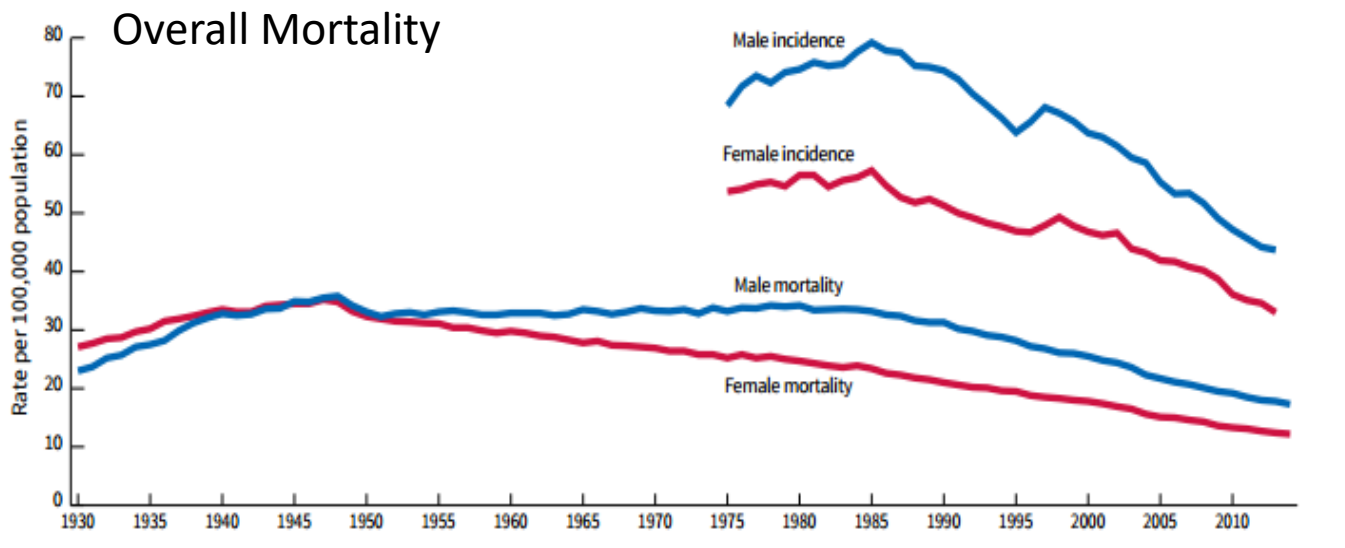
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# Epidemiology - 2025



**FIGURE 1** Leading sites of estimated new cancer cases and deaths by sex, United States, 2025. Estimates exclude US territories and are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.





# Early Onset CRC

## Excess Body Weight

Abdominal obesity and increased body fat results in chronic inflammation which can cause tumor initiation.



## Western-Style Diet

Diets rich in red and processed meats and low in fiber can contribute to cancer development.

## Diabetes

People with diabetes are 30% more at risk for colorectal cancer. Diabetes causes chronic inflammation contributing to cancer development.

## Increased Antibiotic Usage

Repeatedly using antibiotics causes disruptions in the gut microbiome.



ONCOBITES.BLOG

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NEWS RELEASE 23-APR-2025

## Childhood exposure to bacterial toxin may be triggering colorectal cancer epidemic among the young

Peer-Reviewed Publication

UNIVERSITY OF CALIFORNIA - SAN DIEGO



In an effort to explain a modern medical mystery, an international team of researchers led by the University of California San Diego has identified a potential microbial culprit behind the alarming rise in early-onset colorectal cancer: a bacterial toxin called colibactin.

Produced by certain strains of *Escherichia coli* that reside in the colon and rectum, colibactin is a toxin capable of altering DNA. Now, scientists report that exposure to colibactin in early childhood imprints a distinct genetic signature on the DNA of colon cells—one that may

UC San Diego Health

# Goals in Rectal Cancer

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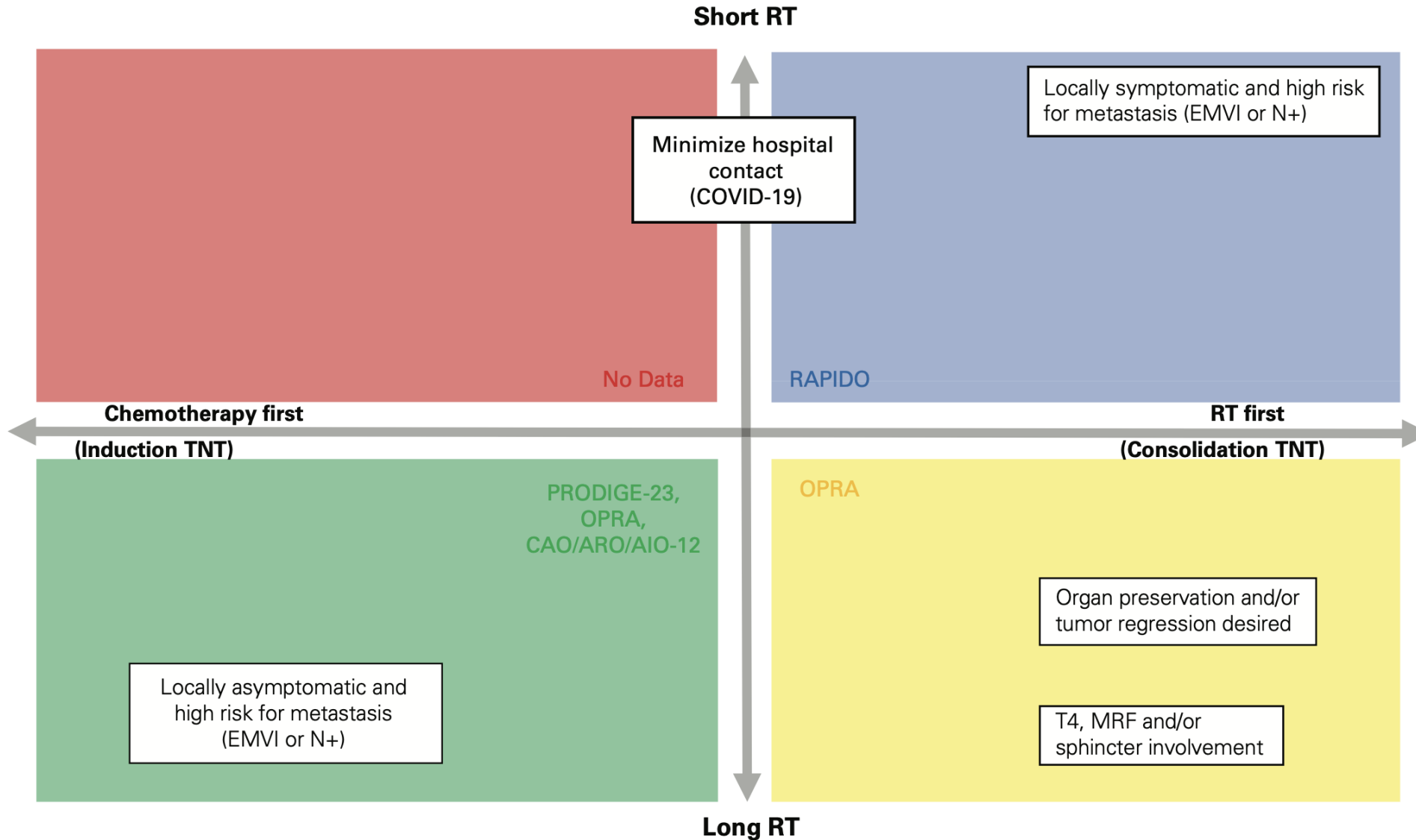
- Cure patient from disease if possible (OS)
- Reduce Burden of Disease otherwise (OS/QoL)
- Reduce Cost of Treatment (QoL)

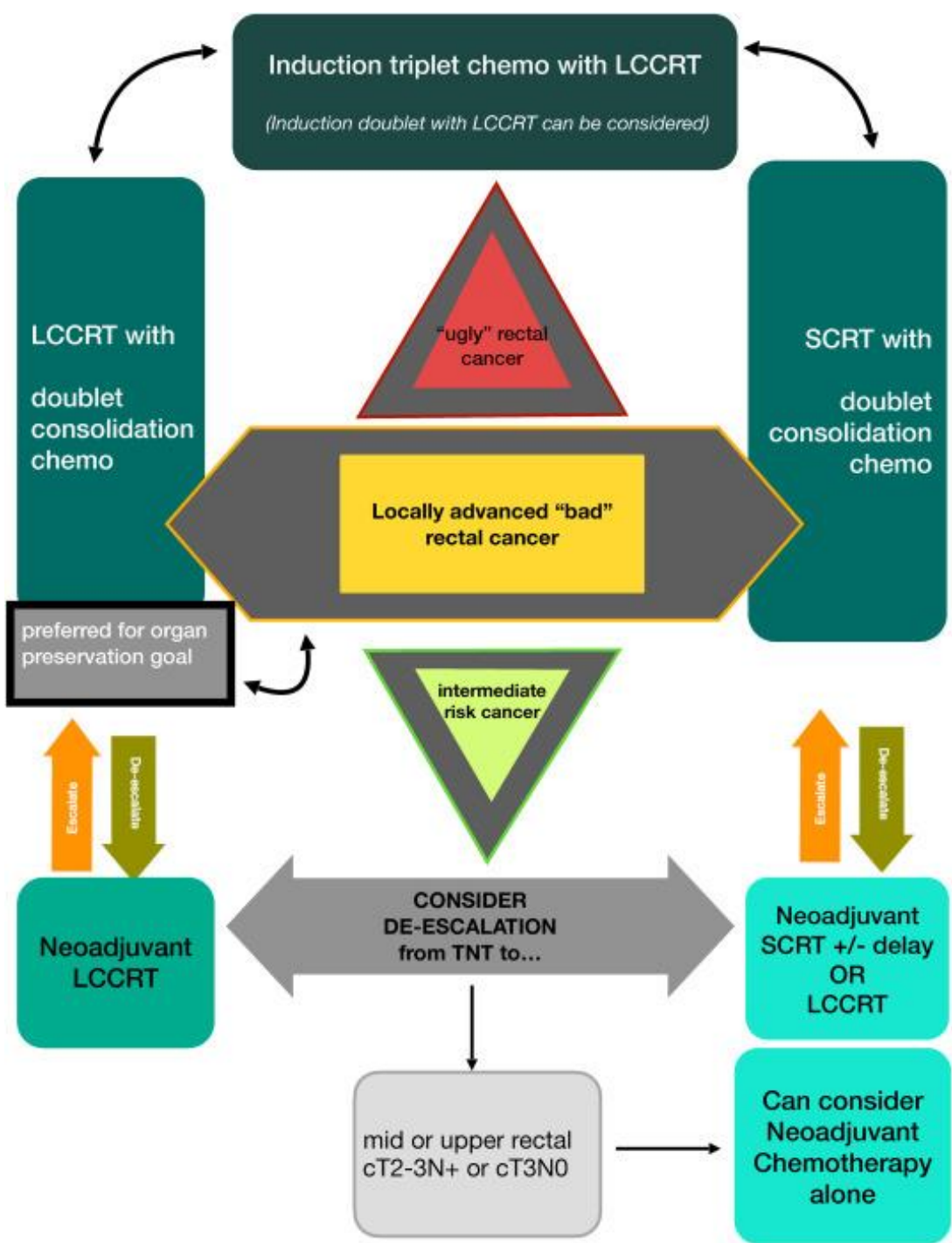


**Table 1. Landmark total neoadjuvant therapy randomized controlled trials**

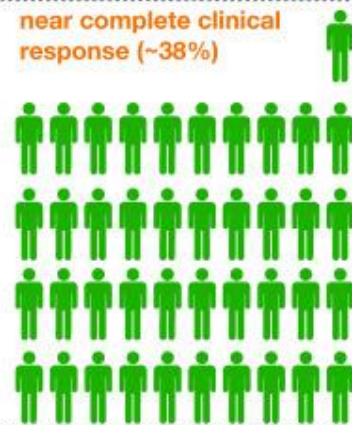
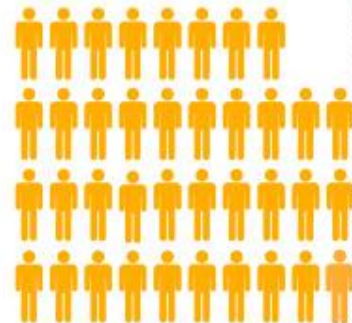
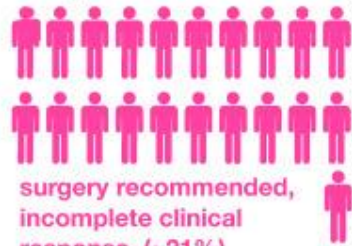
Study (year)	Rectal cancers included	Treatment arms (no. of cycles)	N	Survival outcomes (%)	pCR (%)	Completed chemotherapy (%)	Received surgery (%)	R0 resection (%)	Follow-up (mo)
PRODIGE-23 (2020) <sup>1</sup>	cT3 or cT4	Standard: 5FU-CRT→Surgery	230	DFS: 69* OS: 88	12.1*	75	89	94	46.5
		Induction: FOLFIRINOX(6)→5FU-CRT→Surgery	231	DFS: 76* OS: 91	27.8*	81	94	95	
RAPIDO (2020) <sup>2</sup>	cTa-b, or EMVI+, CN2, MRF+, or LPLN+	Standard: 5FU-CRT→Surgery→±FOLFOX(12)/CAPOX(8)	450	DRTF: 30* OS: 89	14.3*	66 †	89	90	54
		Consolidation: SCRT→FOLFOX(9)/CAPOX(6)→Surgery Standard: 5FU/OX-CRT→Surgery	462	DRTF: 24* OS: 89	28.4*	85	92	90	
POLISH II (2019) <sup>3</sup>	Primary or locally recurrent cT4, or a palpable fixed cT3	Standard: 5FU/OX-CRT→Surgery	254	DFS: 43 OS: 49	12	NR	92	71	84
		Consolidation: SCRT→FOLFOX(3)→Surgery	261	DFS: 41 OS: 49	16	99	93	77	
STELLAR (2022) <sup>4</sup>	Primary cT3-4 or N+ in mid to distal rectum	Standard: CAPE-CRT→Surgery→CAPOX(6)	293	DFS: 62 OS: 75*	12.3*	58	78.5	87.8	35
		Consolidation: SCRT→CAPOX(4)→Surgery→CAPOX(2)	298	DFS: 65 OS: 87*	21.8*	59 (98 neoadjuvant only)	78.9	91.5	
CAO/ARO/AIO-12 (2019) <sup>6</sup>	cT3 if < 6 cm from AV; > cT3b if 6–12 cm from AV; cT4, or LPLN+	Consolidation: 5FU/OX-CRT→FOLFOX(3)→Surgery	156	NR	25	85	91	90	NR
		Induction: FOLFOX(3)→5FU/OX-CRT→Surgery	150	NR	17	92	95	92	
OPRA (2020) <sup>7</sup>	AJCC stage III–IV	Consolidation: 5FU-CRT→FOLFOX/CAPOX(4 mo)→Surgery	155	DFS: 77 DMFS: 83	NR	NR	42* ‡	NR	25
		Induction: FOLFOX/CAPOX(4 mo)→5FU-CRT→Surgery	152	DFS: 78 DMFS: 81	NR	NR	57* ‡	NR	

# UCSD NAPRC – Multi-D Tumor Board

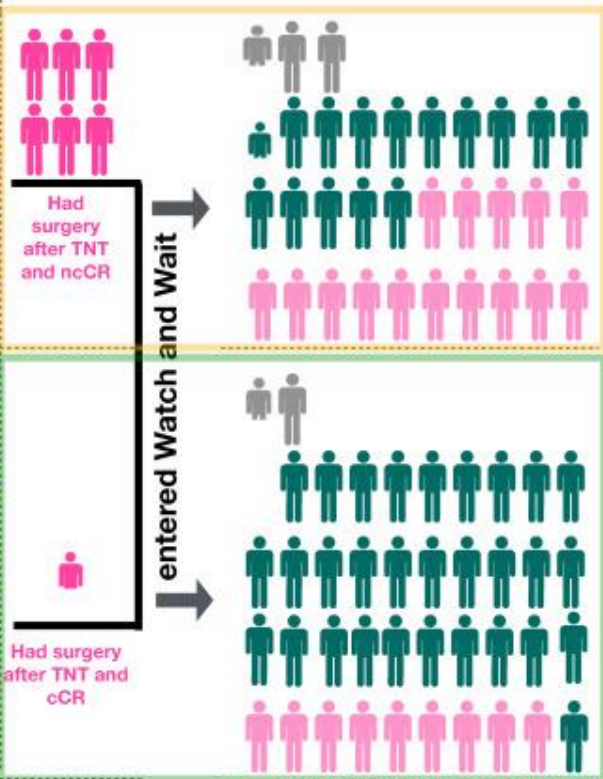




For 100 persons treated with TNT



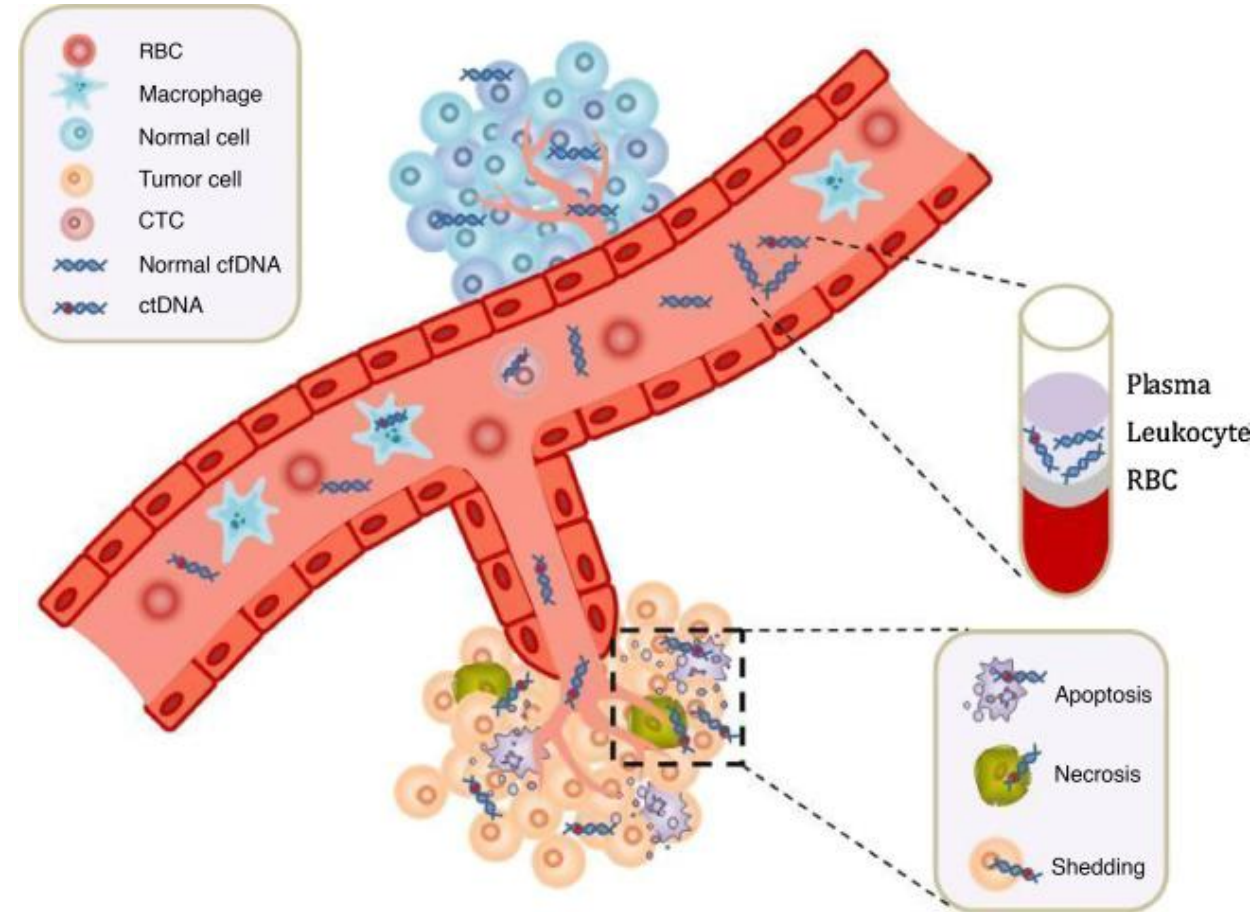
Complete clinical response (~41%)

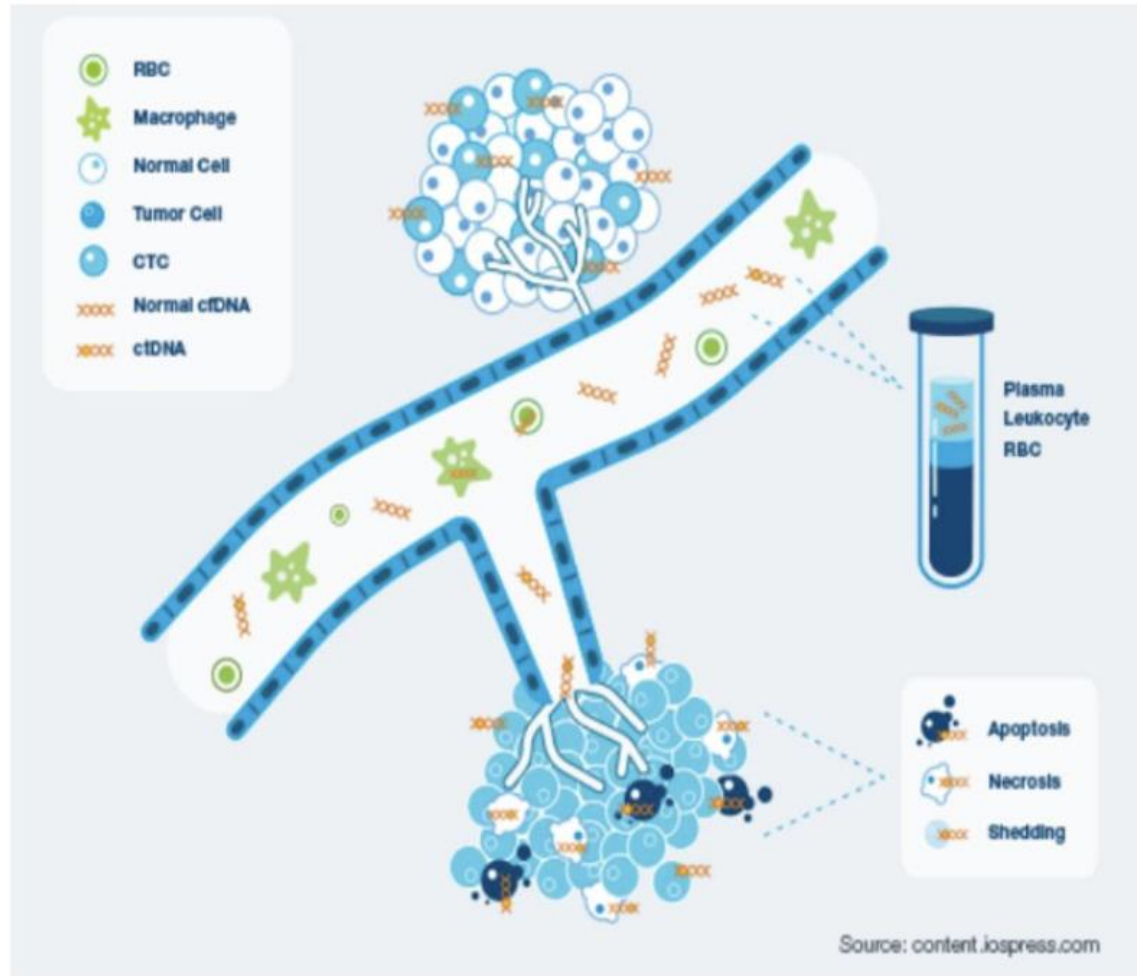


- Preserved rectum and sustained clinical response
- Surgery eventually recommended for disease recurrence (note: 25-30% of these patients later developed distant metastases after TME recommended for local recurrences, similar risk to those who needed surgery at baseline for incomplete response to neoadjuvant treatment)
- Preserved rectum but developed un-resectable/distant metastases

# Post Treatment Surveillance

Examination type	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Physical examination and history</b>	Every 3-6 months	Every 3-6 months	Every 6 months	Every 6 months	Every 6 months
<b>CEA</b> (carcinoembryonic antigen test)	Every 3-6 months	Every 3-6 months	Every 6 months	Every 6 months	Every 6 months
<b>Colonoscopy</b> (colon and rectal cancer patients)	Colonoscopy at 1 year (rectal cancer patients: may be done at 3-6 months if it was not done before surgery). If advanced adenoma found, repeat in 1 year; otherwise repeat in 3 years. If 3-year colonoscopy is clear, repeat every 5 years.				
<b>Sigmoidoscopy</b> (for rectal cancer patients who received LAR)	Every 6 months can be considered				
Abdominal and chest CT scan ( <b>colon and rectal</b> ) and pelvic CT scan (recommended if primary tumor was located in the rectum)	Yes	Yes	Yes	As determined by your doctor	As determined by your doctor

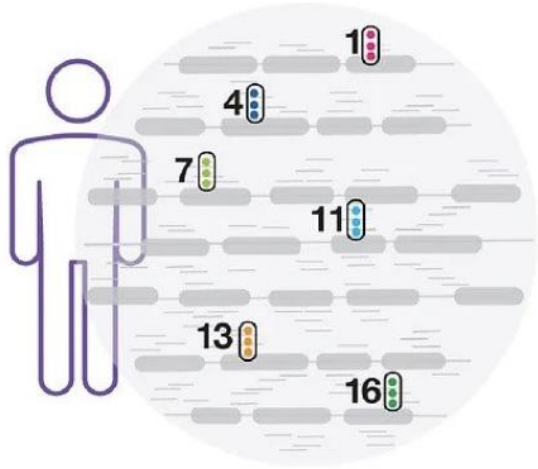




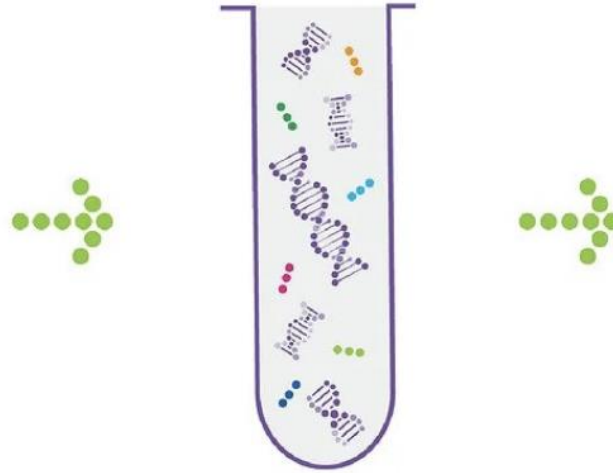
## WHY IS CIRCULATING TUMOR DNA (ctDNA) INTERESTING FOR MRD ASSESSMENT?

- Every patient's tumor has a unique molecular profile and a dynamic evolution.
- Cancer cells release circulating tumor DNA (ctDNA) into the bloodstream that reflects each tumor's unique genetic fingerprint.
- ctDNA is a powerful tool that can be used to measure and assess the absence or presence of MRD based on the tumor's unique molecular profile.
- Dynamic real-time biomarker: the normal half-life is less than an hour.

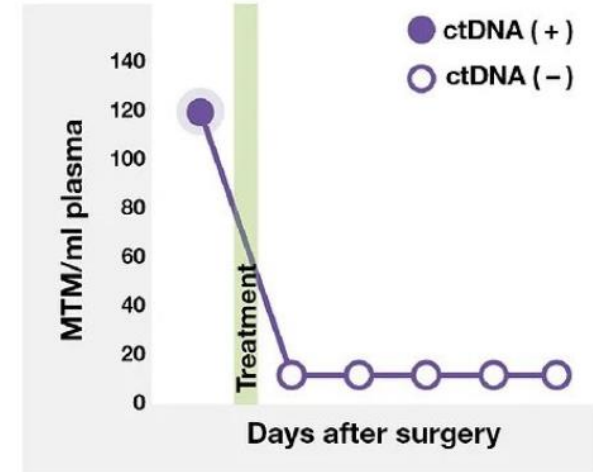
Whole exome sequencing  
and individualized selection  
of 16 clonal, somatic variants



Patient-specific primer design  
and multiplex PCR assay plus  
next generation sequencing



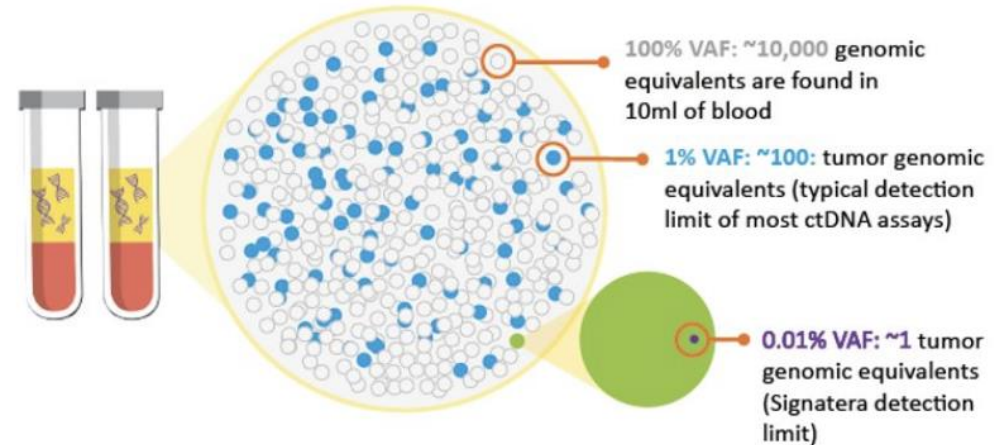
Longitudinal monitoring  
for the presence of ctDNA



## SENSITIVITY & SPECIFICITY

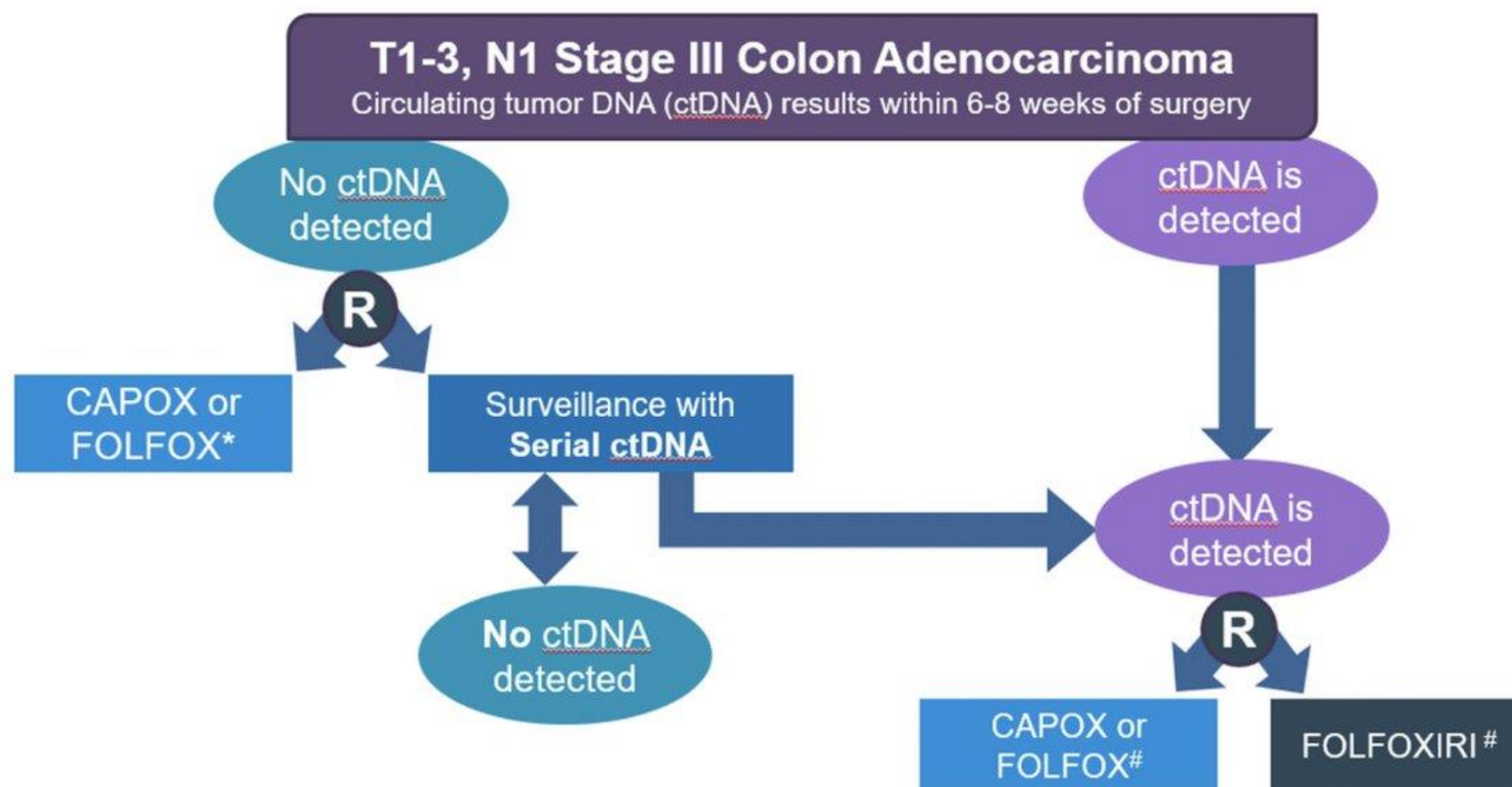
Signatera™ is optimized to detect extremely low quantities of ctDNA, and determines the presence or absence of molecular residual disease.

Ultra sensitive MRD Detection at VAFs as low as 0.01% by tracking 16 ctDNA specific markers (>99% of cases)

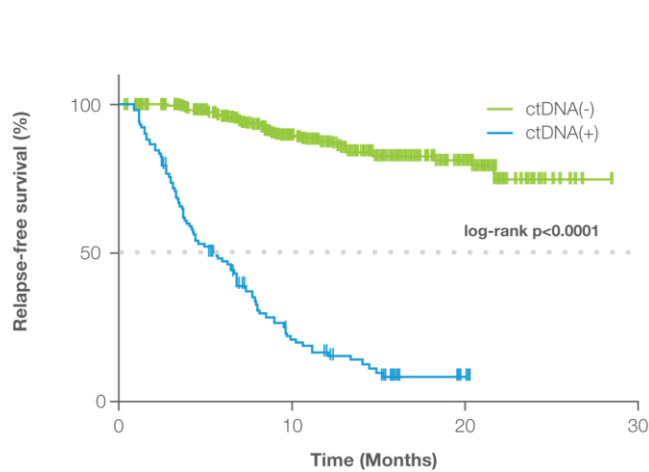


# CIRCULATE-US: ctDNA-guided Adjuvant Therapy for Stage III Colon Cancer

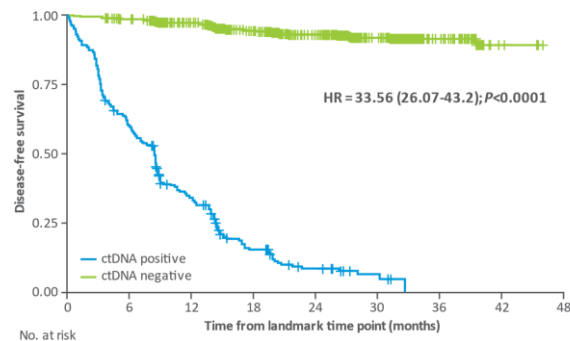
This study is designed for patients who have recently undergone resection of their colon cancer and identified a low-risk stage III cancer defined by T-stages of 1-3 and N-stage of 1. ctDNA testing is done in the context of the trial with the Natera Signatera assay.



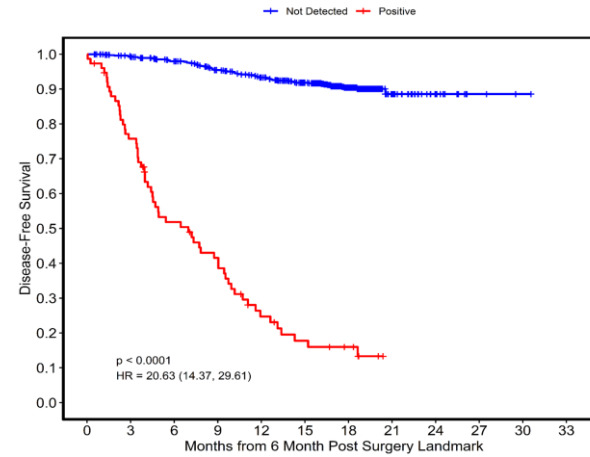
# Tumor Informed ctDNA is the most prognostic factor for DFS and OS in resected stage II/III colon cancer



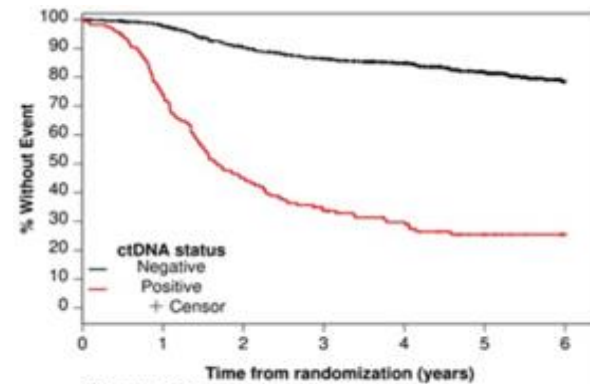
**MDACC-INTERCEPT 2024**



**GALAXY 2024**

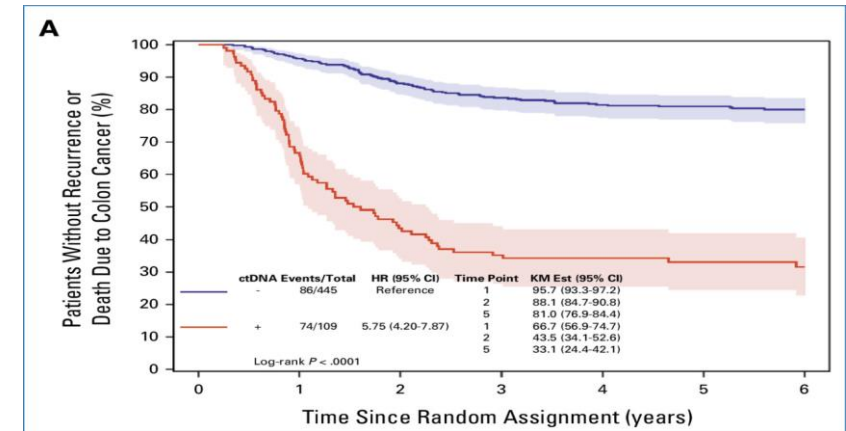


**BESPOKE 2025**



Time from randomization (years)	0	1	2	3	4	5	6
Patients-at-Risk	767	705	616	562	484	324	92
	173	121	73	48	38	17	7

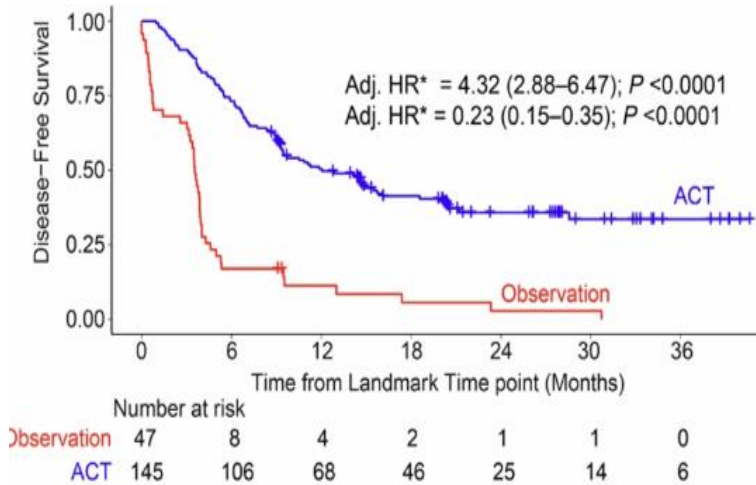
**CALGB (Alliance)/SWOG 80702**



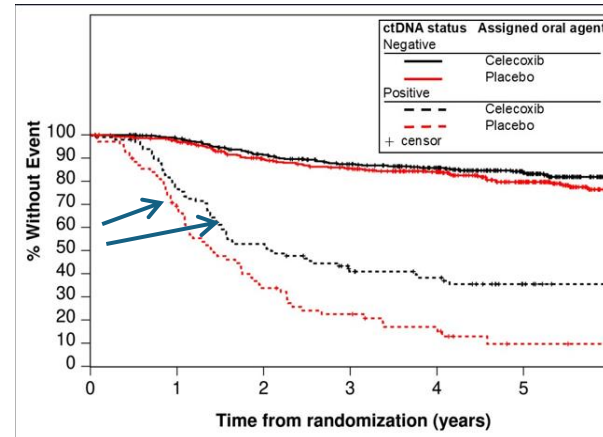
**IDEA Fr / Gr 2025**

**Tumor informed ctDNA is the most prognostic factor in CRC, outperforming stage, CEA, high-risk features and other biomarkers**

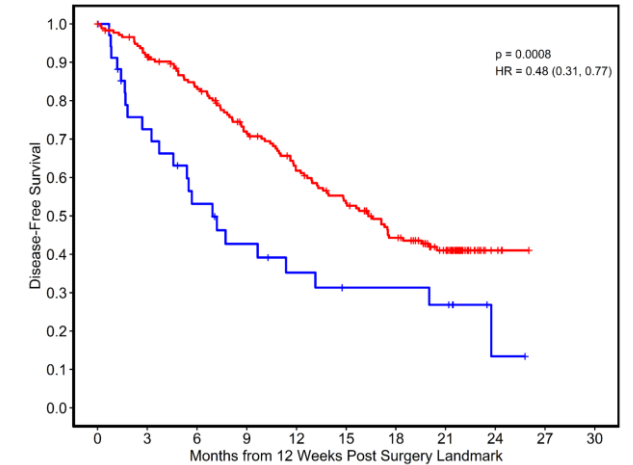
# Multiple trials have consistently demonstrated benefit of Adjuvant Chemotherapy in ctDNA positive patients....



**GALAXY 2024**



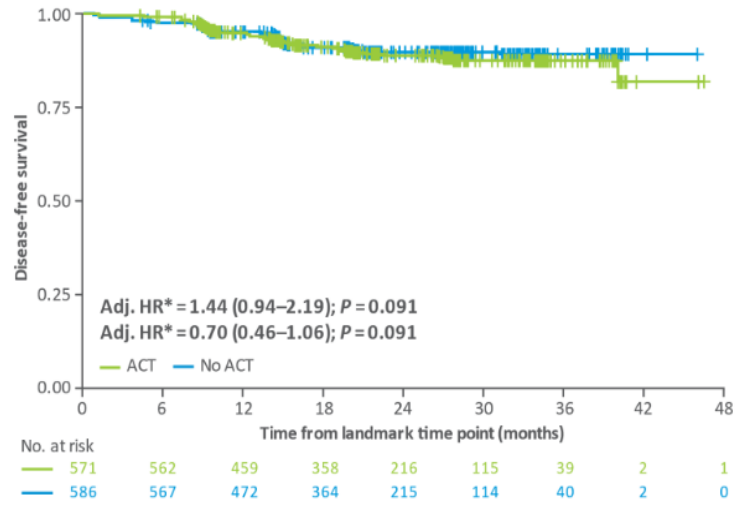
**CALGB (Alliance)/SWOG 80702**



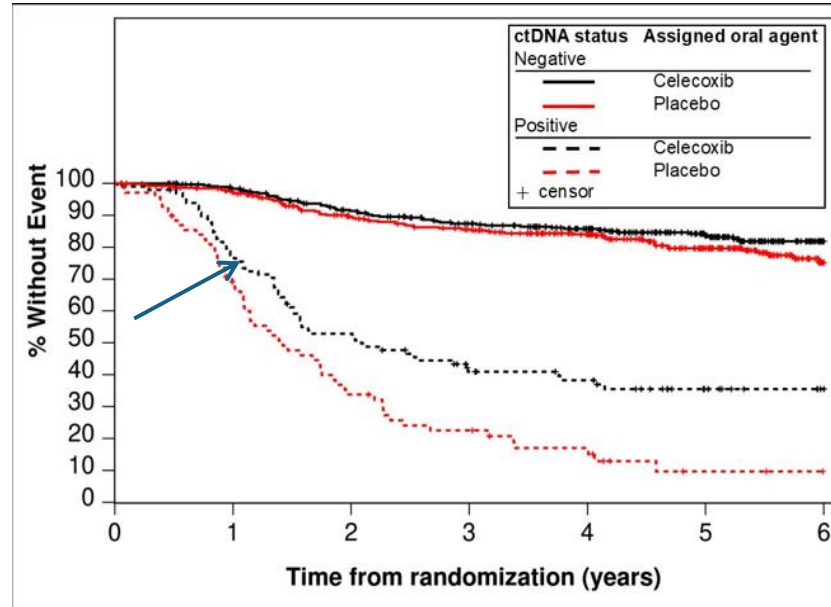
**BESPOKE 2025**

	GALAXY (2-yr DFS)	CALGB 80702 (3-yr DFS)	BESPOKE (2-yr DFS)
Intervention arm	35.8%	41%	40.3%
Control arm	2.8%	22.6%	24.7%

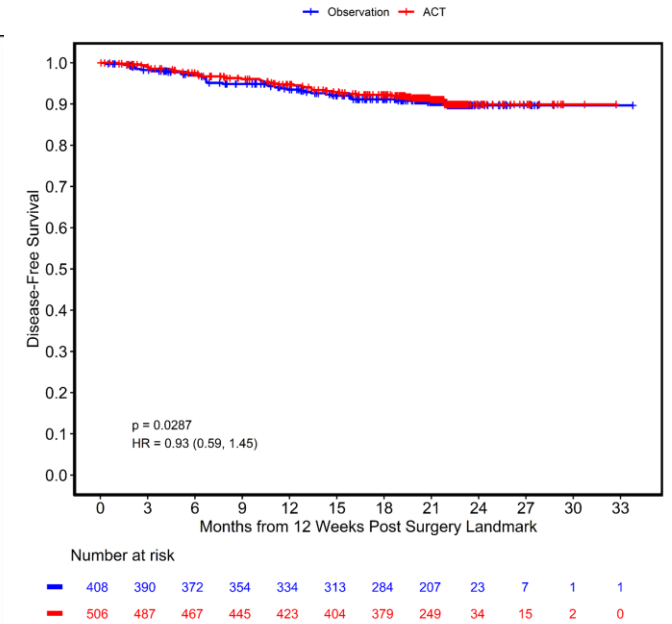
# ... and lack thereof ctDNA negative patients



**GALAXY 2024**



**CALGB (Alliance)/SWOG 80702**



**BESPOKE 2025**

	GALAXY (2-yr DFS)	CALGB 80702 (3-yr DFS)	BESPOKE (2-yr DFS)
Intervention arm	89%	87%	89%
Control arm	89%	85%	89%

[nature](#) > [nature cancer](#) > [articles](#) > [article](#)

Article | Published: 03 August 2020

# Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab

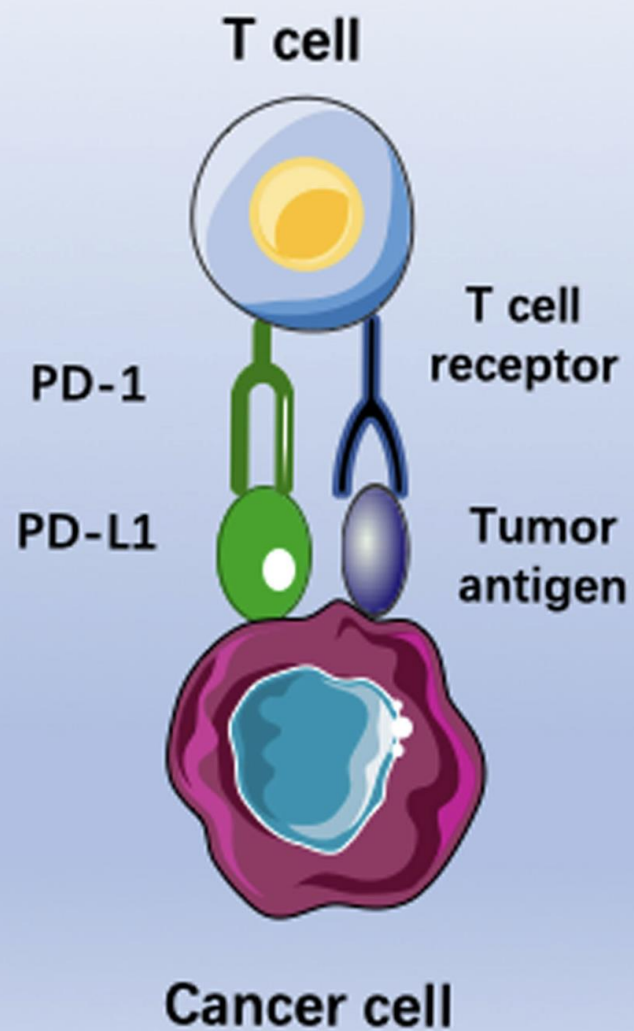
[Scott V. Bratman](#), [S. Y. Cindy Yang](#), [Marco A. J. Iaforla](#), [Zhihui Liu](#), [Aaron R. Hansen](#), [Philippe L. Bedard](#), [Stephanie Lheureux](#), [Anna Spreafico](#), [Albiruni Abdul Razak](#), [Svetlana Shchegrova](#), [Maggie Louie](#), [Paul Billings](#), [Bernhard Zimmermann](#), [Himanshu Sethi](#), [Alexey Aleshin](#), [Dax Torti](#), [Kayla Marsh](#), [Jenna Eagles](#), [Iulia Cirlan](#), [Youstina Hanna](#), [Derek L. Clouthier](#), [Scott C. Lien](#), [Pamela S. Ohashi](#), [Wei Xu](#), ... [Trevor J. Pugh](#) 

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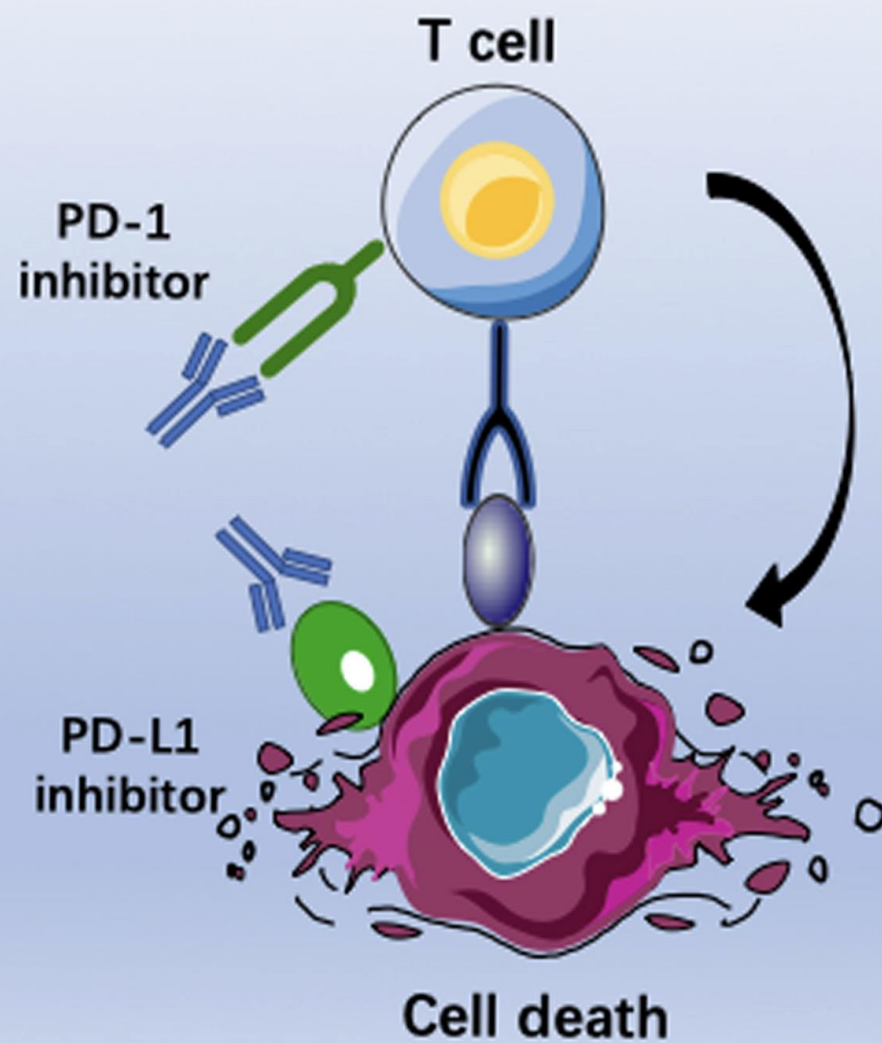
[Nature Cancer](#) **1**, 873–881 (2020) | [Cite this article](#)

**21k** Accesses | **603** Altmetric | [Metrics](#)

## A: Inhibition of T cell activity

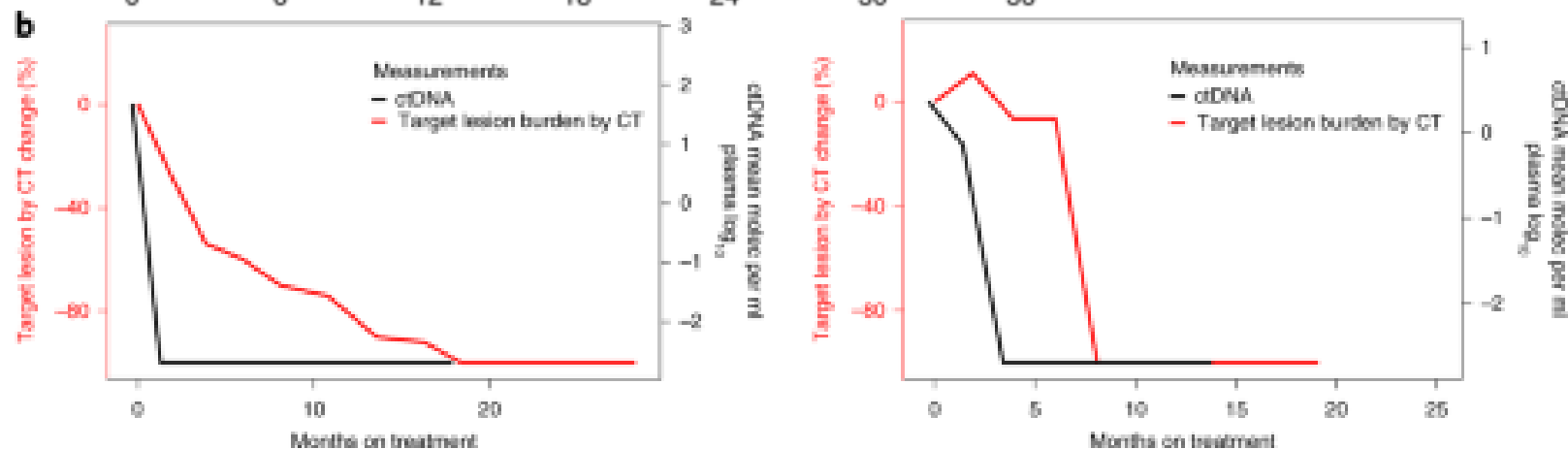
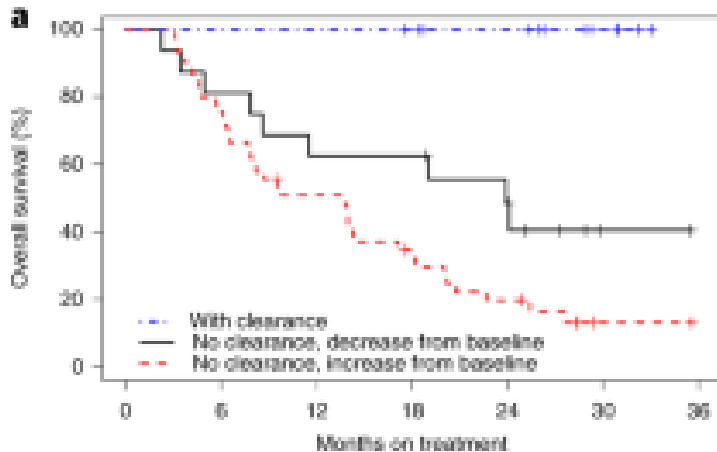
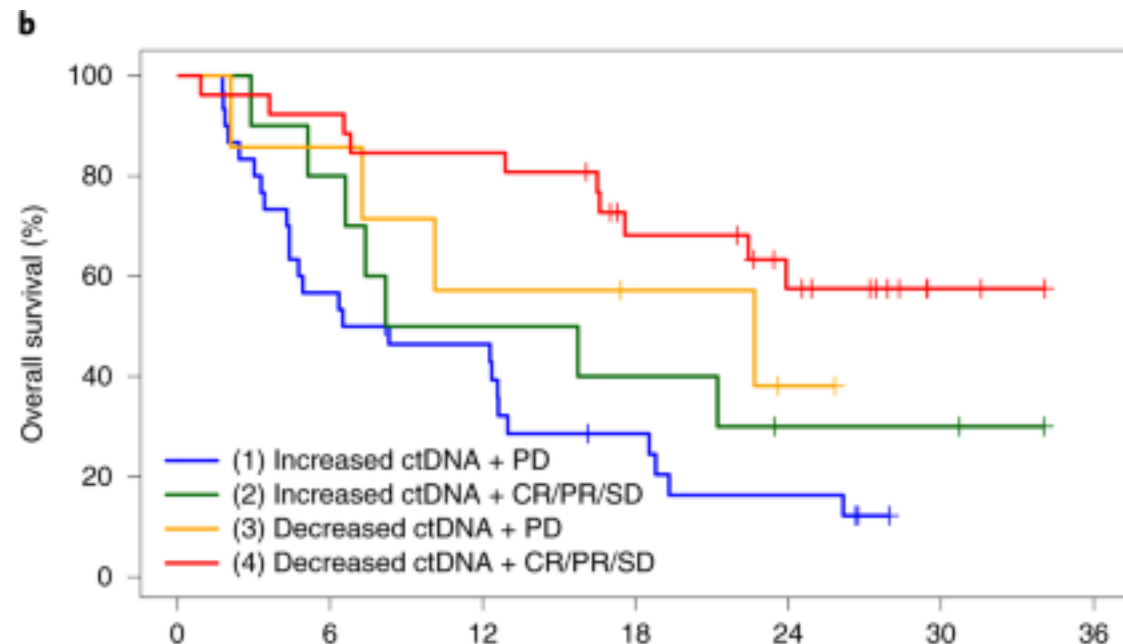


## B: Activation of T cell activity



**a**

<i>N</i> = 73	Cycle 3 PD	Cycle 3 CR/PR/SD
Cycle 3 increase ctDNA	30	10
Cycle 3 decrease ctDNA	7	26



*The* **NEW ENGLAND**  
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**PD-1 Blockade in Mismatch Repair–Deficient, Locally  
Advanced Rectal Cancer**

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

**ABSTRACT**

**Table 1. Demographic and Disease Characteristics of the Patients at Baseline.**

Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	
White	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic or Latinx ethnic group — no. (%)*	1 (6)
ECOG performance-status score — no. (%)†	
0	12 (75)
1	4 (25)
Tumor stage — no. (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status — no. (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge (range) — cm	5 (0.9–8.9)

\* Race and ethnic group were reported by the patient.

† The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

**Table 2. Individual Patient Data.\***

Patient No. (Sex, Age)	Tumor Stage; Nodal Status	Germline Pathogenic Variant†	Mismatch-Repair Status, Chromogenic IHC Assay	PD-L1 Level	TIL Level	<i>BRAF</i> V600E Mutation	Tumor Mutational Burden‡	Completed 6 mo of Dostarlimab Therapy	CRT or Surgery	Response on Endoscopic Visualization	Digital Examination; Endoscopic Biopsy	Response on Rectal MRI	Response on FDG-PET
1 (F, 38 yr)	T4; positive	<i>MSH2</i> (c.687delA)	<i>MSH2</i> and <i>MSH6</i> absent	+	+++	No	88.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
2 (F, 30 yr)	T3; positive	<i>MSH2</i> (c.8942+3A→T)	<i>MSH2</i> and <i>MSH6</i> absent	++	+	No	45.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
3 (F, 61 yr)	T1 to T2; positive	None	<i>MSH2</i> and <i>MSH6</i> absent	+++	+++	No	62.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
4 (F, 28 yr)	T4; positive	None	<i>MSH2</i> and <i>MSH6</i> absent	+	++	No	65.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
5 (F, 53 yr)	T1 to T2; positive	<i>MSH2</i> (c.942+3A→T)	<i>MSH2</i> absent	+	+	No	103.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
6 (F, 77 yr)	T1 to T2; positive	<i>MSH6</i> (c.1969delC)	<i>MSH6</i> absent	+++	+++	No	93.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
7 (F, 77 yr)	T1 to T2; positive	None	<i>MLH1</i> and <i>PMS2</i> absent	++	++	No	75.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
8 (F, 55 yr)	T3; positive	<i>MSH2</i> (c.1784T→G)	<i>MSH2</i> absent	++	+	No	78.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR

9 (M, 68 yr)	T3; positive	None	MSH2 and MSH6 absent	+++	++	No	62.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
10 (F, 78 yr)	T3; negative	None	MLH1 and PMS2 absent	+	+	No	37.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
11 (F, 55 yr)	T3; positive	<i>PMS2</i> (c.2500 _2501delinsG)	MSH2 and MSH6 absent	++	++	No	52.7	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
12 (M, 27 yr)	T3; positive	None	PMS2 absent	+++	+++	No	54.4	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
13 (M, 26 yr)	T3; positive	<i>MLH1</i> (c.1489dupC)	MLH1 and PMS2 absent	NA	NA	No	47.8	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	CR at 3 mo	CR
14 (M, 43 yr)	T3; positive	<i>MSH6</i> (c.3476dupA)	MSH6 absent	NA	NA	No	74.1	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	Near-CR at 3 mo	CR
15 (M, 59 yr)	T3; positive	NA	PMS2 absent	NA	NA	NA	NA	No; ongoing, 5 wk	No	NE	NE; NE	NE	NE
16 (M, 51 yr)	T4b; positive	NA	MSH2 absent	NA	NA	NA	NA	No; ongoing, 3 wk	No	NE	NE; NE	NE	NE

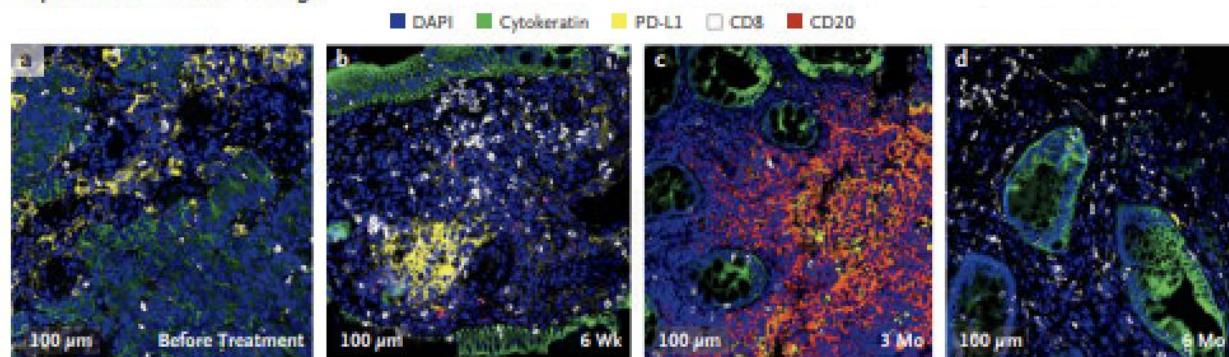
\* CR denotes complete response, CRT chemoradiotherapy, FDG-PET <sup>18</sup>F-fluorodeoxyglucose–positron-emission tomography, IHC immunohistochemical, NA not available, NE not able to be evaluated, PD-L1 programmed death ligand 1, and TIL tumor-infiltrating lymphocyte.

† All alterations identified are associated with the Lynch syndrome.

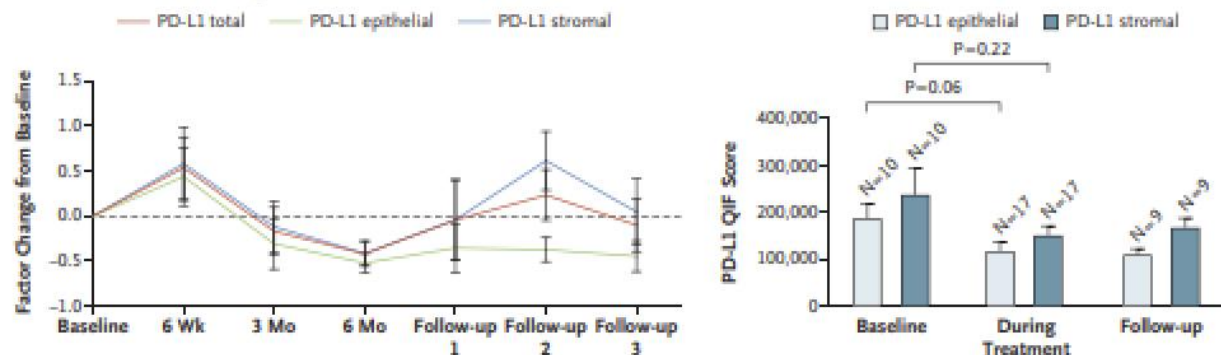
‡ Units are reported in mutations per megabase.



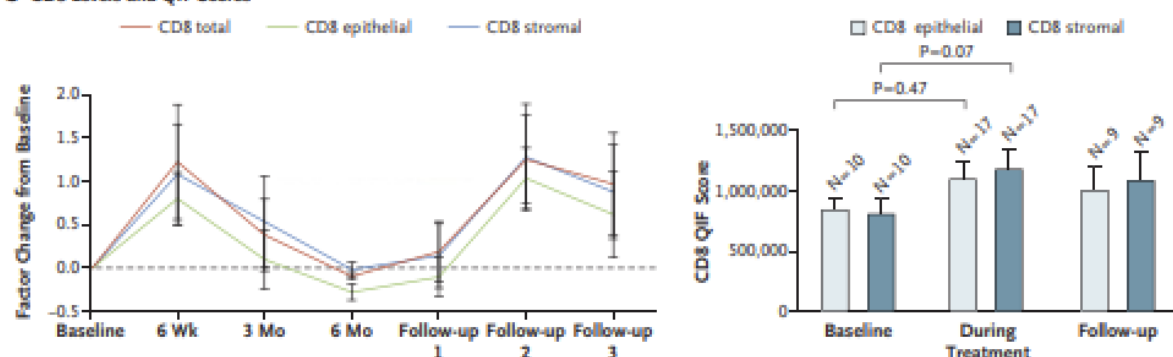
### A Representative Fluorescence Images



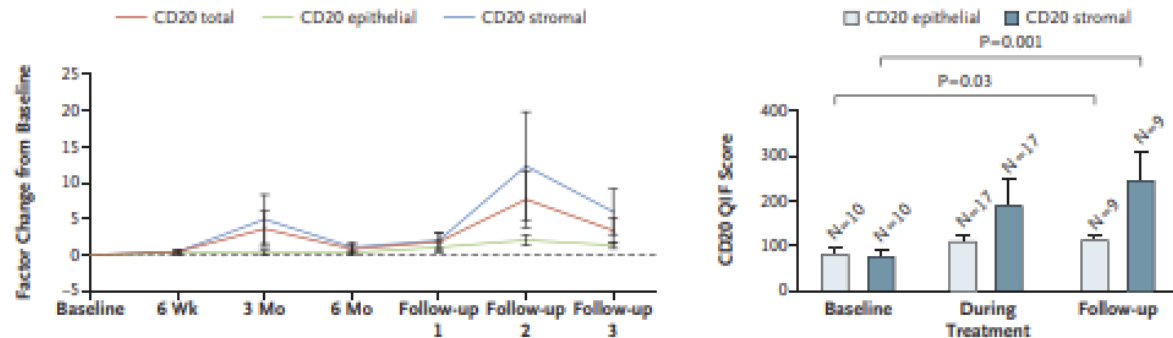
### B PD-L1 Protein Levels and QIF Scores



### C CD8 Levels and QIF Scores



### D CD20 Levels and QIF Scores



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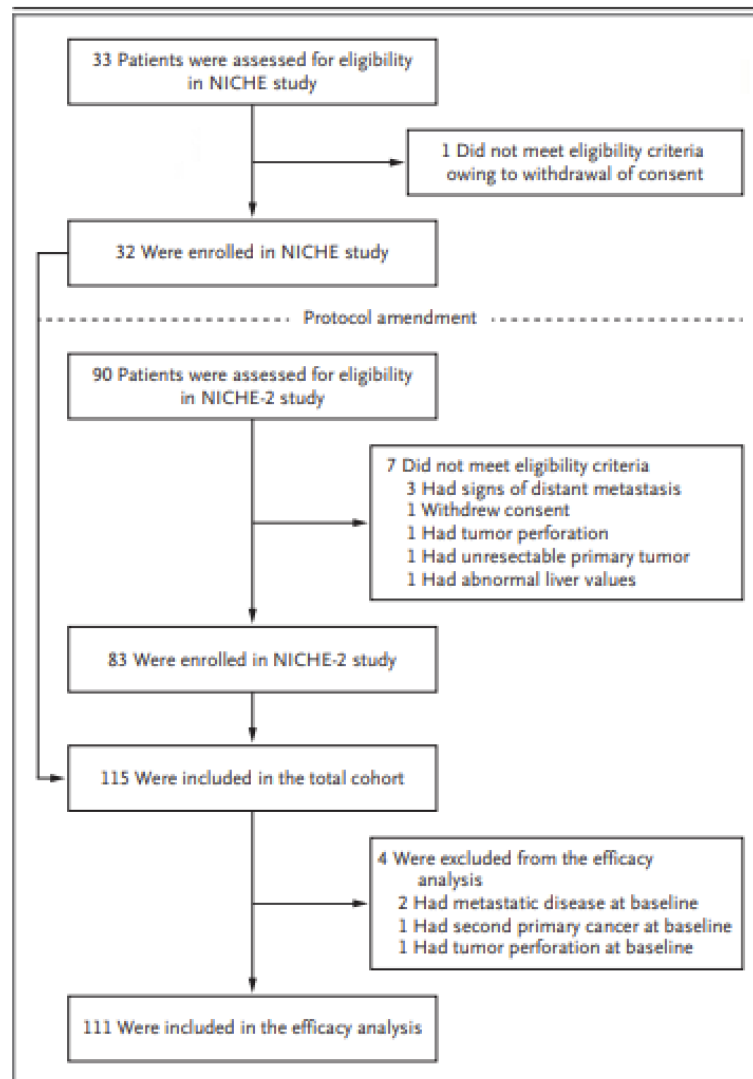
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Neoadjuvant Immunotherapy in Locally Advanced  
Mismatch Repair–Deficient Colon Cancer

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**Figure 1. Screening and Enrollment, before and after Protocol Amendment.**

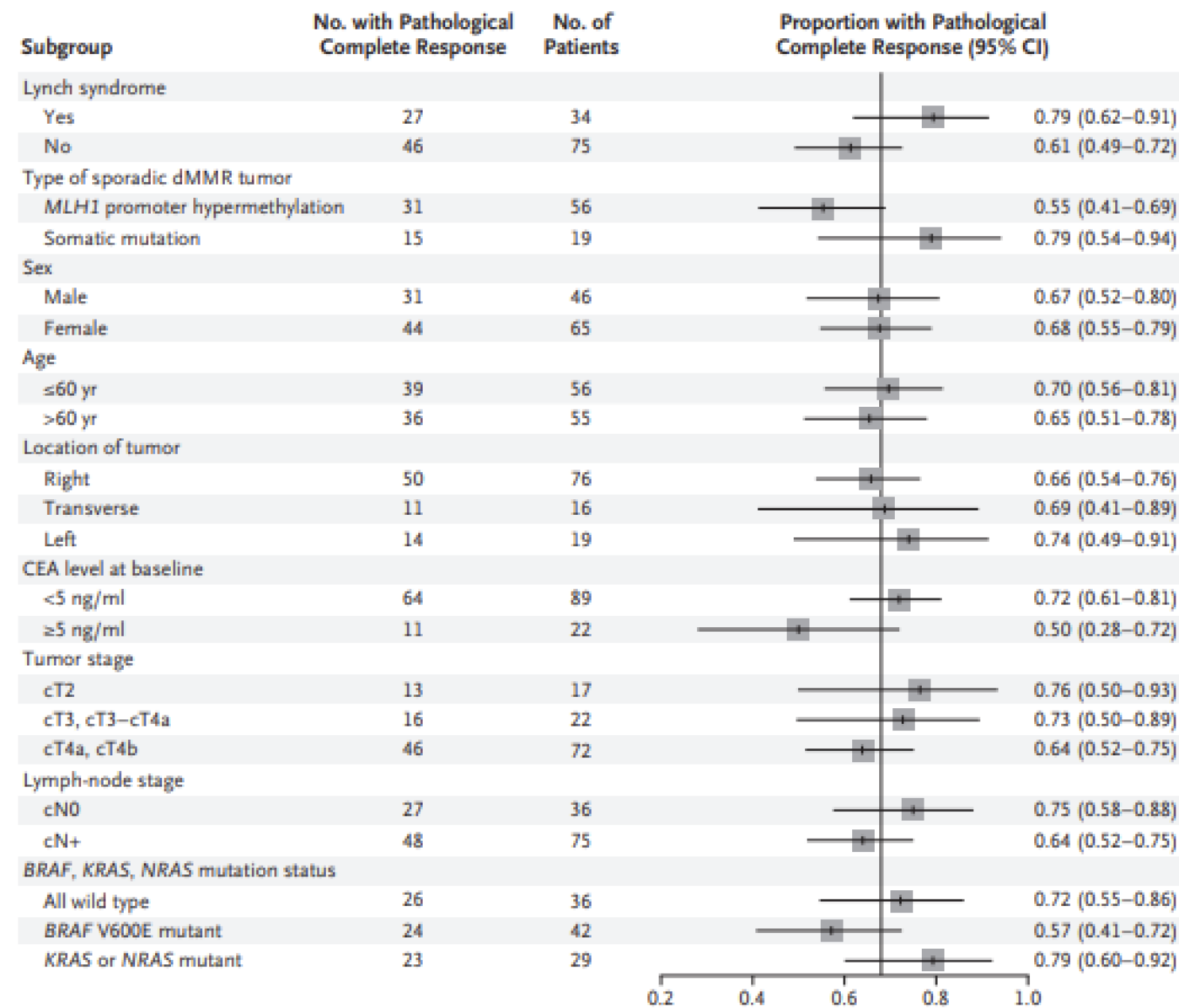
A total of 115 patients with mismatch repair-deficient colon cancer were enrolled. A total of 32 patients were enrolled in the NICHE cohort. A protocol amendment in October 2020 then led to the enrollment of 83 patients in the NICHE-2 cohort, in which patients were eligible if they had disease classified by radiographic assessment as cT3 or higher, N+, or both according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system, version 8, in which T refers to the size and extent of the tumor (with higher numbers indicating greater advancement) and N+ indicates that cancer is present in the lymph nodes.

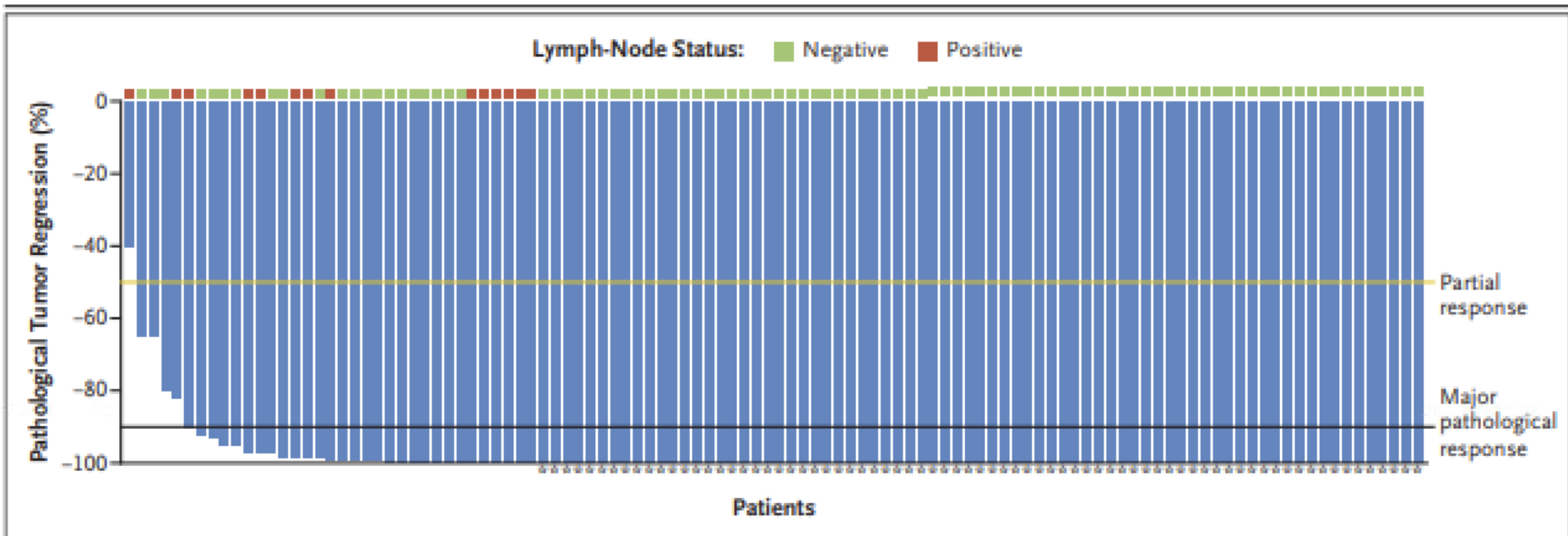
**Table 1. Demographic and Disease Characteristics of the Patients.**

Characteristic	Patients (N=115)
Female sex — no. (%)	67 (58)
Median age (range) — yr	60 (20–82)
WHO performance-status score — no. (%)*	
0	100 (87)
1	15 (13)
Race or ethnic group — no. (%)†	
White	97 (84)
Asian	6 (5)
Black	5 (4)
Other	7 (6)
Tumor stage — no. (%)‡	
cT2	17 (15)
cT3 or cT3–T4a	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status — no. (%)§	
cN–	38 (33)
cN+	77 (67)
Primary tumor location — no. (%)	
Right	78 (68)
Transverse	17 (15)
Left	20 (17)
Lynch syndrome — no. (%)	37 (32)
Unexplained dMMR — no. (%)¶	2 (2)
Non-Lynch syndrome dMMR — no. (%)	76 (66)

**Table 2. Pathological Responses among Patients in the Efficacy Analysis.\***

Residual Viable Tumor	Patients (N=111)
	no. (%)
≤50% Residual viable tumor	109 (98)
≤10% Residual viable tumor: major pathological response	105 (95)
0% Residual viable tumor: complete pathological response	75 (68)
11–49% Residual viable tumor: partial pathological response	4 (4)
≥50% Residual viable tumor, indicating lack of pathological response	1 (1)
Unable to be evaluated†	1 (1)





**Figure 2. Pathological Responses among Patients in the Efficacy Analysis.**

The waterfall plot shows the percentage of pathological tumor regression per tumor among the 110 tumors that could be evaluated for a pathological response. Boxes above each bar indicate the corresponding pathological lymph-node status. Patients with a pathological complete response in both the primary tumor and the lymph nodes are indicated by an asterisk. The black horizontal line indicates the threshold for a major pathological response, specified as at least 90% tumor regression. The yellow line indicates the threshold for a partial response, specified as at least a 50% regression.

CORRESPONDENCE



**The Duration of Immunotherapy for  
Mismatch Repair–Deficient Cancers**

