Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Measurable Residual Disease (MRD) Kinetics and Procedural Outcomes



Pashtoon Murtaza Kasi, MD, MS

Associate Professor, Oncology and Therapeutics Research

Endowed Rad Family Chair in Gastrointestinal Oncology

Medical Director of GI Medical Oncology

City of Hope, Orange County; kasi@coh.org

X @pashtoonkasi

Disclosures

- Grant/Research Support from Grant/Research Support from Agenus, CytoDyn, Inc., Haystack, Merck, and Novartis.
- Consultant for Agenus, Bexion Pharmaceuticals, Boston Scientific, Elicio Therapeutics, Exact Sciences, Illumina, Neogenomics, Regeneron, RenovoRx, and Sirtex.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The procedure is half the answer

1. **Did the procedure clear the disease?**
   Residual molecular disease after resection, ablation or liver-directed therapy

2. **When can the blood tell us?**
   Kinetics: half-life, the post-procedure cfDNA surge, and the MRD window

3. **What do we do with the answer?**
   Escalate, de-escalate, or enroll in a trial

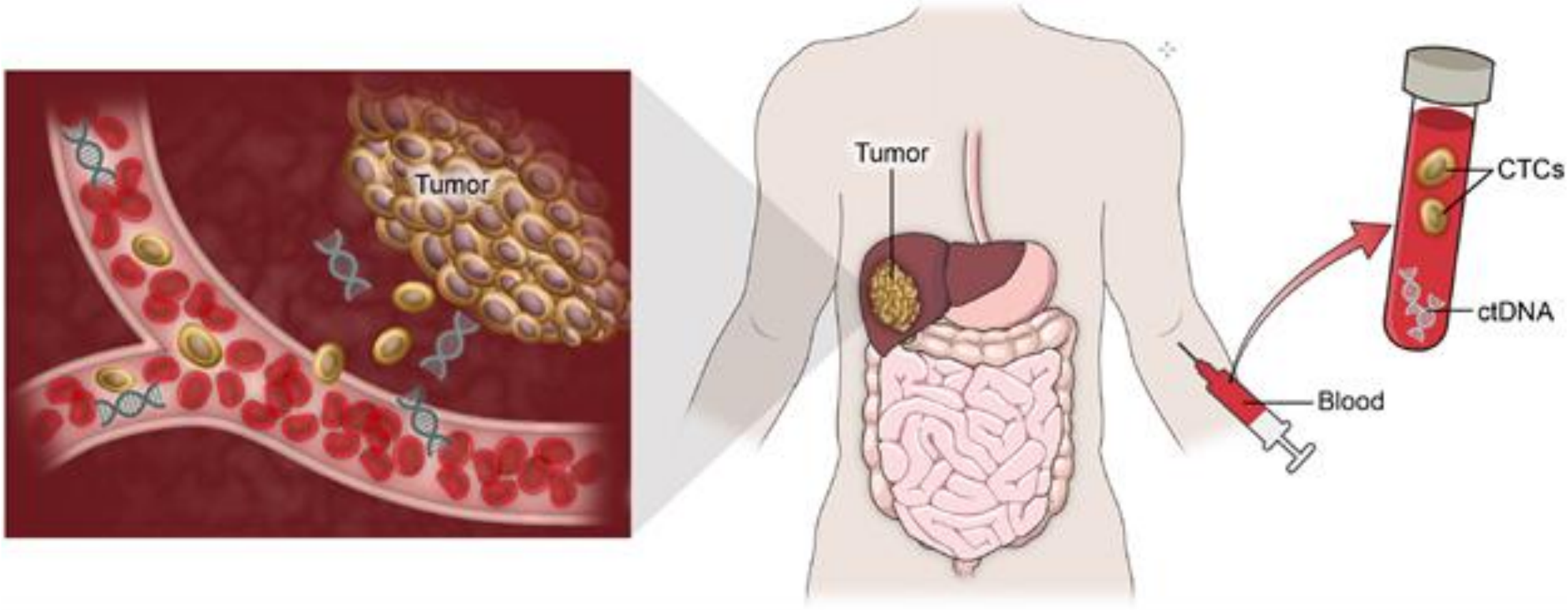
Endoscopic Oncology 2.0

Technique removes what we can see.

Molecular insight measures what we can't.

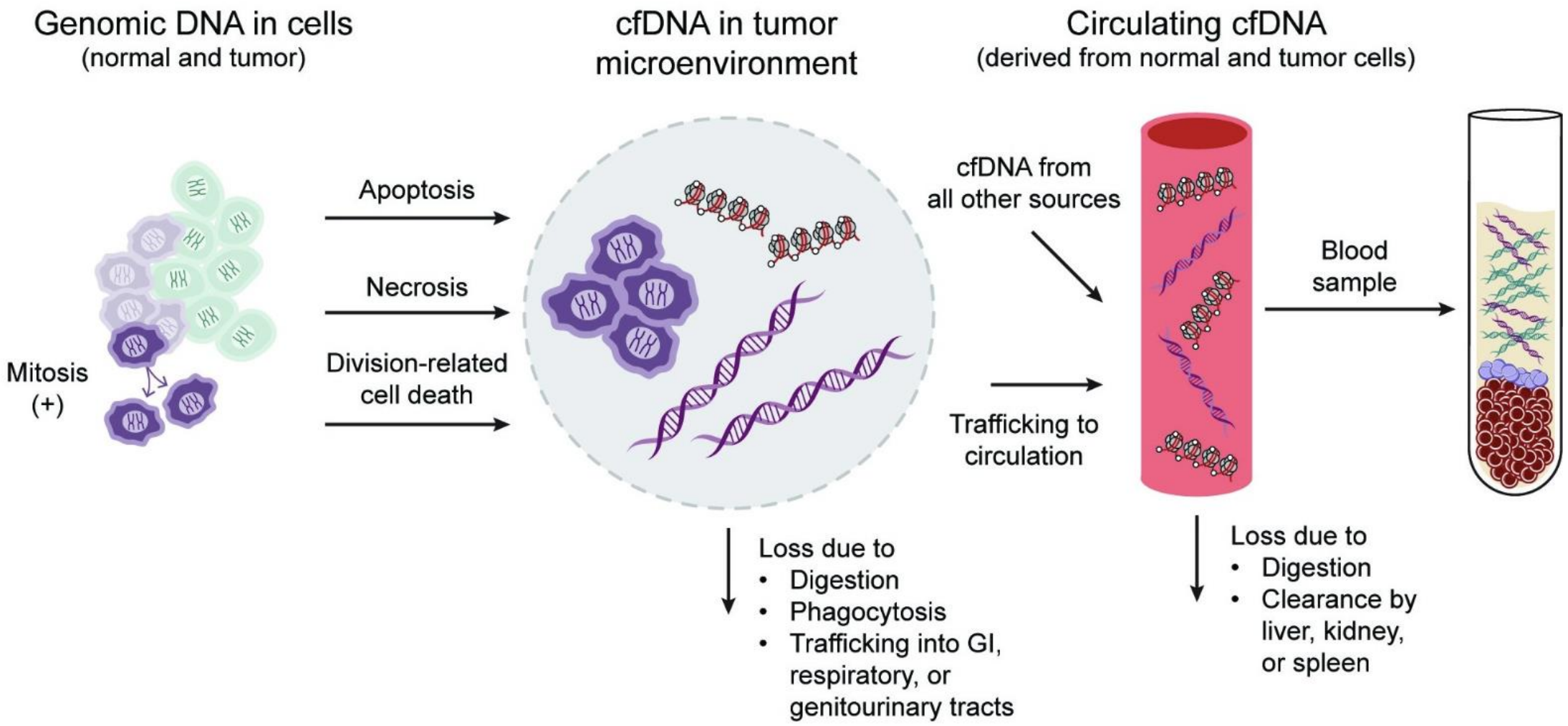
ctDNA turns a procedure into a measurable experiment.

“Liquid Biopsies are an integral part of **my standard of care** for delivering **personalized care** for our patients with **cancer**”

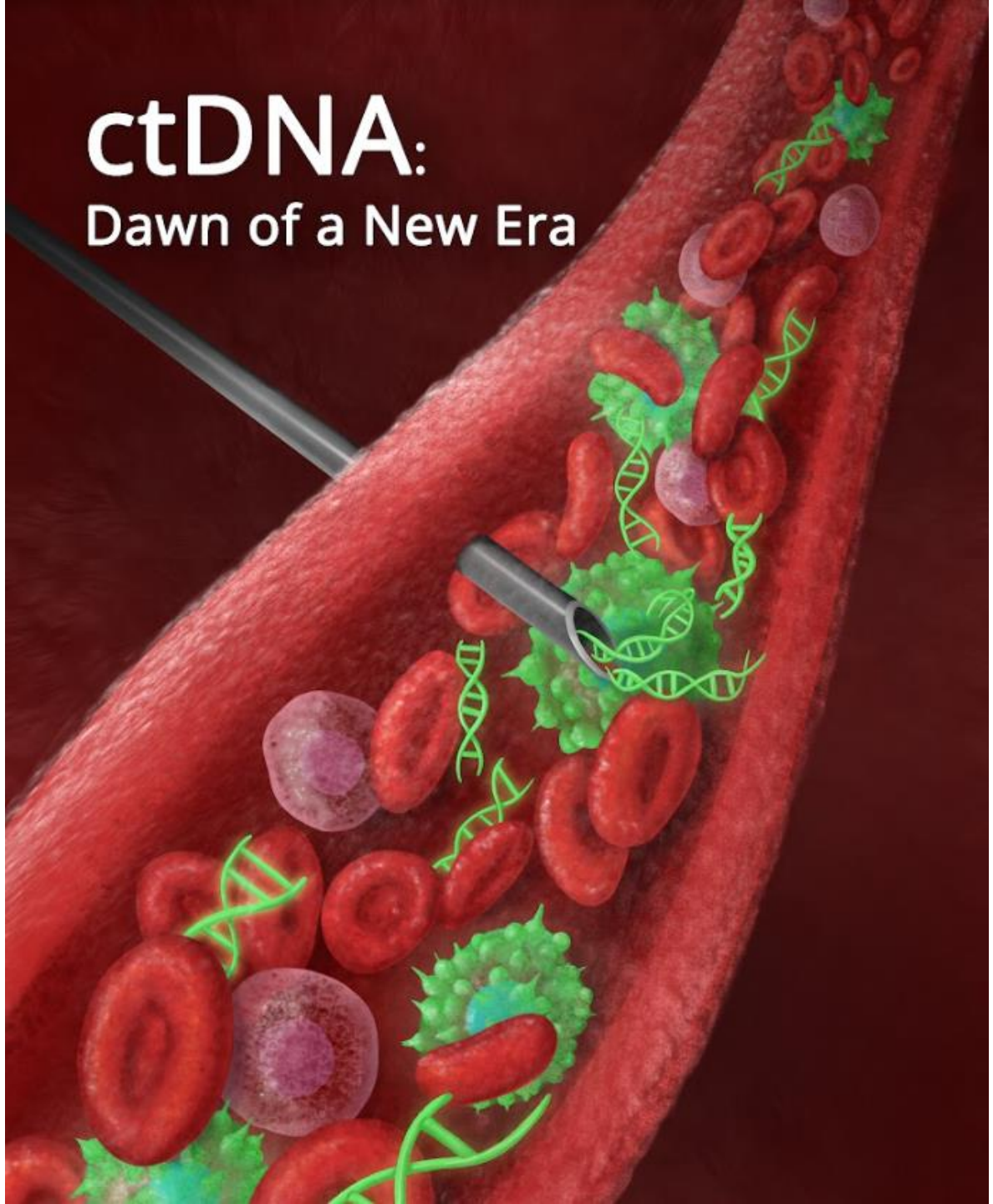


@pashtoonkasi

Depiction of origin and fates of circulating tumor DNA relative to cell-free DNA



Bredno, J. et al, 2021. Clinical correlates of circulating cell-free DNA tumor fraction. PLOS ONE 16, e0256436.

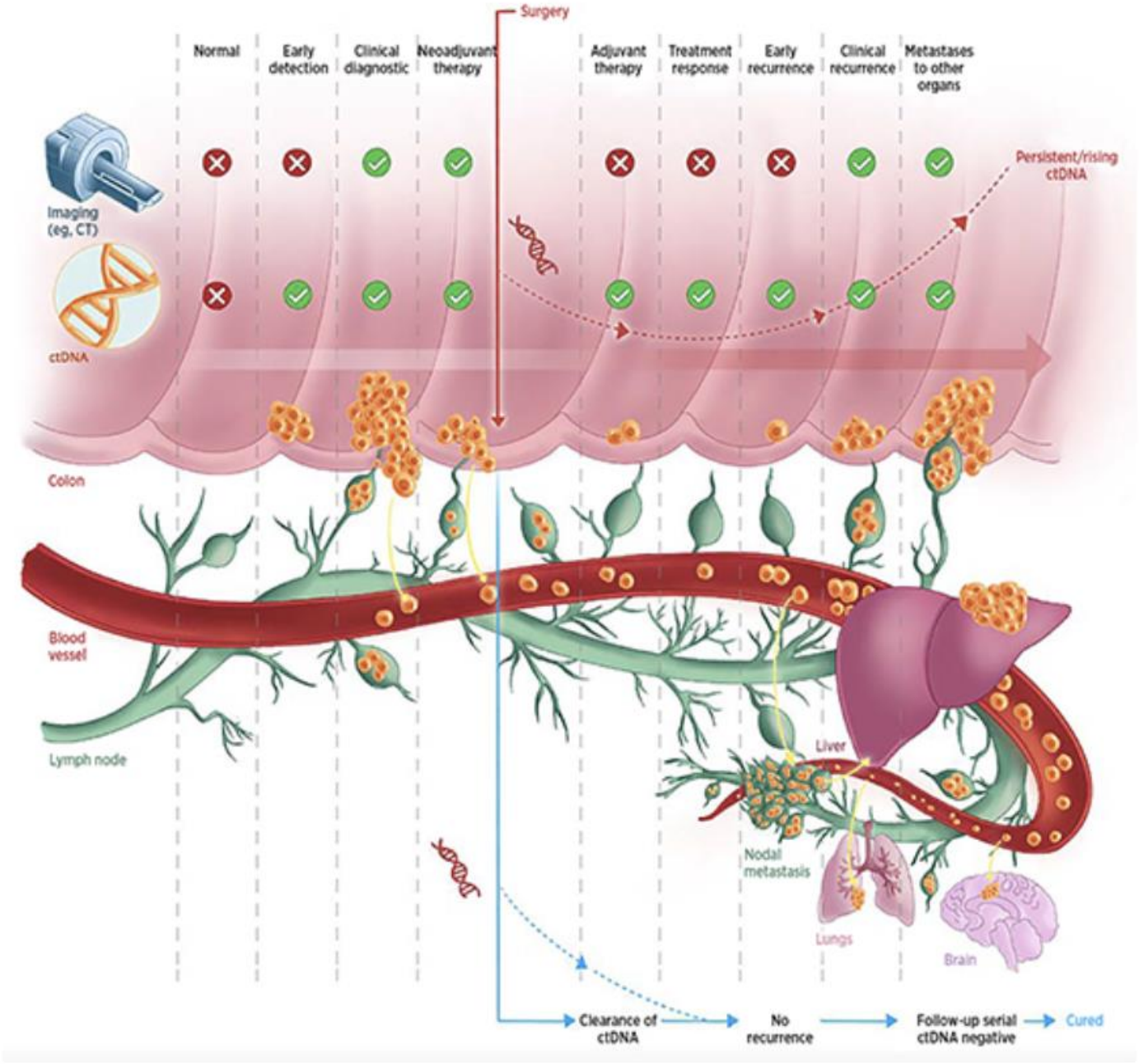


ctDNA: Dawn of a New Era

Location	Available On Demand
Time	Sat, Jun 4, 2022 | 9:00 AM – 10:30 AM EDT
Track(s)	Special Sessions

2022 ASCO® ANNUAL MEETING
ADVANCING EQUITABLE CANCER CARE THROUGH INNOVATION

- Liquid Biopsies
- ⇈Precision Medicine



- Diagnosis
- Minimal Residual Disease
- Treatment Response
- Acquired Resistance

ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

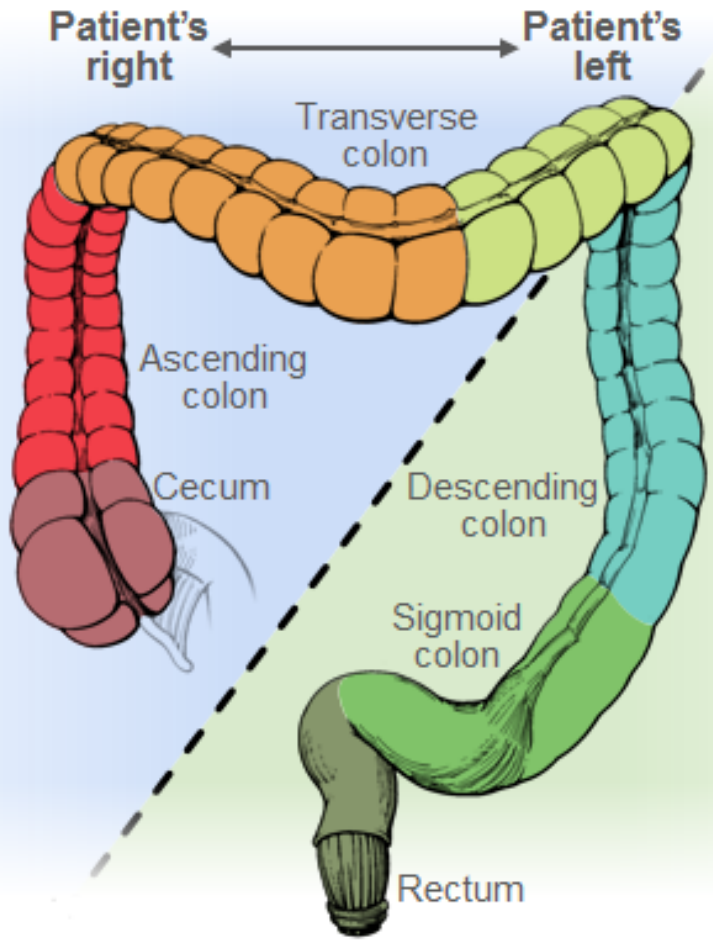
RIGHT vs. LEFT

MIDGUT DERIVATIVE

- ↑ females
- ↑ sessile serrated lesions
- ↑ mucinous tumors

Overall WORSE prognosis

- ↑ CIMP-high
- ↑ BRAF
- ↑ MSI-high
- ↑ CMS-1-MSI immune tumors
- ↑ CMS-3-metabolic tumors
  (↑ KRAS)



HINDGUT DERIVATIVE

- ↑ males

Overall BETTER prognosis

- ↑ CMS-4-MSI mesenchymal
- ↑ CMS-2-canonical distally
- ↑ TP53
- ↑ APC

EGFR → RAS → $BRAF^{V600E}$ → MEK → ERK

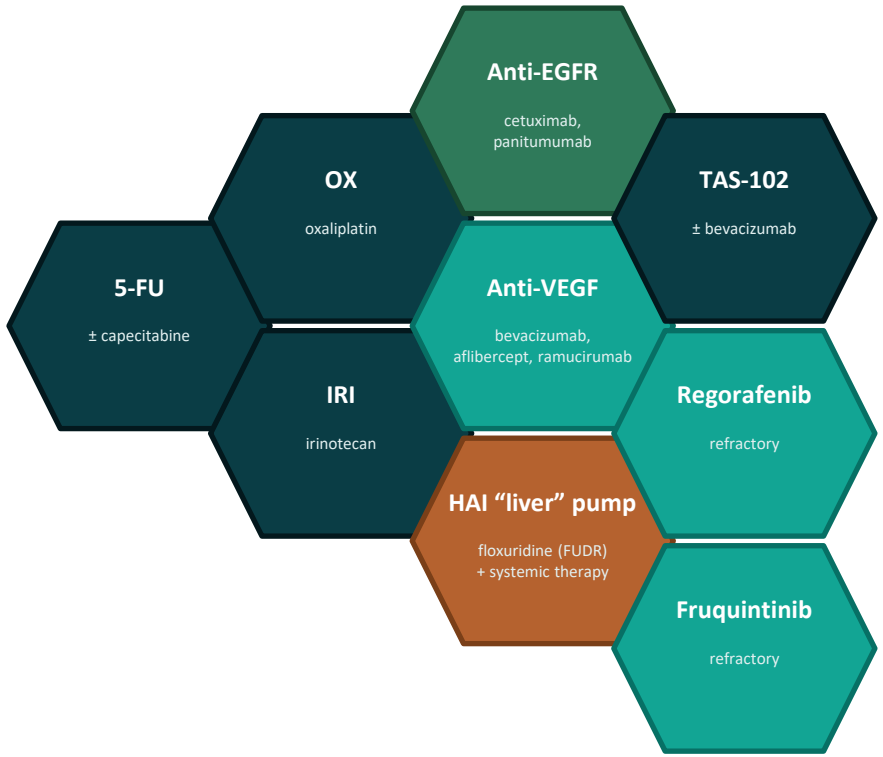
@pashtoonkasi

Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

THE LANDSCAPE ON ONE SLIDE

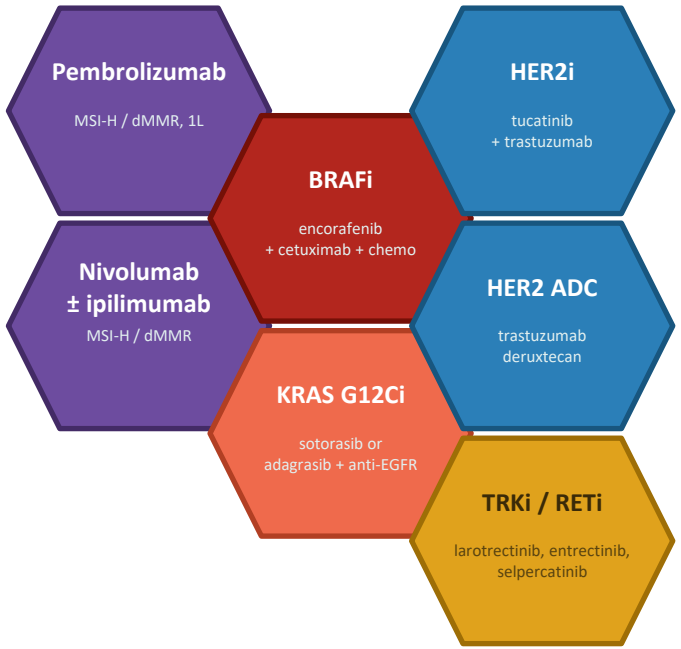
FDA-approved options in metastatic colorectal cancer, 2026

AVAILABLE TO EVERY PATIENT



Backbone + biologic partner and/or regional therapy → later lines

REQUIRES A BIOMARKER RESULT



Immunotherapy for dMMR/MSI-High versus targeted therapies driven by alteration

Legend

- Cytotoxic backbone
- Anti-EGFR
- Antiangiogenic
- Liver-directed
- Immunotherapy
- BRAF V600E
- KRAS G12C
- HER2 amplified
- NTRK / RET fusion

Red marks BRAF V600E — historically the poorest-prognosis subgroup in metastatic disease.

Biomarker required first

- MSI-H / dMMR → pembrolizumab, nivolumab ± ipilimumab
- BRAF V600E → encorafenib + cetuximab + chemotherapy
- HER2+ and RAS WT → tucatinib + trastuzumab, T-DXd
- KRAS G12C → G12C inhibitor + anti-EGFR
- NTRK / RET fusion → TRK or RET inhibitor
- RAS/BRAF WT and left-sided → anti-EGFR

Hepatic arterial infusion

Floxuridine via implanted pump with systemic therapy, for liver-limited or liver-dominant disease, at experienced centers.

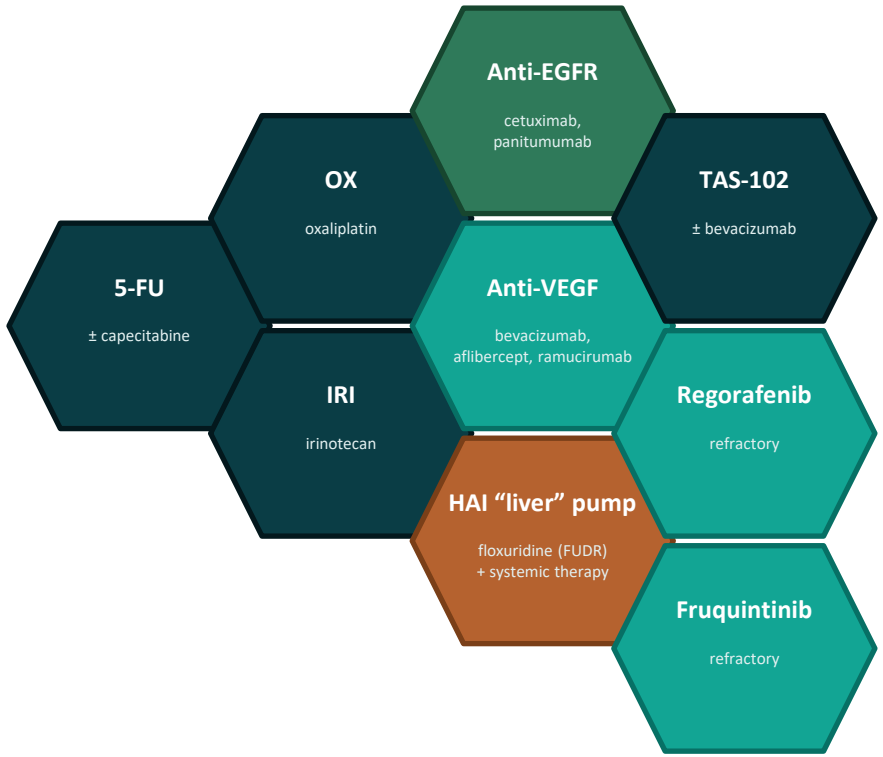
FDA-approved options only; several carry accelerated approval. Concept adapted and updated from Kasi PM et al. Lancet 2019. Trastuzumab deruxtecan is approved tumor-agnostically for HER2 IHC 3+ solid tumors.

X: @pashtoonkasi

THE SAME LANDSCAPE, MECHANISTICALLY

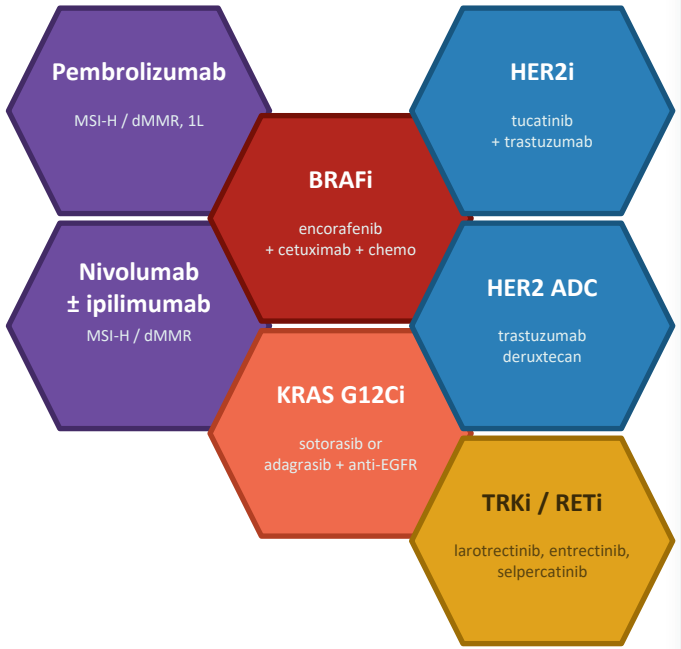
Where the drugs act on the RAS/RAF cascade

AVAILABLE TO EVERY PATIENT



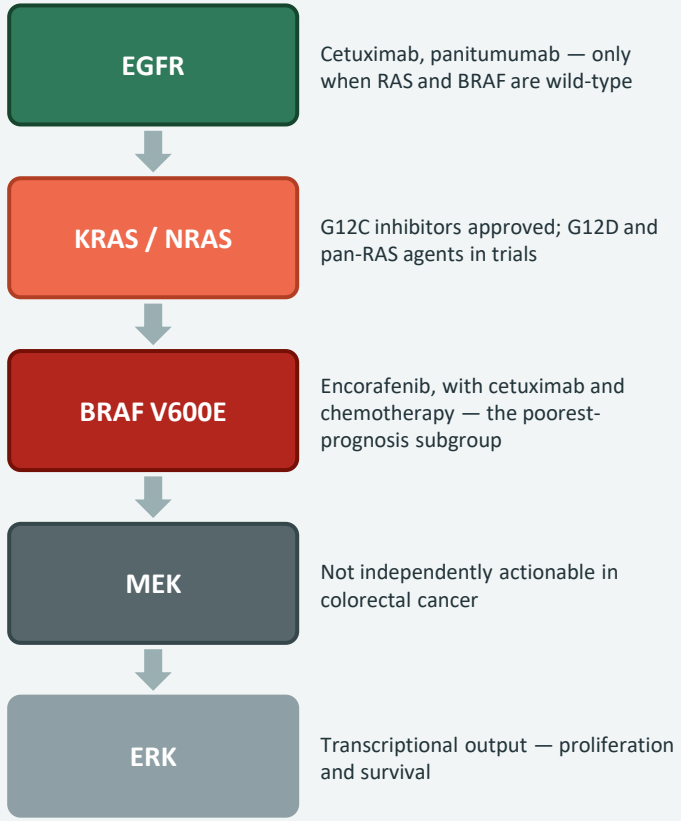
Backbone + biologic partner and/or regional therapy → later lines

REQUIRES A BIOMARKER RESULT



Immunotherapy for dMMR/MSI-High versus targeted therapies driven by alteration

RAS / RAF SIGNALLING



HER2 (blue on the left) signals into this same cascade — amplification predicts anti-EGFR failure. Only two nodes are directly druggable in colorectal cancer today, which is why the pathway is attacked in combination rather than at a single point.

FDA-approved options only; several carry accelerated approval. Concept adapted and updated from Kasi PM et al. Lancet 2019. Trastuzumab deruxtecan is approved tumor-agnostically for HER2 IHC 3+ solid tumors.

X: @pashtoonkasi

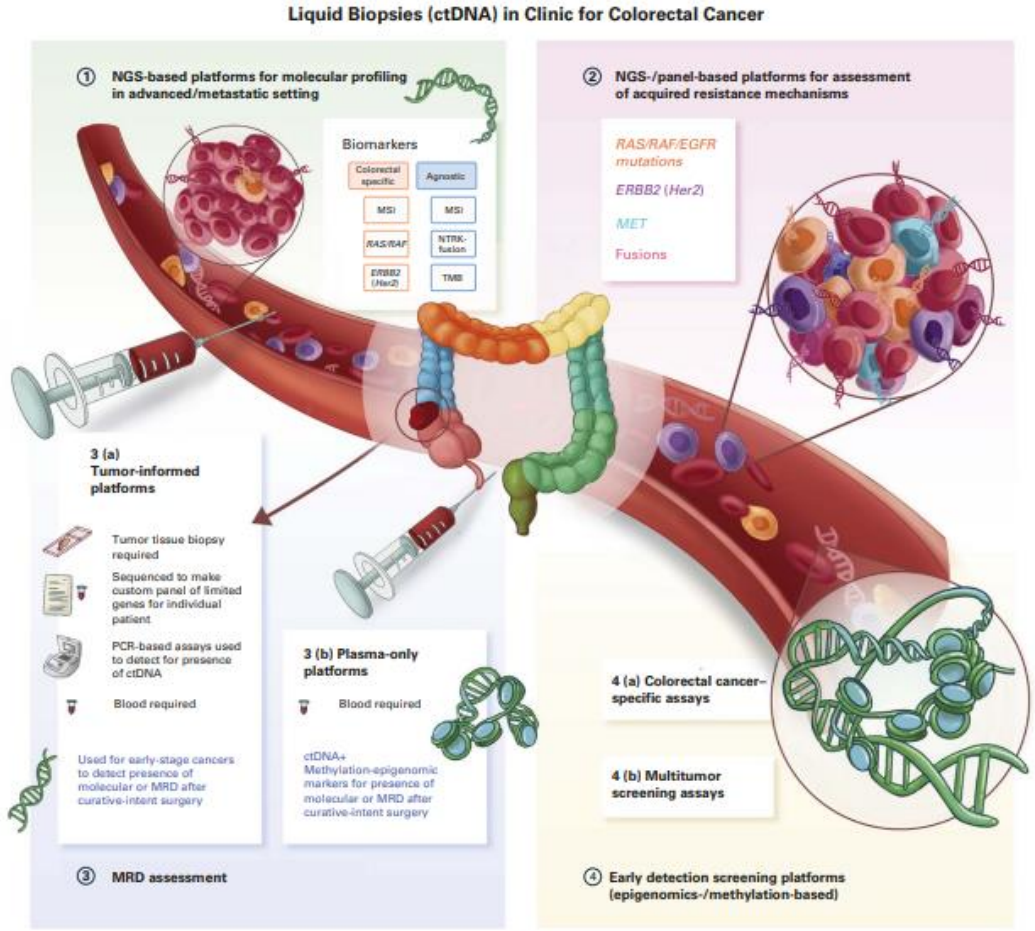
SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices

Midhun Malla, MD, MS[1]; Jonathan M. Loree, MD, MS[2]; Pashtoon Murtaza Kasi, MD, MS[3]; and Aparna Raj Parikh, MD[4]

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

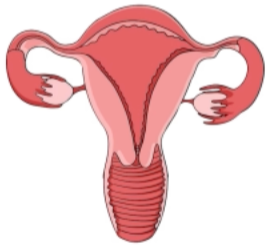
194
Downloaded 6,674 times



Opportunities for Precision Medicine are Missed Up to 30% of the Time

Frequency of tissue insufficiency

OVARIAN CANCER [1]



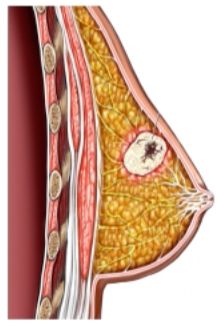
~10%

GI CANCERS [1-2]



~10%

BREAST CANCER [1-3]



~20%

BILIARY TRACT CANCERS [4]



~25%

NSCLC [5-6]



~30%

PROSTATE CANCER [7]



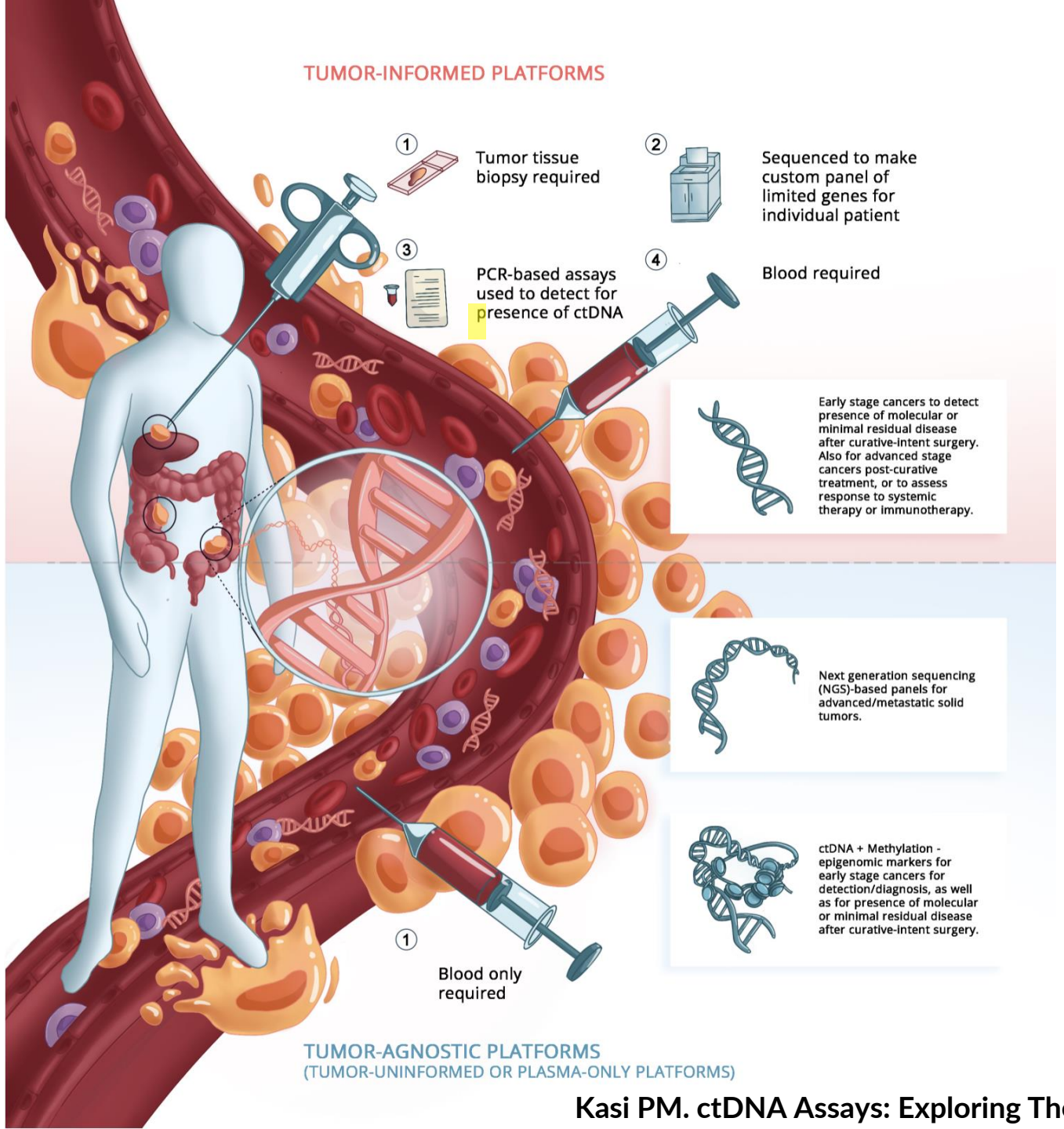
~30%

GI = gastrointestinal, NSCLC = non-small cell lung cancer

1. Zehir A, Benayed R, Shan RH, et al. *Nat Med*. 2017;23(6):703-713; 2. Nakamura Y, Taniguchi H, Ikeda M, et al. *Nat Med*. 2020;26(12):1859-1846; 3. Meric-Bernstam F, Brusco L, Shaw K, et al. *J Clin Oncol*. 2015;33(25):2753-2762; 4. Lamarca A, Kapacee Z, Breeze M, et al. *J Clin Med*. 2020;9(9):2854; 5. Hagemann IS, Devarakonda S, Lockwood CM, et al. *Cancer*. 2015;121(4):631-639; 6. Aggarwal C, Thompson JC, Black TA, et al. *JAMA Oncol*. 2019;5(2):173-180; 7. Hussain M, Corcoran C, Sibilla C, et al. *Clin Cancer Res*. 2022;28(8):1518-1530.

1 Settings/Platforms/Biology

Going from whole-exome based testing to whole-genome based testing



Tumor-informed Platforms Versus Tumor-agnostic (tumor-uninformed or plasma-only) Platforms

ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

MRD assays: how low can we see?

Tumor-agnostic

Plasma only

- No tissue needed
- Mutations, methylation, fragmentomics
- Lower sensitivity at low tumor burden

Tumor-informed (WES)

Exome-guided panel

- Tracks ~16–50 patient-specific variants
- Filters CHIP by design
- Detection ~1 in 10,000 molecules

Tumor-informed (WGS)

Genome-wide signature

- Tracks thousands of variants
- Detection in the parts-per-million range
- Best suited to post-procedure, low-shed settings



Detection limits are approximate and assay-dependent.

Units of Measurement

VAF%

- Variant Allele Fraction

VAF represents the percentage of sequencing reads that support a specific variant allele relative to the total number of reads at that genomic locus

MTM

- Mean Tumor Molecules/ml

Absolute measurement

Focuses on the number of target molecules in a given volume

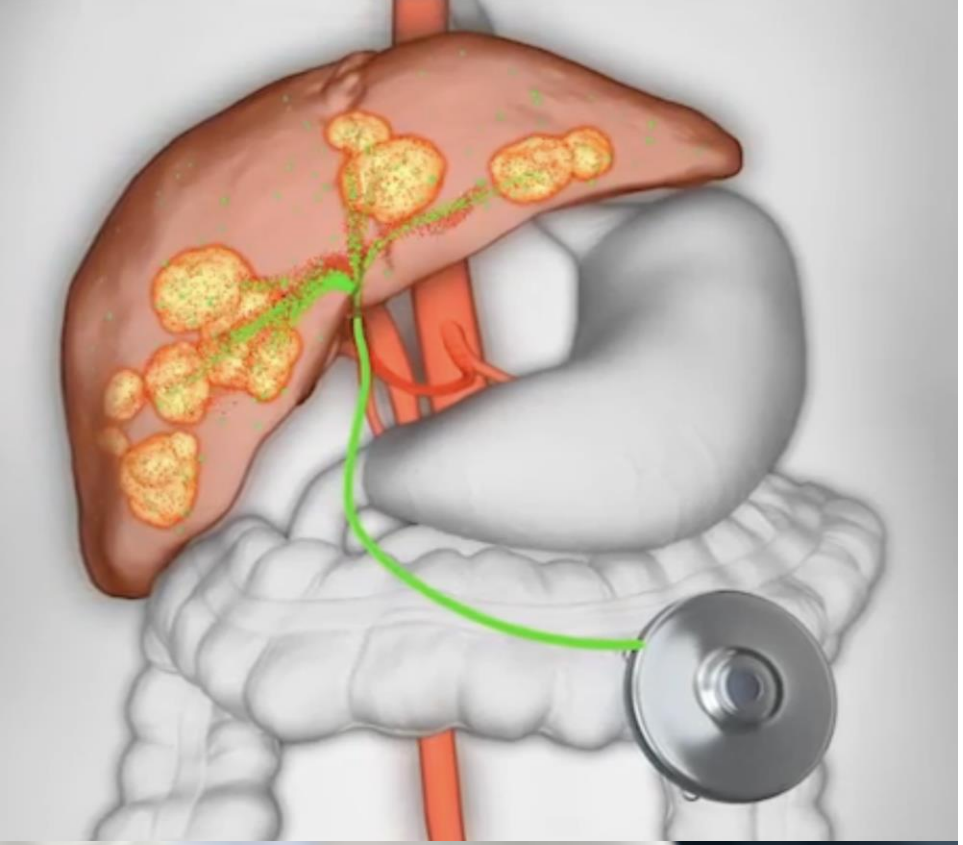
PPM

- Parts per million

Relative measurement

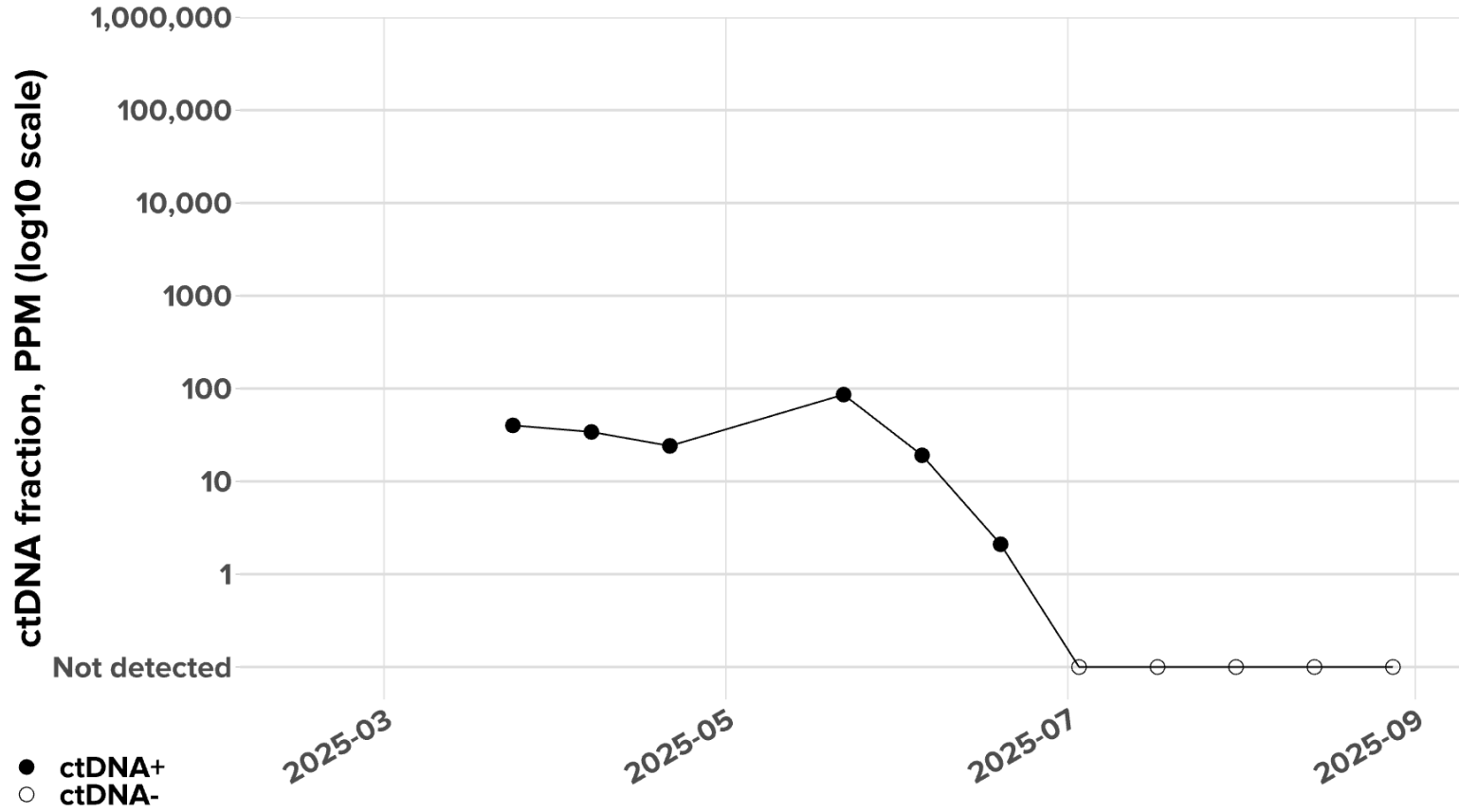
Focuses on the ratio of ctDNA molecules containing MRD targets out of the total cfDNA molecules measured (ctDNA + normal cfDNA)

1.67 parts per million (PPM) = 1.67×10^{-6} tumor fraction = 0.000167% VAF





Longitudinal results



Result History

2025-08-28	**Not detected**	Not applicable
2025-08-14	**Not detected**	Not applicable
2025-07-31	**Not detected**	Not applicable
2025-07-17	**Not detected**	Not applicable
2025-07-03	**Not detected**	Not applicable
2025-06-19	**Detected**	2 PPM
2025-06-05	**Detected**	19 PPM
2025-05-22	**Detected**	86 PPM
2025-04-21	**Detected**	24 PPM
2025-04-07	**Detected**	34 PPM
2025-03-24	**Detected**	40 PPM

1 Can we reliably use ctDNA kinetics?

Does it correspond with outcomes (response/overall survival)?

ctDNA as a rapid surrogate of tumor response



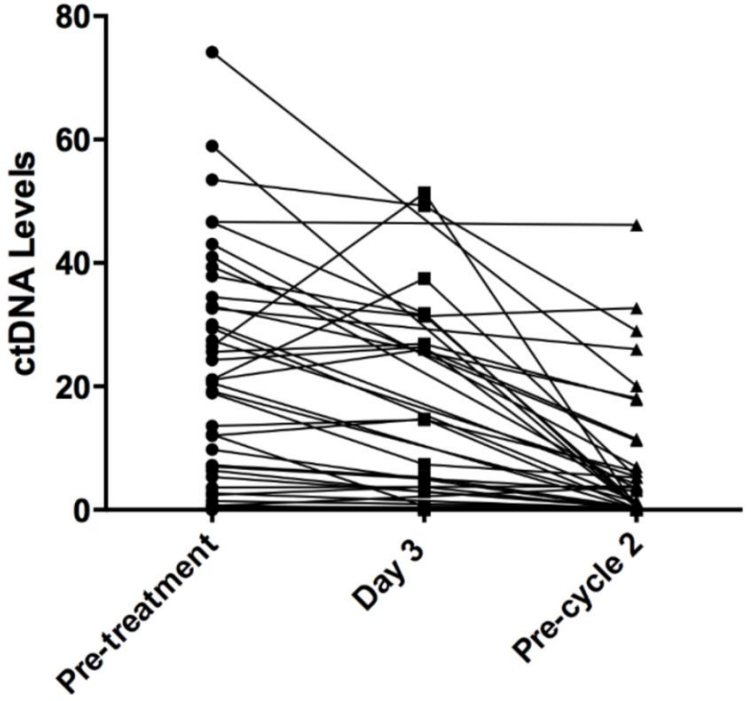
Half-life of ctDNA in circulation is measured in minutes/hours

Protein markers (CEA) may have half-life of days, with post-treatment spikes

Similar findings also seen in urinary ctDNA.

Husain et al CCR ‘17

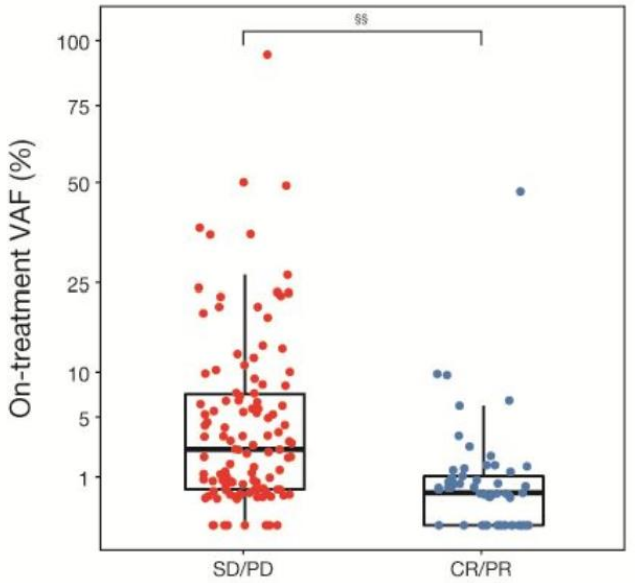
ctDNA levels fall >90% in 2 weeks in responding CRC patients

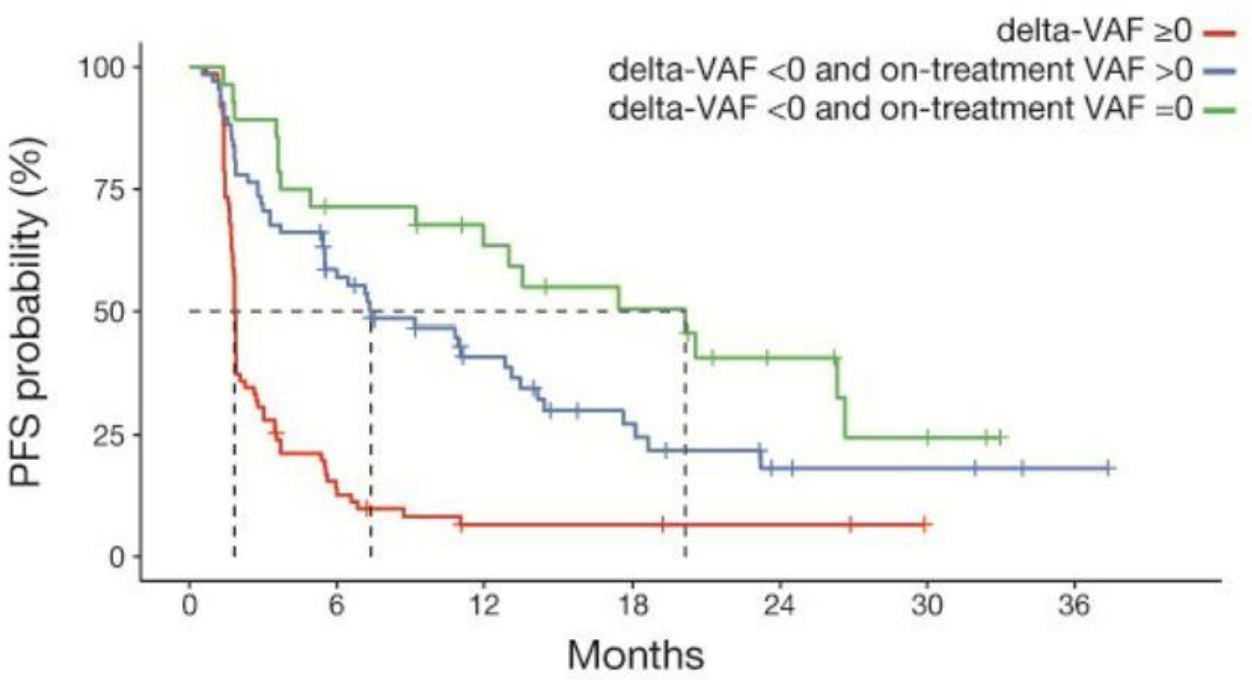


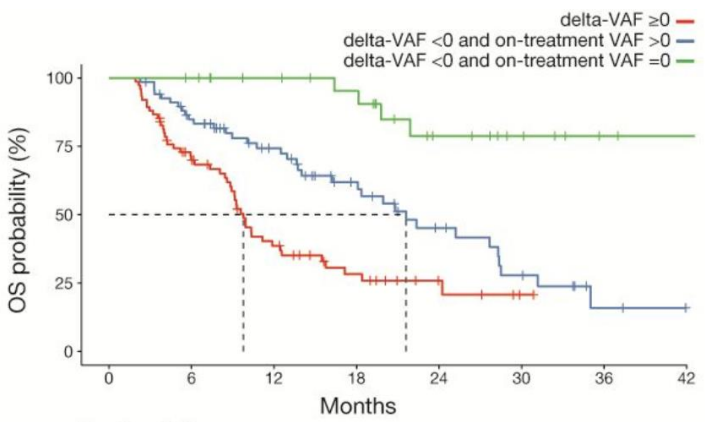
Tie et al Annals Oncology ‘15

CANCER DISCOVERY

August 14, 2020

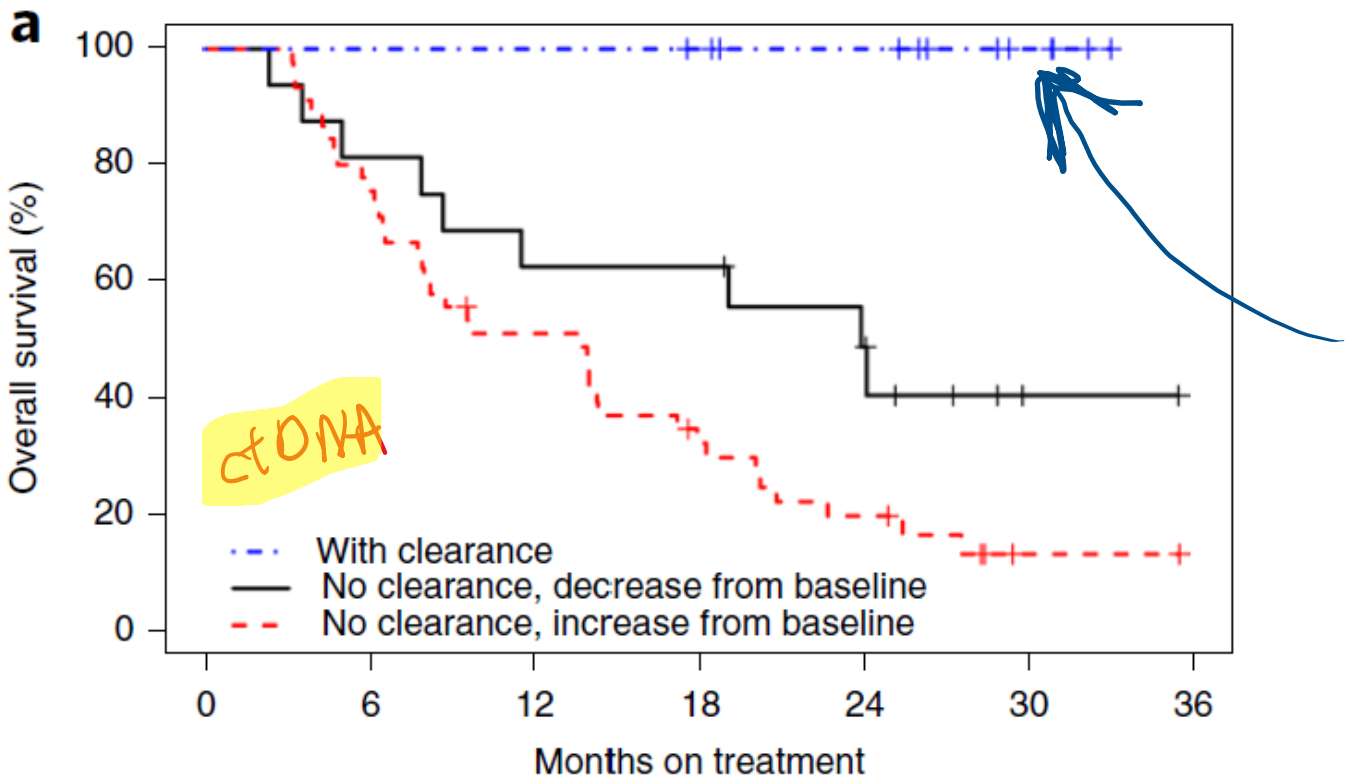


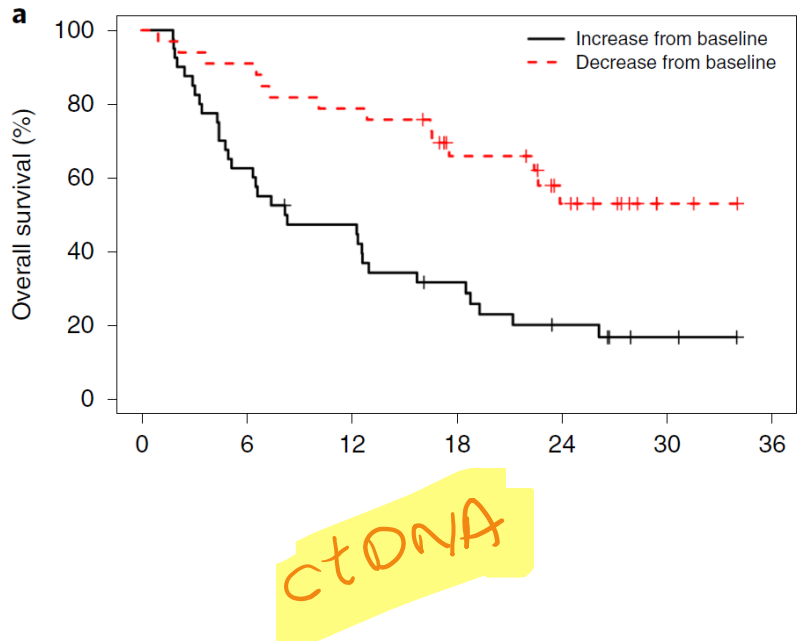


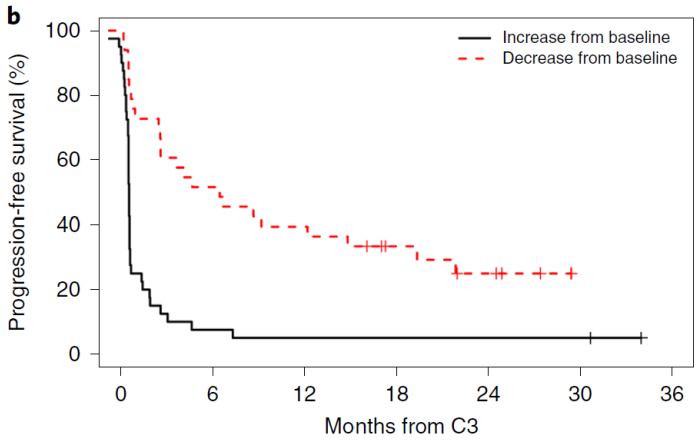


nature cancer

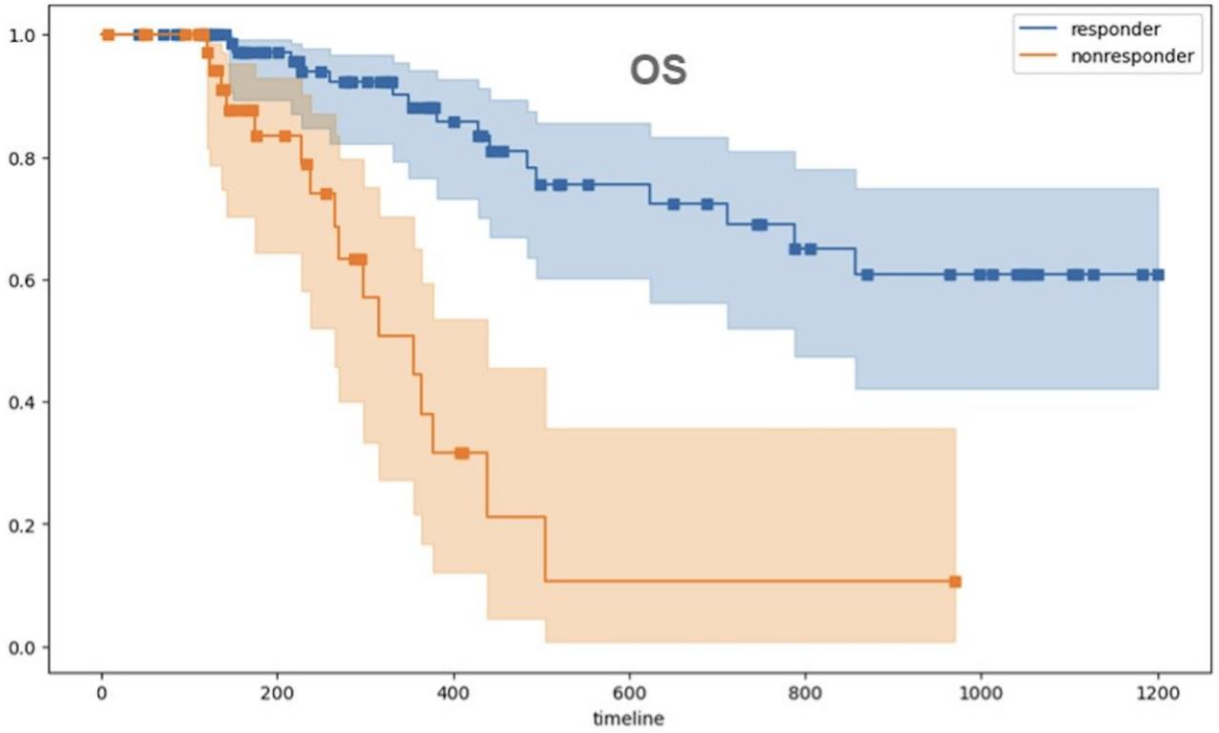
03 August 2020







ctDNA response assessment and survival



Clinical outcome	Cohort	MR category	Median in months [CI]
OS	Chemotherapy	non-responder	11.8 [8.7-14.6]
		responder	**NR [26.3-NR]**
	All regimens	non-responder	17.8 [10.5-23.4]
		responder	**NR [23.7-NR]**
TTNT	Chemotherapy	non-responder	5.8 [4.0-7.5]
		responder	**10.3 [7.3-NR]**
	All regimens	non-responder	6.1 [4.5-7.6]
		responder	10.1 [8.2-16.1]

Kasi PM, ASCO GI, 2023. J Clin Oncol 41, 2023 (suppl 4; abstr 246).

ASCO Daily News®

Kinetics of Liquid Biopsies in Predicting Response to Immunotherapy

October 1, 2020

Pashtoon M. Kasi, MD, MS

@pashtoonkasi

3 Biology

Pre-analytical variables

Tumor heterogeneity “Shedding”

Cannot forget biology; high shedders versus low shedders

Precision Medicine and Imaging

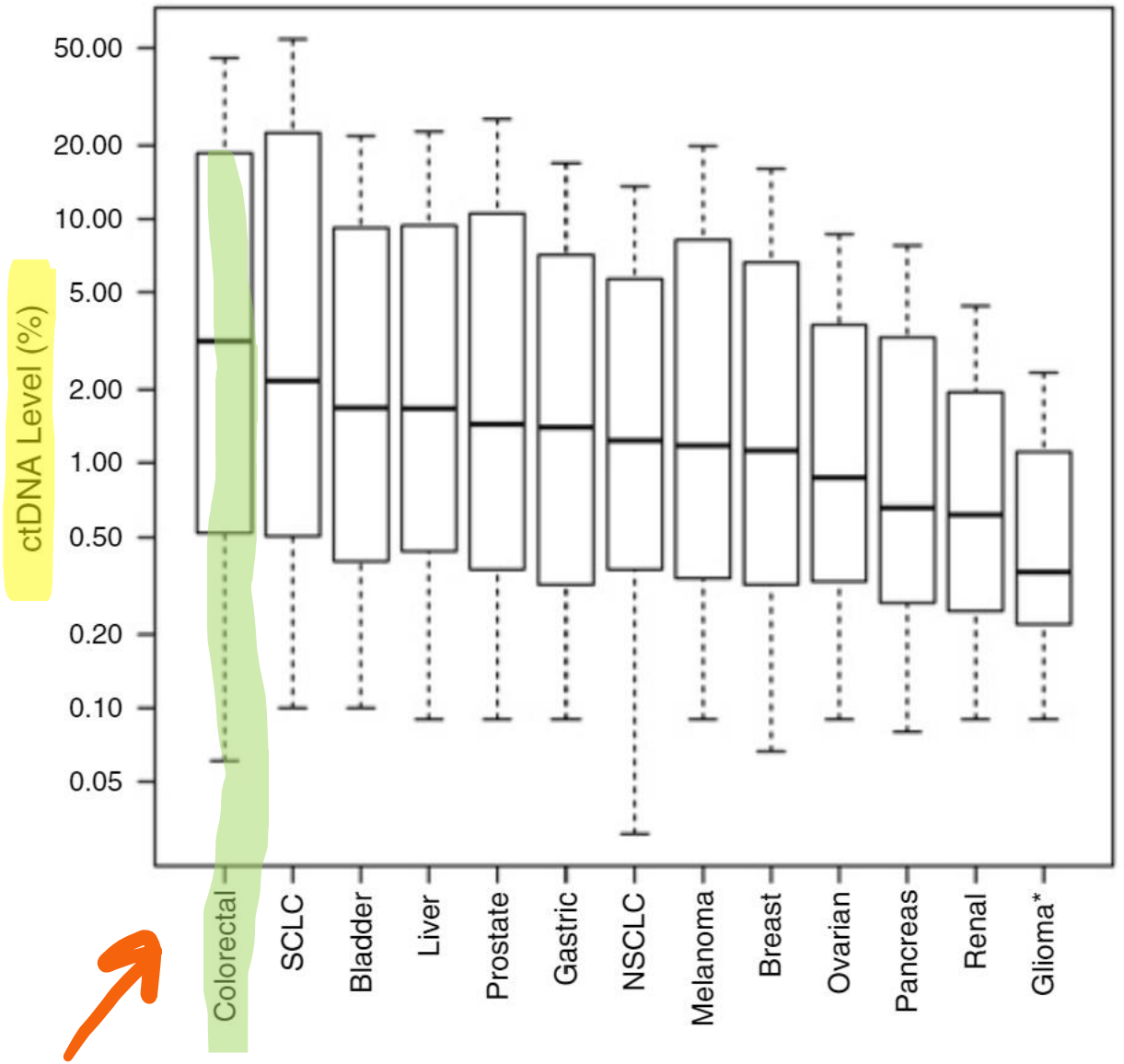
Clinical Cancer Research

The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients

Oliver A. Zill[1], Kimberly C. Banks[1], Stephen R. Fairclough[1], Stefanie A. Mortimer[1], James V. Vowles[1], Reza Mokhtari[1], David R. Gandara[2], Philip C. Mack[2], Justin I. Odegaard[1], Rebecca J. Nagy[1], Arthur M. Baca[1], Helmy Eltoukhy[1], Darya I. Chudova[1], Richard B. Lanman[1], and AmirAli Talasaz[1]

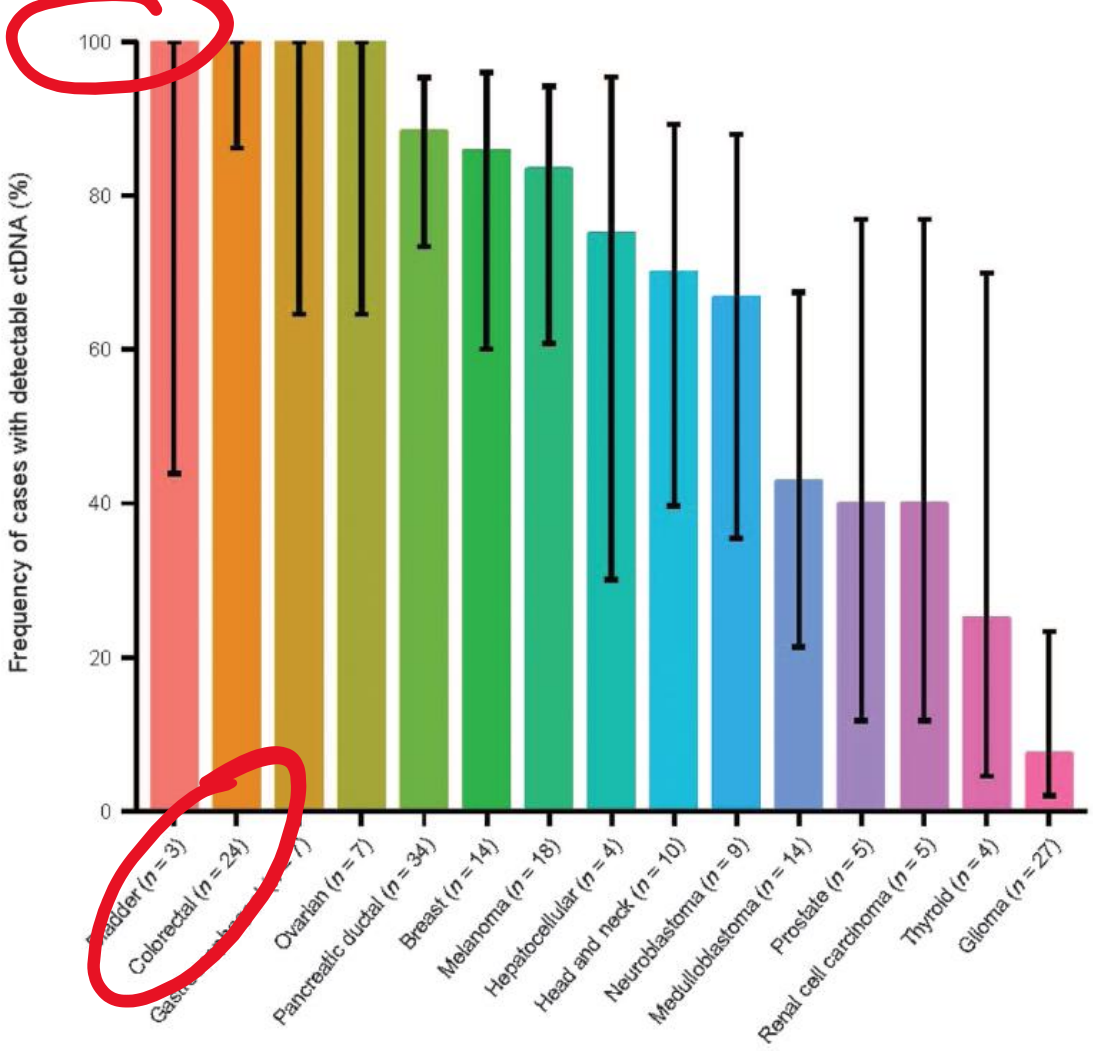
Clinical Cancer Research

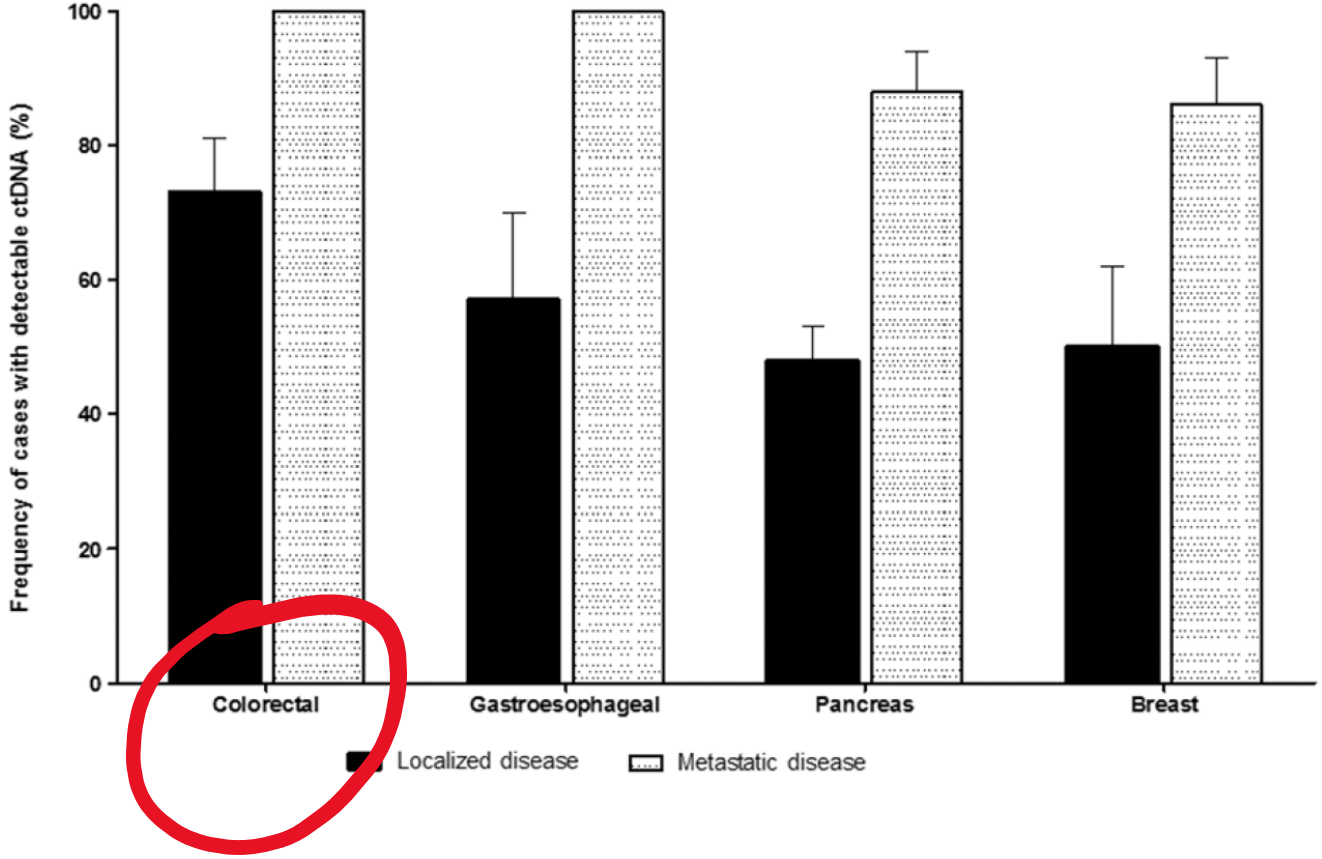
August 2018
Volume 24, Issue 15



@pashtoonkasi

Zill OA, et al. *Clin Cancer Res*. 2018;24:3528.





- Detectable levels of ctDNA
  - Varies between different tumors and between different stages of the tumor
  - 49 to 78% of patients with localized tumors and in 86 to 100% of patients with metastatic tumors of these four types

(Bettegowda, Sausen et al. 2014)

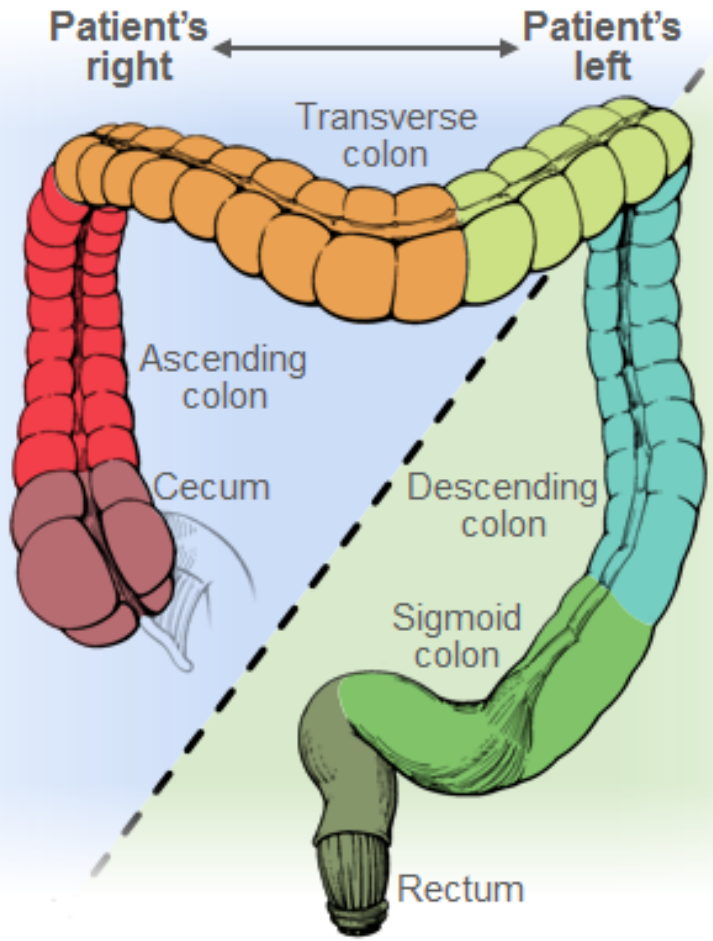
RIGHT vs. LEFT

MIDGUT DERIVATIVE

- ↑ females
- ↑ sessile serrated lesions
- ↑ mucinous tumors

Overall WORSE prognosis

- ↑ CIMP-high
- ↑ BRAF
- ↑ MSI-high
- ↑ CMS-1-MSI immune tumors
- ↑ CMS-3-metabolic tumors
  (↑ KRAS)



HINDGUT DERIVATIVE

- ↑ males

Overall BETTER prognosis

- ↑ CMS-4-MSI mesenchymal
- ↑ CMS-2-canonical distally
- ↑ TP53
- ↑ APC

EGFR → RAS → $BRAF^{V600E}$ → MEK → ERK

@pashtoonkasi

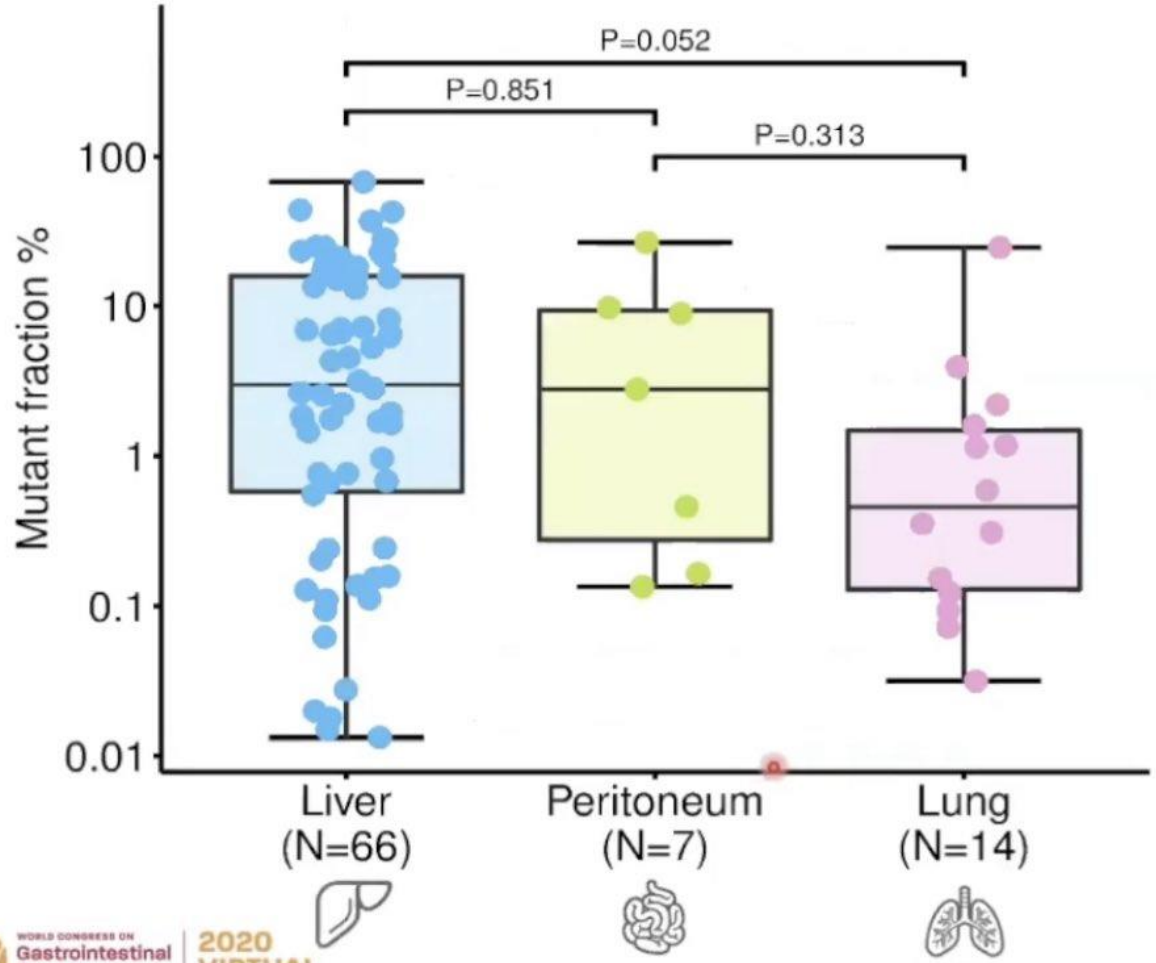
Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.



Lee J, et al: Multimodal circulating tumor DNA (ctDNA) colorectal neoplasia detection assay for asymptomatic and early-stage colorectal cancer (CRC). ***Journal of Clinical Oncology*** *39:3536-3536,* ***2021***

ctDNA excretion from each metastatic site

Among cases with *RAS* mutation by plasma-BEAMing (n=87)*



		Tissue		Total
		MT	WT	
Plasma	MT	79	8	87
	WT	25	112	137
Total		104	120	224

* Excluding the cases with *RAS* wild type by plasma assay

**derived from Kruskal-Wallis test with Holm method

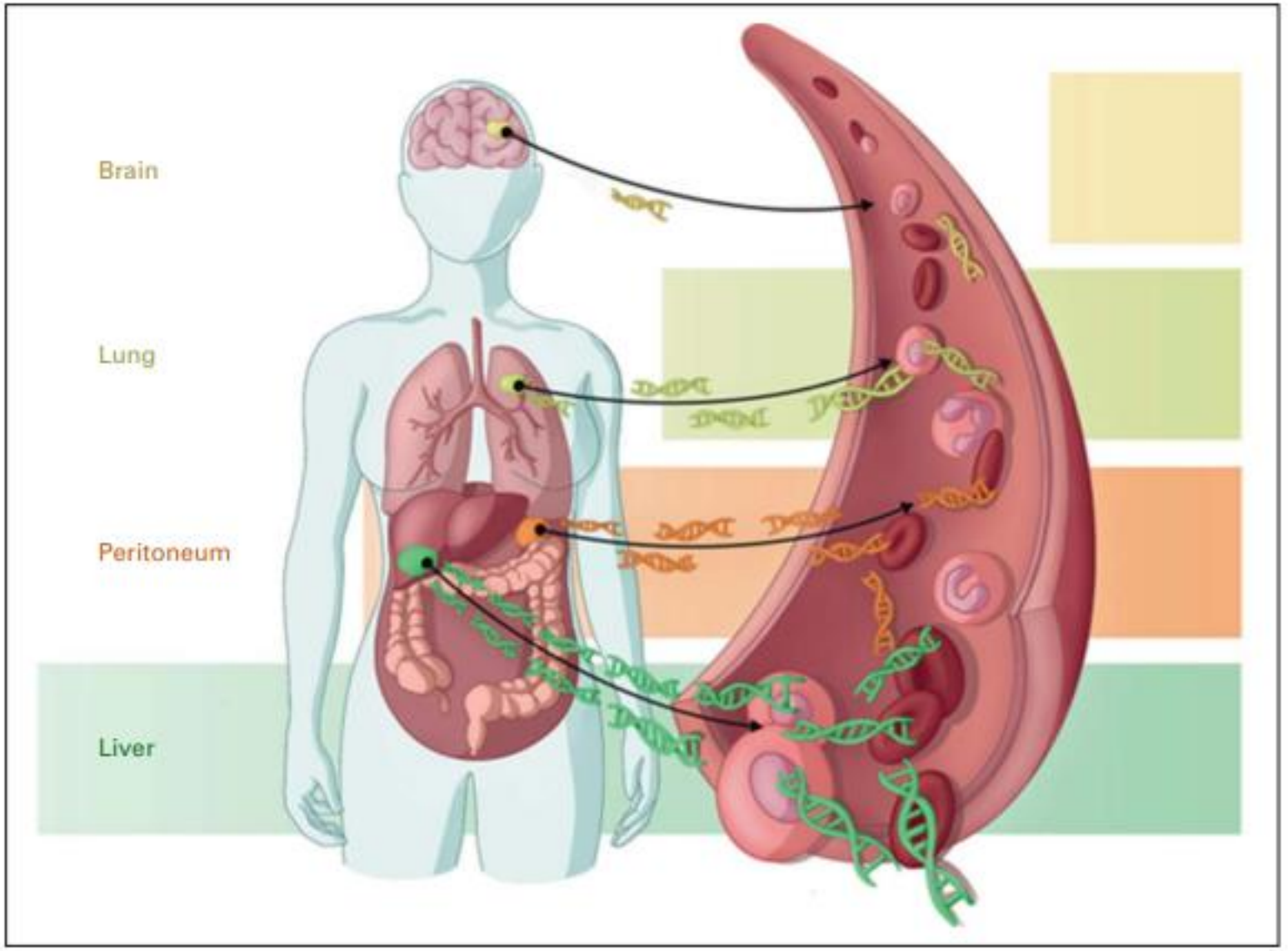
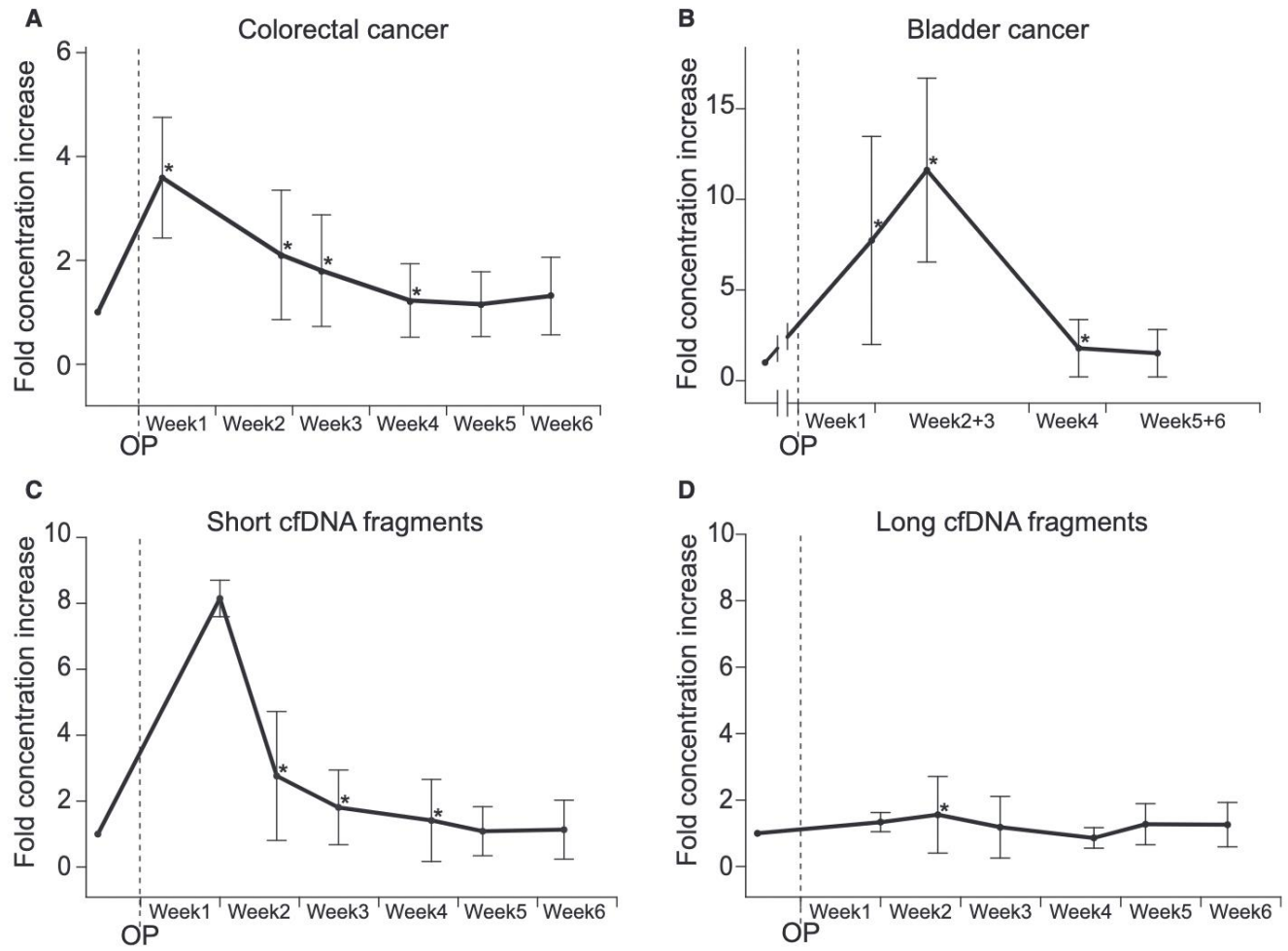


FIG 1. Shedding and amount of detectable circulating tumor DNA varies by location of metastatic site. Liver metastases appear to shed the most DNA, followed by the peritoneum and lung.

Kasi PM, Fehringer G, Aleshin A, Kopetz S. Reply to F. Dayyani et al. **JCO Precis Oncol**. 2022 Jul;6:e2200275. doi: 10.1200/PO.22.00275. PMID: 35834757.



Surgical trauma induced **cfDNA** affects **ctDNA** detection

Henriksen TV. **The effect of surgical trauma on circulating free DNA levels in cancer patients-implications for studies of circulating tumor DNA**. Mol Oncol. 2020 Aug;14(8):1670-1679.

ctDNA kinetics around a procedure

Baseline
Pre-procedure tumor signal

→

Procedure
Resection, ablation, HAI

→

cfDNA surge
Normal DNA dilutes signal

→

MRD window
~2–10 weeks post-op

→

Surveillance
Serial draws every ~3 mo

Clearance is fast

- ctDNA half-life is roughly 2 hours (114 min in Diehl et al.)
- Complete removal should drop signal within days
- Persistent signal after the surge suggests residual disease

Timing is everything

- Tissue injury releases wild-type cfDNA
- Early draws dilute tumor fraction and risk false negatives
- A single negative test is not a cure; trends matter more

Diehl F, et al. Nat Med 2008. Kotani D, et al. Nat Med 2023 (GALAXY 4-week landmark); GALAXY CRLM update, ESMO GI 2026 (2–10 week window).

Post-procedure MRD is prognostic

2,240
Patients
Resected stage II–IV CRC

HR 12.0
Disease-free survival
MRD+ vs MRD−

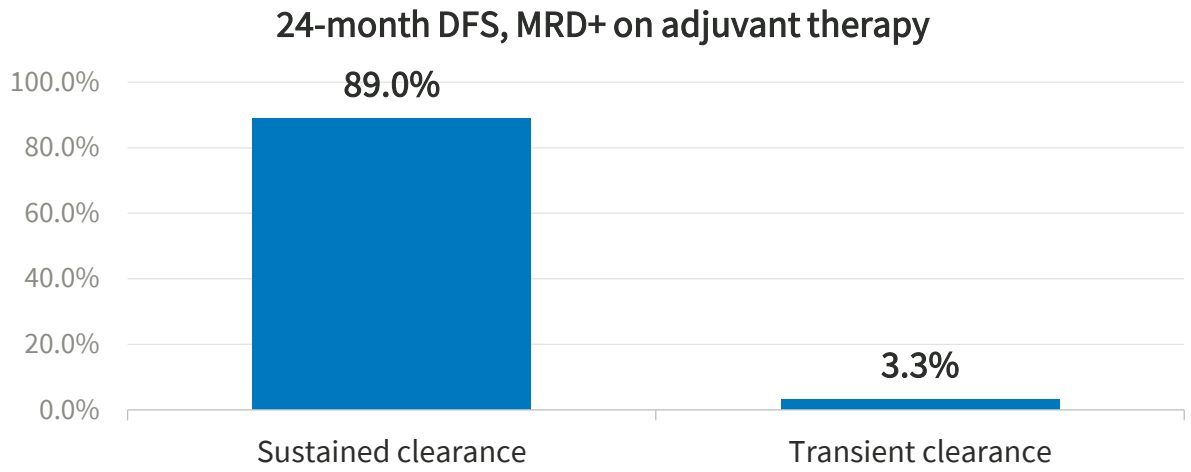
HR 9.7
Overall survival
MRD+ vs MRD−

1.9%
Spontaneous clearance
Without recurrence (2/105)

Sustained vs transient clearance

Among MRD-positive patients on adjuvant therapy, 24-month DFS depended on whether ctDNA clearance was sustained.

The trajectory, not the single result, predicts the outcome.



Nakamura Y, et al. Nat Med 2024 (CIRCULATE-Japan GALAXY; median follow-up 23 months).

Acting on MRD: humbling trials

DYNAMIC · Stage II colon

- ctDNA-guided vs standard management
- Adjuvant chemo use: 15% vs 28%
- 2-year RFS noninferior: 93.5% vs 92.4%

De-escalation worked

DYNAMIC-III · Stage III colon

- ctDNA-negative: 3-yr RFS 85.3% vs 88.1%; noninferiority not shown
- Oxaliplatin exposure: 34.8% vs 88.6%
- ctDNA-positive: chemo escalation did not improve RFS

Neither de-escalation nor escalation won

Negative ≠ cured. Positive ≠ fixable with more of the same. MRD+ patients need new mechanisms, not more cycles.

Tie J, et al. N Engl J Med 2022 (DYNAMIC). Tie J, et al. ESMO 2025 LBA9 / Nat Med 2025 (DYNAMIC-III).

The liver raises the stakes

49%

MRD+ after hepatectomy

63/129 evaluable, upfront surgery

HR 4.15

Disease-free survival

MRD+ vs MRD−

Why the HAI pump is an ideal MRD model

- Defined procedure date: a clean baseline for kinetics
- Liver-directed therapy controls hepatic disease; ctDNA reports on the whole body
- Serial draws on pump therapy capture response and escape in real time
- City of Hope Orange County: HAI pump program with 40+ patients treated
- Ongoing trial: CHAMP (NCT07842965), leronlimab + HAI + systemic chemotherapy

GALAXY CRLM update, ESMO GI 2026 Abstract 80.

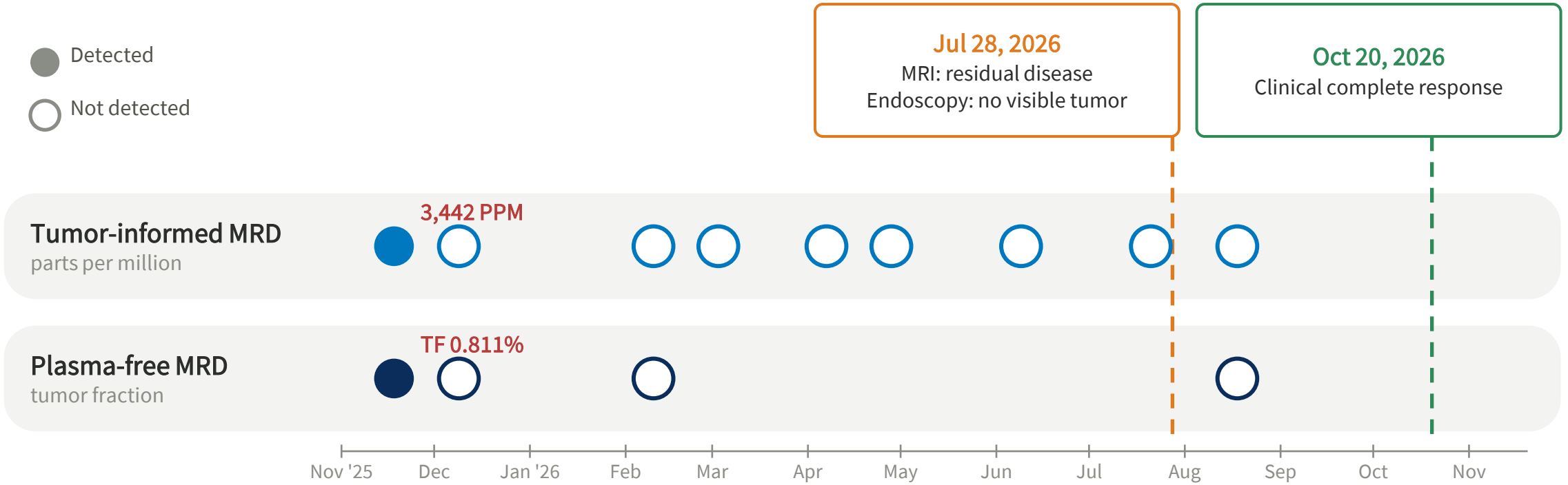
Matching kinetics to the procedure

Procedure	Clinical question	Kinetic to watch	Evidence
Endoscopic resection (T1 CRC, early esophageal)	Completion surgery after high-risk features?	Post-resection clearance	Emerging
Rectal TNT → watch and wait	Is the clinical complete response real?	Clearance on TNT; re-emergence	Emerging
Colectomy	Who needs adjuvant chemotherapy?	MRD status at 2–10 weeks	Strong
Hepatectomy / ablation	Adjuvant or liver-directed therapy?	Post-procedure MRD status	Moderate
HAI pump therapy	Is micrometastatic disease controlled?	Serial trajectory pattern	Investigational

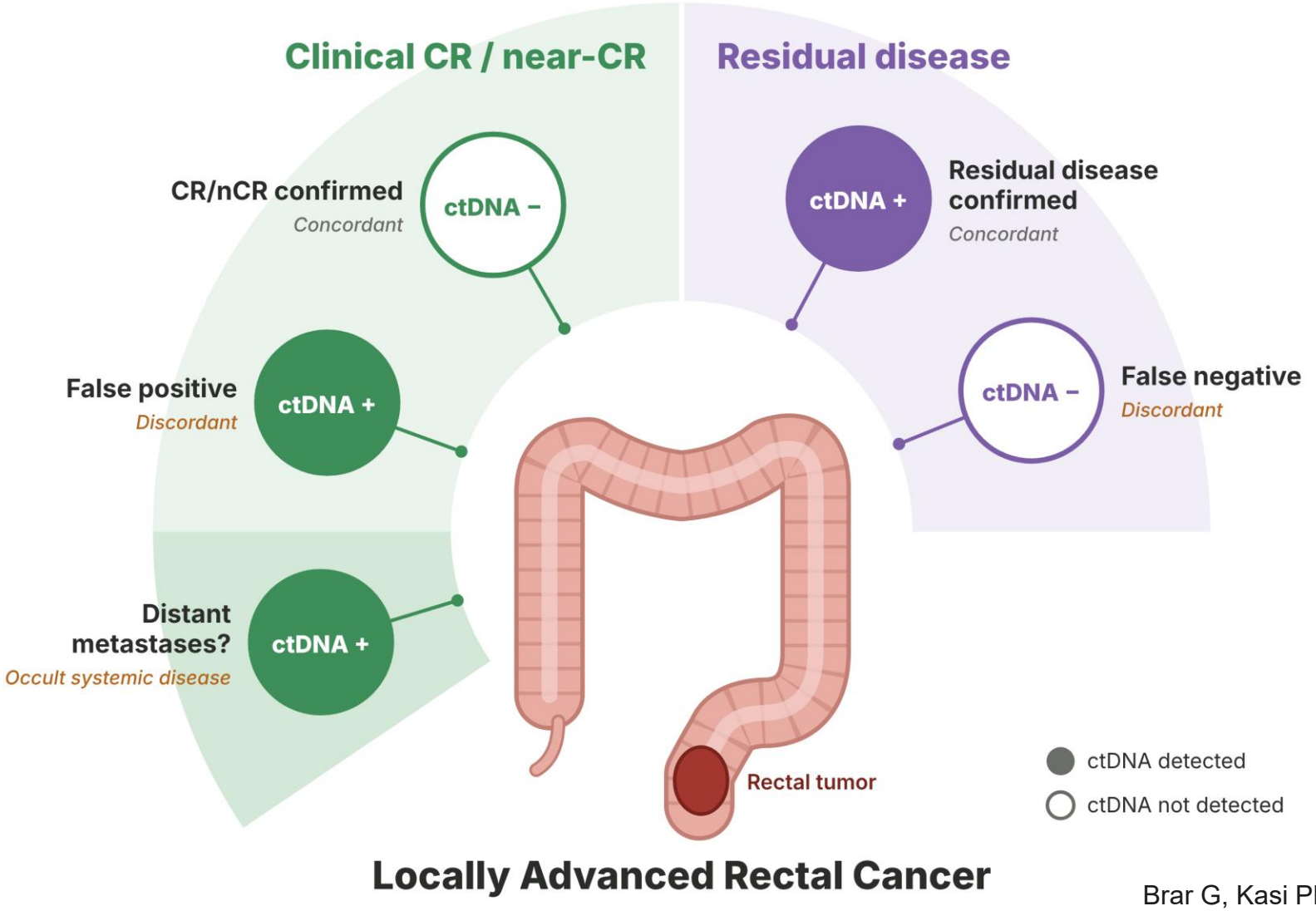
4 Rectal Cancer

Watch-and-Wait And Transanal/Endoscopic Treatment Options – utility and value of ctDNA

Case: MSI-High rectal Cancer on immunotherapy ctDNA cleared before MRI

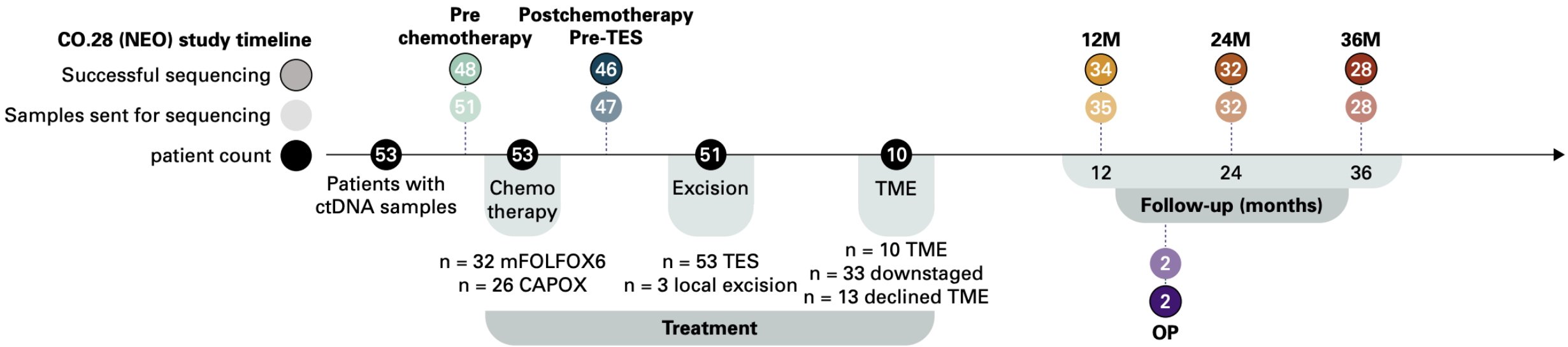


Cleared in 3 weeks; negative on 11 straight draws across 2 assays ~10 months before cCR

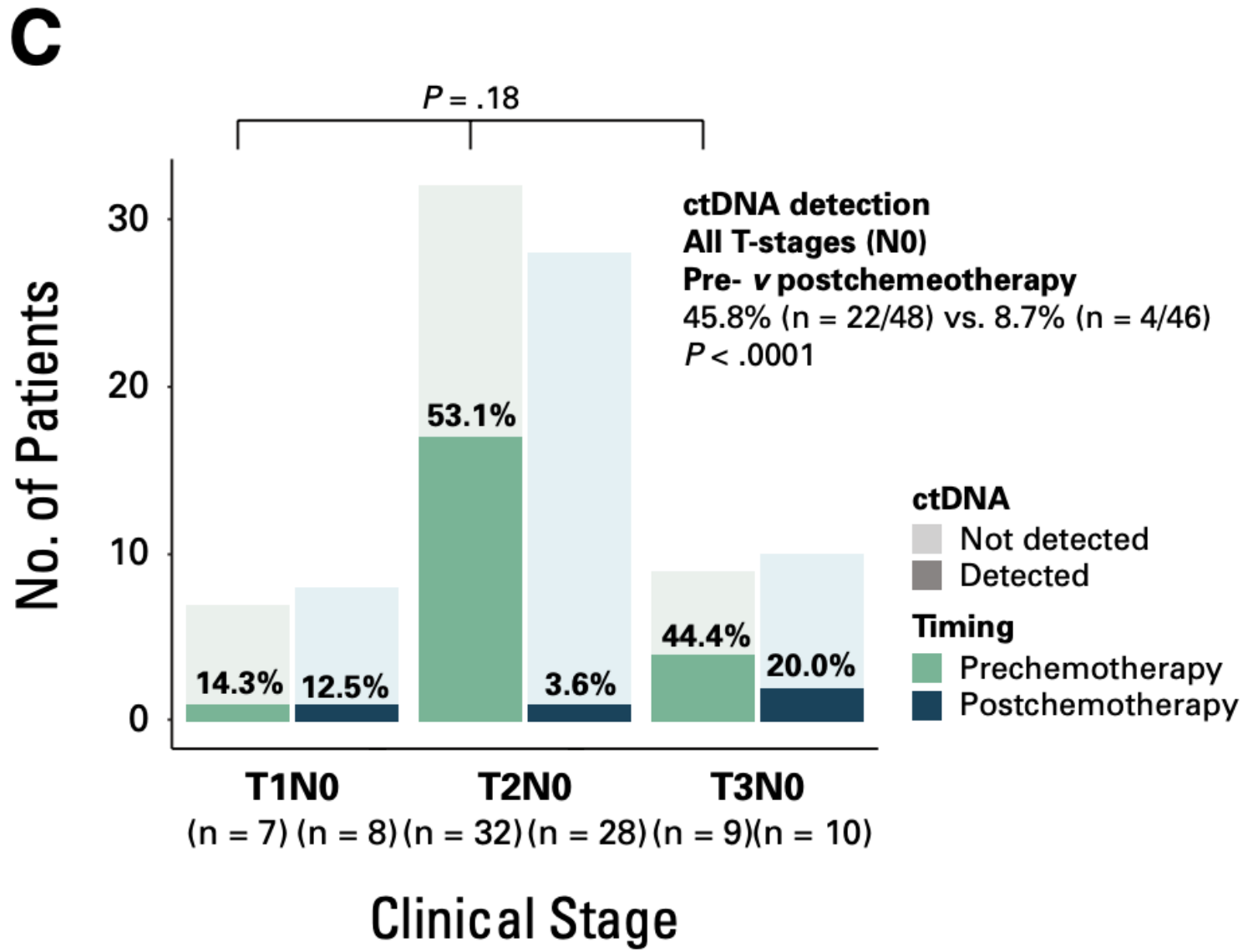


Brar G, Kasi PM. The utility of ctDNA in rectal cancer. Oncologist. 2025 Nov 11;30(11):oyaf354. PMID: 41143680.

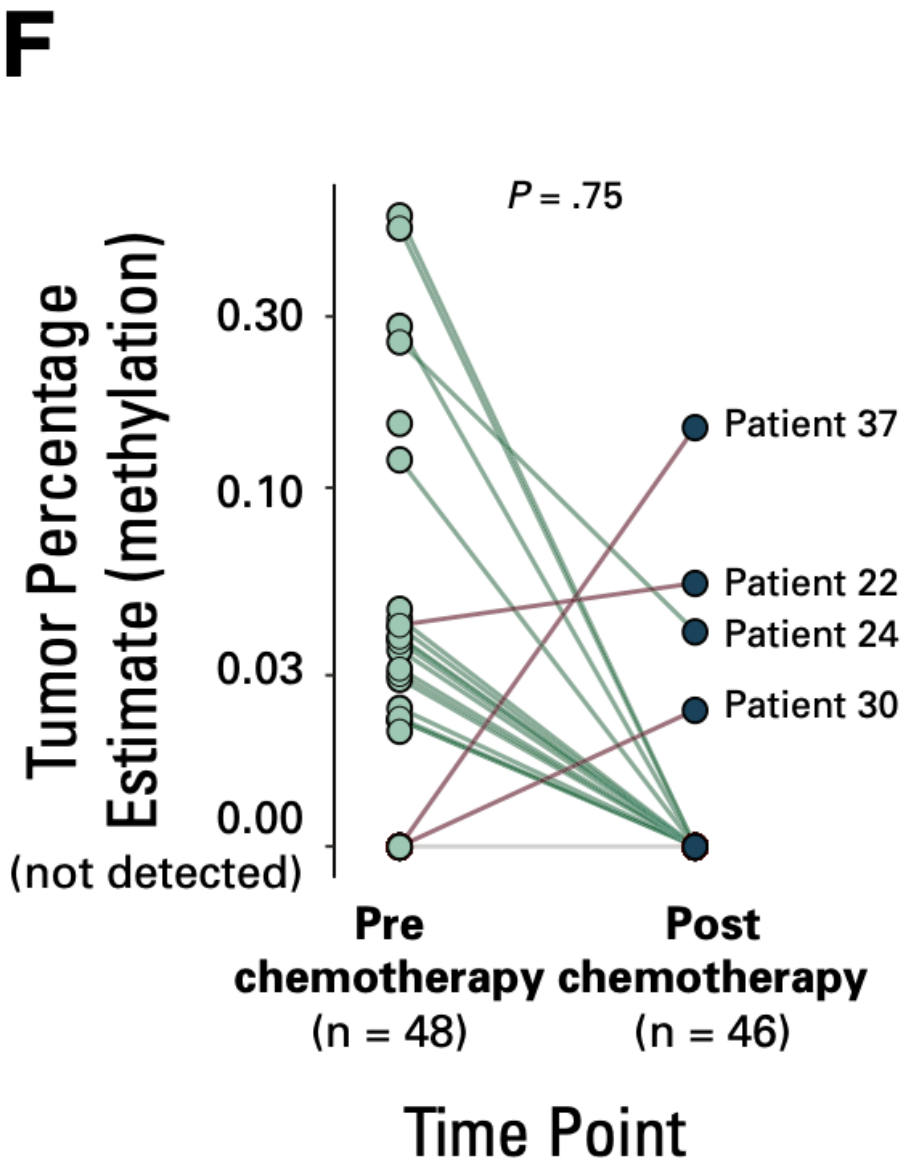
Phase II NEO Trial (CO.28)



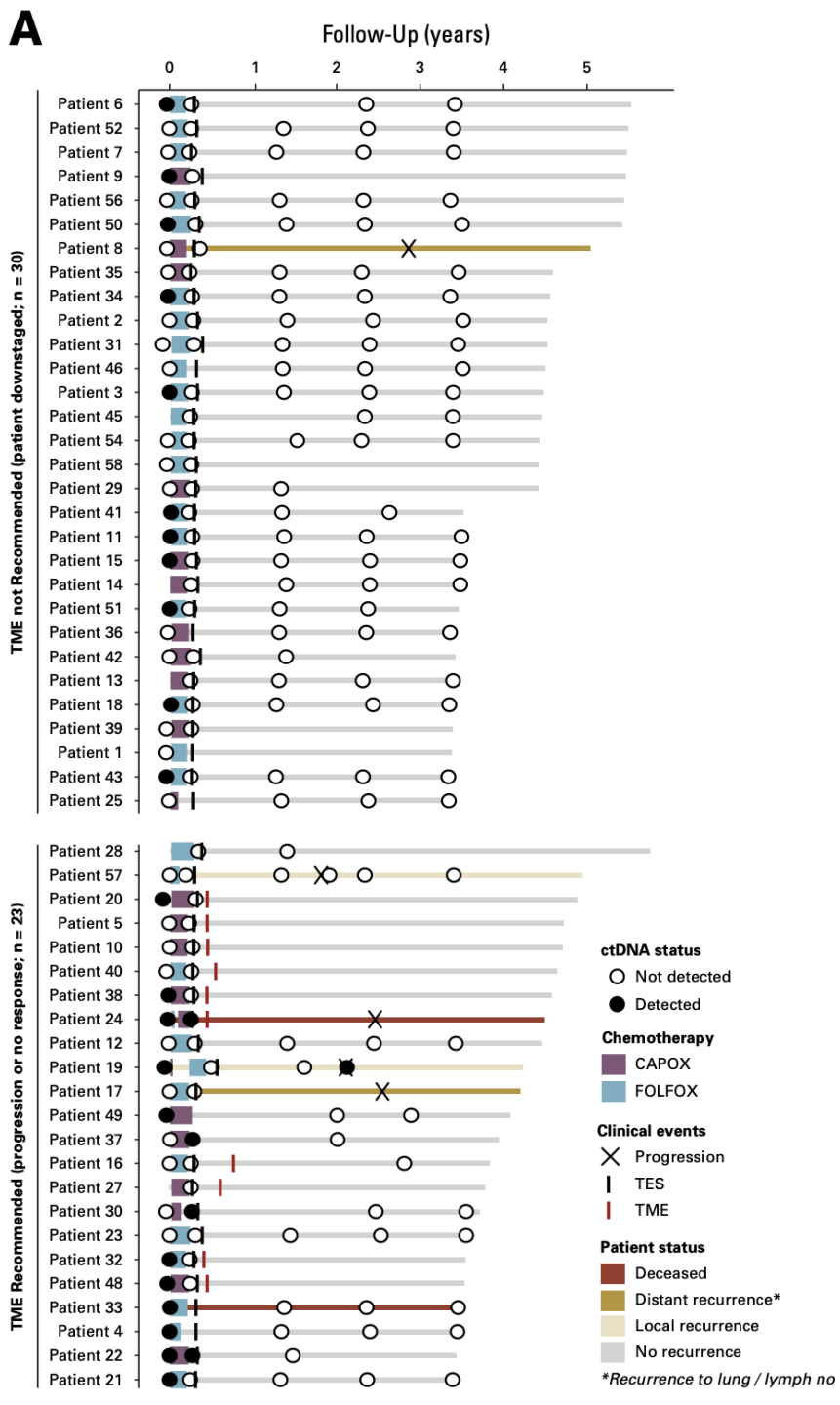
Loree JM, Titmuss E, Brown CJ, et al. Tumor-Free Circulating Tumor DNA in Node-Negative Rectal Cancers Undergoing Neoadjuvant Chemotherapy, Excision, and Observation in the Phase II NEO Trial (CO.28).
JCO Precis Oncol. 2026;10(10):e2600459. doi:10.1200/PO-26-00459

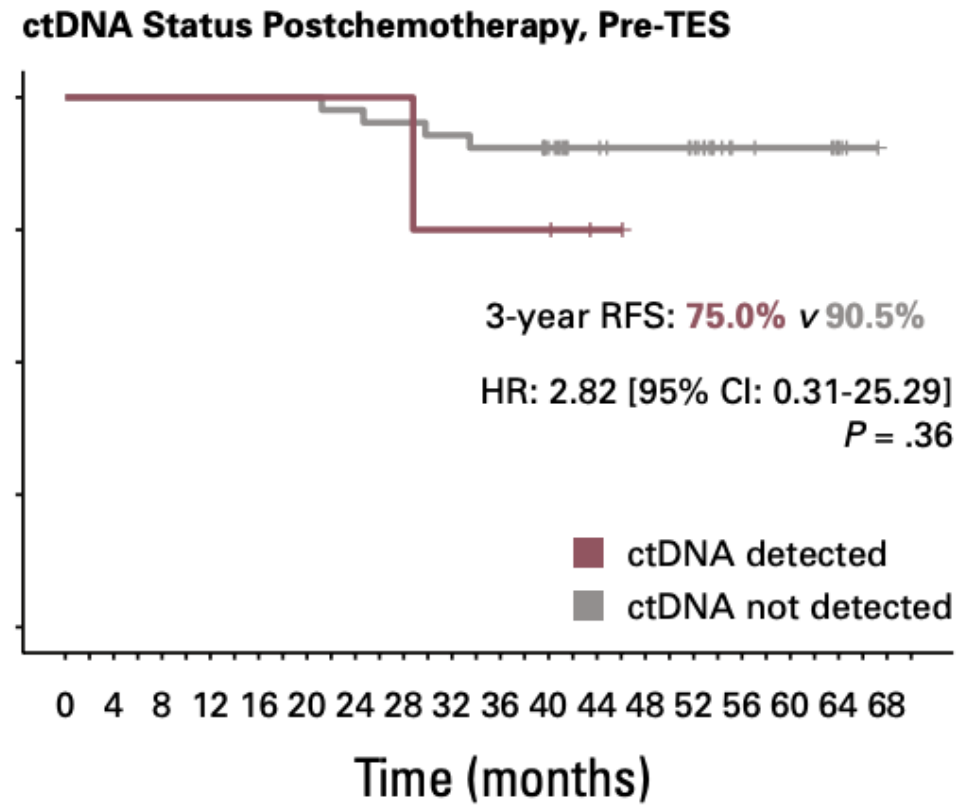


Loree JM, Titmuss E, Brown CJ, et al. Tumor-Free Circulating Tumor DNA in Node-Negative Rectal Cancers Undergoing Neoadjuvant Chemotherapy, Excision, and Observation in the Phase II NEO Trial (CO.28).
JCO Precis Oncol. 2026;10(10):e2600459. doi:10.1200/PO-26-00459



Loree JM, Titmuss E, Brown CJ, et al. Tumor-Free Circulating Tumor DNA in Node-Negative Rectal Cancers Undergoing Neoadjuvant Chemotherapy, Excision, and Observation in the Phase II NEO Trial (CO.28).
JCO Precis Oncol. 2026;10(10):e2600459. doi:10.1200/PO-26-00459


A
Follow-Up (years)
0
1
2
3
4
5
TME not Recommended (patient downstaged; n = 30)
Patient 6
Patient 52
Patient 7
Patient 9
Patient 56
Patient 50
Patient 8
Patient 35
Patient 34
Patient 2
Patient 31
Patient 46
Patient 3
Patient 45
Patient 54
Patient 58
Patient 29
Patient 41
Patient 11
Patient 15
Patient 14
Patient 51
Patient 36
Patient 42
Patient 13
Patient 18
Patient 39
Patient 1
Patient 43
Patient 25
TME Recommended (progression or no response; n = 23)
Patient 28
Patient 57
Patient 20
Patient 5
Patient 10
Patient 40
Patient 38
Patient 24
Patient 12
Patient 19
Patient 17
Patient 49
Patient 37
Patient 16
Patient 27
Patient 30
Patient 23
Patient 32
Patient 48
Patient 33
Patient 4
Patient 22
Patient 21
ctDNA status
Not detected
Detected
Chemotherapy
CAPOX
FOLFOX
Clinical events
Progression
TES
TME
Patient status
Deceased
Distant recurrence*
Local recurrence
No recurrence
*Recurrence to lung / lymph no


ctDNA Status Postchemotherapy, Pre-TES
3-year RFS: 75.0% v 90.5%
HR: 2.82 [95% CI: 0.31-25.29]
P = .36
ctDNA detected
ctDNA not detected
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68
Time (months)

Phase II NEO Trial (CO.28)

- Knowledge Generated The tissue-free ctDNA assay detected ctDNA in 45.8% of patients with **early-stage node-negative rectal cancer prechemotherapy**.
- Postchemotherapy, ctDNA detection is lower and patients with ctDNA detected **were more likely to have been recommended total mesorectal excision**.
- Relevance ctDNA detection after therapy was associated with adverse risk features and warrants further exploration **as a decision aid in nonoperative management for rectal cancer**.

Take-home messages

1. **Every procedure is an experiment**
   ctDNA kinetics tell us what the procedure left behind.

2. **Timing matters**
   Respect the cfDNA surge; sample in the MRD window, then serially.

3. **Trajectory beats a snapshot**
   Sustained vs transient clearance separates outcomes.

4. **Knowing is not yet acting**
   MRD+ patients need trials of new mechanisms, not more cycles.
   May guide who needs surgery e.g. TME versus ongoing observation.

Thank you!



kasi@coh.org; X - @pashtoonkasi

City of Hope®